1. INTRODUCTION

The rapid progress of technology throughout the last decade has contributed greatly to an advance in Radiotherapy techniques. Conventional Radiotherapy with 2D patient information and 2D Treatment Planning has given way to Conformal Radiotherapy (3D-CRT) and more recently Intensely Modulated Radiation Therapy (IMRT). 3D patient information from improved imaging modalities, 3D treatment planning and field shaping with intensity modulation has allowed for a huge improvement in Tumour Control Probability (TCP) and a reduction in healthy tissue damage i.e. Normal Tissue Complication Probability (NTCP).

Treatment planning has further improved with the integration of Radiobiology; The aim being to offer Patient Specific or ‘tailor made’ treatments for each individual patient. Radiobiology applications in treatment planning can allow us to better understand the biological effects on tumours and healthy tissue following irradiation. We can obtain qualitative information as well as quantitative about a tumour and it’s surrounding healthy tissue and seek to reach the main goal of Radiotherapy, to maximize TCP and to reduce NTCP.

Figure 1.1

The aim is to better understand, the relationship between absorbed dose and biological response, and recognize the factors that affect this relationship. We specify the biological effect or end-point that can occur following irradiation and use the dose response curve concept to define it; little effect at zero dose large effect at higher dose. [27]

Figure 1.1, shows what we seek to improve. For a given dose value e.g. 20Gy we want a value as high as possible for TCP while keeping the NTCP as low as possible. Figure 1.1 [B] shows an ideal situation where we have managed to reduce NTCP while maintaining the TCP value compared to Figure 1.1 [A] where although the TCP value is ok, we still have unwanted NTCP at this low dose.

A set of mathematical models, known as radiobiological Dose-Response models, have been developed, to model the biological effects and complications that arise following irradiation. The overall objective is to be able to apply these in clinical practice with confidence, and ensure more successful treatments are given to patients.
This investigation serves to assess these models and their predictive power of NTCP following irradiation of the lung. Clinical data, from patients treated for inoperable stage III non-small cell lung cancer is obtained and the consequent biological effect (severity of pneumonitis) observed as a result of this radiation treatment is assessed by the models. By gaining more knowledge about the 3D dose-distribution and the incidence of radiation pneumonitis through the evaluation of the models, the main treatment goal, which is to maximise TCP and minimise NTCP can be achieved.

Post treatment data is obtained regarding the clinical outcome or clinical endpoint for each patient. The severity of the outcome with reference to the lung tissue complications is scored on the RTOG/EORTC and LENT/SOMA scales (table 1) with the maximum severity, in this case, considered to be Radiation Pneumonitis. The clinical endpoint is a specific biological effect that may or may not have occurred, after a certain period, following irradiation.

### Table 1 Clinical radiation pneumonitis scoring criteria (RTOG/EORTC, LENT/SOMA). [2]

<table>
<thead>
<tr>
<th>RTOG/EORTC TC scoring grades</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Symptoms (acute scheme)</td>
<td>No (very mild/no RP)</td>
<td>Mild symptoms or dry cough or Dyspnnea on exertion</td>
<td>Persistant cough requiring narcotic antitussive agents</td>
<td>Persistant cough requiring narcotic antitussive agents or radiological evidence of acute pneumonitis</td>
<td>Severe respiratory insufficieny Assisted ventilation</td>
</tr>
<tr>
<td>Clinical Symptoms (late scheme)</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough)</td>
<td>Moderate symptomatic fibrosis (severe cough) Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis Dense radiographic changes</td>
<td>Severe respiratory insufficieny Assisted ventilation</td>
</tr>
<tr>
<td>SOMA Scoring grades</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Clinical Symptoms</td>
<td>No RP</td>
<td>(mild/no RP)</td>
<td>(RP)</td>
<td>(RP)</td>
<td></td>
</tr>
<tr>
<td>Most minor symptoms/no treatment</td>
<td>Moderate symptoms/conservative treatment</td>
<td>Severe symptoms/aggressive treatment</td>
<td>Irreversible functional damage/ major therapeutic intervention</td>
<td></td>
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The models are assessed on their ability to predict a NTCP value that corresponds to the resulting clinical endpoint following treatment. Furthermore a software tool for the calculation of NTCP's by the models is developed, in an attempt to provide an important tool for optimization of radiotherapy treatment planning.
With our findings from this study, our aim is to further strengthen, support and challenge already existing literature on dose-response modelling. We endeavour to highlight the strengths and weaknesses in the predictive ability of the models, and through this contribute to the attempts being made to improve the chances of radiobiology modelling being used as a prognostic tool, clinically with confidence, in the future.

1.1 Radiobiology

The irradiation of a patient in radiotherapy leads to a range of biological effects that occur at an atomic, a molecular and a cellular level.\(^{[29]}\) The magnitude of these effects governs the effect of the radiotherapy treatment i.e. its success in tumour control and the prevention of normal tissue complications.

Mathematical models encompassing a possible radiobiology element of a treatment planning system would aim to represent and predict the response of normal tissue and malignant tissue to radiation exposure.

The response of healthy and malignant tissue to radiation is essentially a result of the amount of damage inflicted upon the DNA (Deoxyribonucleic acid) in the cells of each of the corresponding tissues. Significant damage to DNA whether direct or indirect will eventually result in cell death, something we desire in the clonogenic cells of tumours but not in healthy tissue cells.

Cell death fundamentally means that no further reproduction of the cell will occur. The interaction of radiation with a cell and the subsequent damage, of its DNA, if sufficient may have the effect of stopping reproduction which leads to cell death. The cell cycle has terminated and no more synthesis and mitosis will occur. The effects of this maybe visible in a short time period or a longer period of time depending on whether a tissue is early or late responding.

1.1.1 The Cell Cycle

When addressing the issue of tissue response to radiation we are interested in the damage inflicted upon cells in tissues and more specifically the damage to the DNA within these cells, which is the driving force behind cell functionality and existence.

Each cell in the human body goes through a cell cycle (see Figure 1.2). The distribution of cells in this cell cycle is exponential which means there are a varying number of cells in each of the phases. The Radiosensitivity of a cell in the cell cycle is different for each phase and the resulting tissue response will be affected by this.
A limited number of studies on cell lines have shown that cells are most sensitive in the G2 and M (Mitosis) phases of the cycle, and less sensitive towards the end of the S phase of the cycle. The high sensitivity of cells in the G2 phase is believed to be due to the cells having little time to repair radiation damage before they divide in the M phase.

Cell progression through the cell cycle and the associated synchrony of cells has been explored in the past, with an attempt to modify therapies accordingly to maximize damage to clonogenic cells in tumours during irradiation. The variation of speeds through phases of the cell cycle however is abundant both in healthy and malignant tissue making it difficult to observe a uniform synchrony.

Regarding the response of cells, Withers (1975) summarized the biological factors that characterize normal and malignant tissue response during fractionated radiotherapy. They are known as the four R’s of radiotherapy with Radiosensitivity the newly added 5th R.

**Repair:** Cell recovery few hours after irradiation. This is possible if the DNA has not been substantially damaged. Strand breaks on DNA macromolecules (See section 1.1.2) are repaired after irradiation and normal function can resume for the tissue in question. Some strand breaks rejoin but gene function is not restored and mutation can occur (Figure 1.3). Recovery is linked to, the survival of a cell a specific time after irradiation has occurred and restoration of tissue functionality. The ability that a cell has to recover and consequently restore tissue function is strongly dependant on dose delivery.

**Redistribution:** Movement of cells into more sensitive regions of the cell cycle following irradiation, so the next time they are irradiated, they are more likely to be damaged.

**Repopulation:** Cell proliferation during a course of radiation may increase the number of tumour cells that must be killed. In some classes of tissue inward migration of surviving clonogenic cells from a surrounding unirradiated area can occur.

**Reoxygenation:** During fractionated radiotherapy the time period between treatments is favourable for the treatment of malignant tissue and also the survival of healthy tissue. Following irradiation a tumour is left with only hypoxic cells, as its aerobic cells (O2 present) have been destroyed. A gap between treatments allows the tumour to become reoxygenated thus making it more sensitive to radiation each time it is irradiated during a course of treatment. Furthermore the tumour cells move into more radiosensitive phases of the cell cycle.
The time interval between dose deliveries allows repair and repopulation to occur in the Normal tissues. Most normal tissues are considered to be well oxygenated. The enhancement of radiation damage by oxygen is dose modifying. \[27\] So for a given radiation dose the surviving fraction of cells is larger for Hypoxic tissue than Oxic tissue. To quantify this oxygen enhancement ratio (OER) is defined as:

$$\text{Oxygen enhancement ratio} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce the same effect with oxygen}}$$

For the same biological effect. The OER for X-rays is between 2.5 and 3. Studies by (Palcic and Skarsgard 1984), showed that at low doses of radiation below 3Gy the OER was reduced, so for fractionated radiotherapy where doses range between 1.8Gy – 2Gy per day the effect of oxygen as a radiosensitizer may not be as pronounced. \[27\] In healthy tissues the presence of Oxygen does not enable enzymatic processes to repair damage inflicted upon the DNA during irradiation due to the interaction of oxygen and free radicals (See section 1.1.2).

Radiosensitivity: The Radiosensitivity of a tissue is strongly dependant on the aforementioned factors. There is a trade off in each case. A gap between treatments will enable repair and repopulation but also gives rise to Reoxygenation and Redistribution which will have a detrimental effect on the cells of a tissue in the next treatment. Every tissue will be characterized by a unique Radiosensitivity that depends on the organ, or tumour in question. The aim of radiobiology is to further identify these and the mechanisms which govern them.

1.1.2 Dose Delivery

The biological effects seen in healthy and malignant tissues following irradiation during treatments are strongly dependant not only on the magnitude of the dose but also on the pattern of dose delivery. Dose rate and fractionation play an important role in optimizing radiotherapy treatments maximizing tumour control and minimizing healthy tissue damage. Elkind and Sutton, 1960, discovered that the effect of a dose of radiation is reduced if it is delivered in two fractions separated by a small time period of a couple of hours. This enabled the recovery from sub-lethal damage. They found that recovery occurred to a considerable level within 15 minutes to an hour and after 4 hours complete recovery was seen in most normal tissues. \[27\] Recovery from Potentially lethal damage has also been observed as cells are seen to divide when they are required to after irradiation.

Fractionation enables repair, repopulation, redistribution and reoxygenation all helping to destroy malignant tissue and maintain healthy tissue. By increasing the number of fractions, and reducing the amount of dose in each fraction we can achieve a higher dose delivery to the tumour whilst allowing for cellular repair of healthy tissue. In conjunction with this dose rate is of high importance. A lower dose rate allows for cellular recovery through sub lethal damage repair. Typical treatments encompass a dose delivery pattern of 2Gy per fraction, one fraction per day, for 5 days in a week, for a total dose delivery of 50 Gy. It has been found that a two day weekend break from treatment has a positive effect on healthy tissue recovery and enables oxidation of malignant tissue.

Radiotherapy fractionation is applied in relation to the tissue being treated. The existence of early and late responding tissues (see section 1.1.5) has resulted in the development of a range of fractionated treatments, such as Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) which is for high doses, low dose per fraction and short treatment times, and Hyperfractionation which works
on the principle of delivering two or more fractions per day, devised to deal with specific cases. It is evident that in order to optimize radiotherapy treatments there is no single 'best' method, and the complexity and individuality involved in each case makes for composite treatment plans.

### 1.1.3 Damage to DNA

During irradiation charged particles traversing through tissue, and subsequently cell nuclei, deposit their energy. The energy deposited per unit mass is the dose that is responsible for damage to a cell's DNA found in the nucleus.

The damage caused to DNA as a result of charged particles can be direct or indirect. The type of damage is dependant on the conditions of the tissue being irradiated such as its water content but even more so, on the Linear Energy Transfer (LET) of the charged particle traversing the tissue. LET is the rate of energy loss along the track of an ionizing particle. [27] This energy loss deposited in matter is known as dose. The ionization density for each type of radiation differs. Heavy particles such as protons and Alpha particles have a higher LET than X-rays or \( \gamma \)-rays. That is to say that these heavier particles cause more ionization per unit distance thus will deposit dose more frequently. DNA is approximately 2nm in diameter so a more frequent energy deposition per unit distance is more likely to cause damage to the DNA helix.

#### Indirect Action

The human body predominantly consists of Hydrogen and Oxygen, the building blocks of water (H\(_2\)O). This large amount of water in the body serves as a medium for radiation interaction during irradiation. The interaction of radiation with water and the consequent damage to DNA as a result of chemical reactions is known as indirect damage.

Radiolysis occurs when ionizing radiation interacts with water. The water molecule (H\(_2\)O) is ionized and an electron (e\(^-\)) is removed from its outer shell. As a result, the water molecule becomes positively charged (HOH\(^+\)). The negatively charged electron and the positively charged water molecule are unstable and free to interact with other atoms. Recombination of the ion pair can occur and in this case no biological damage occurs. However the electron can go on to interact with another water molecule making it negatively charged (HOH\(^-\)) and unstable. Therefore 2 unstable water molecules of opposing charge now exist. The unstable molecules can dissociate into small compounds and it is the interaction of these with macromolecules such as DNA that lead to cell kill.

The unstable positively charged water molecule breaks down into a positively charged hydrogen ion (H\(^+\)) and a hydroxyl free radical (OH\(^*\)). This free radical is uncharged although it contains an unpaired electron in its outer shell that makes it highly reactive.

The unstable negatively charged water molecule breaks down into a negatively charged Hydroxyl ion (OH\(^-\)) and a hydrogen radical (H\(^*\)). The hydrogen radical has a neutral charge but it is highly reactive because hydrogen is only stable in the form H\(_2\). Each of the free radicals produced from the above events will take part in reactions that will lead to the biological damage seen after irradiation.

The combination of two hydroxyl free radicals will lead to the production of hydrogen peroxide:

\[
\text{OH}^* + \text{OH}^* = \text{H}_2\text{O}_2 \quad [1]
\]
Hydrogen peroxide is toxic and will poison a cell’s cytoplasm, causing the cell to die.

Free radicals will also combine with molecular Oxygen which is found readily in the human body:

\[ H^* + O_2 = HO_2^* \]  \[2\]

The hydroperoxyl radical will also cause biological damage.

Indirect action is important because although a macromolecule is not damaged initially, the free radicals produced from the primary reactions with the large amount of water available, go on to cause much damage to the macromolecules of DNA. In direct action we have immediate interaction with the macromolecules, and ionization of atoms that are part of the DNA molecule, but their abundance is less than that of water so the damage events are considerably less over time. [27, 29]

**Direct Action**

Direct damage occurs when the charged particles subsequent to tissue irradiation, deposit dose locally to the DNA macromolecule, creating damage. As the ionization density increases i.e. as the LET increases for a travelling electron the probability of it damaging a strand of the DNA helix increases. More ionization events close to the DNA will lead to biological damage of its structure.

The damage to DNA occurs in the form of strand breaks following irradiation. DNA has a double-helix structure that consists of two strands made up of a sequence of nucleotides to which bases are linked through a sugar group to a phosphate group. The two strands are held together by hydrogen bonding between the bases. In radiobiology we are interested in the damage to the strands and whether this is permanent or repairable because the amount of damage induced by radiation in DNA is greater than the amount of damage that leads to the death of the cell.

The lesions produced in the DNA strands can be in the form of Single Strand Breaks (SSB) or Double Strand Breaks (DSB) (see figure 1.3). The abundance of SSB and DSB ultimately determine the amount of radiation cell killing that occurs, but the reader should be aware that other mechanisms of damage are also likely to contribute to cell killing, see 1.1.5.

**Figure 1.3**

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**Figure 1.3**

[Diagram of DNA structure showing Single Strand Breaks (SSB) and Double Strand Breaks (DSB).]
It is believed that DSB are predominantly responsible for the cell killing that is seen after irradiation. Although the profusion of SSB is greater than that of DSB the subsequent DNA damage produced is more easily and more often repaired if it is a SSB lesion. However the concentration of SSB’s, on a DNA molecule, if close enough can form a DSB which becomes a lethal lesion.

The density of ionizations in the tissue determined by the LET that characterizes incident radiation, will determine the amount of lesions produced. A cluster of several SSB and DSB called a local multiply-damaged site LMDS (Ward 1986) [27] is likely to produce a lethal lesion in the DNA molecule it resides in leading to cell death.

It is important to understand that lesions in the DNA molecule will occur during irradiation of a tissue. These lesions will be a collection of sub-lethal lesions that are repairable and lethal lesions often produced by sub-lethal lesions combining, and it is these that are irreparable leading to cell death. The ability that a cell has to repair the damage inflicted upon it is dependant on many biological factors such as enzymatic processes, Chromatin structure, Membrane Structure, and chromosome abnormality. Moreover survival of a cell may not mean survival to its original condition but to mutated form with residual DNA damage still existent.

Figure 1.4 shows the various developments that can take place for a cell following the interaction of ionizing radiation with DNA.
Many methods have been explored that enable the aforementioned strand breaks to be measured. These are analytically explained in (Basic Clinical Radiobiology, Steel 2002).

### 1.1.4 Radiation Cell Killing

Cell survival is governed by a range of processes. If the influence of these processes is strong it will ensure complete repair following irradiation and prevent the cell from dying. Any weaker influence may enable the cell to survive, but with reduced capabilities and associated mutations. Strand breaks that result from the LET of ionizing radiation contribute to cell death and are considered a major event in the killing process but they may not be the only process responsible.

Chromatin found in the nucleus of a cell is made up of DNA and many proteins, and makes up chromosomes. The specific interaction of the DNA and the proteins found in chromatin may have an effect on enzymatic repair of DNA lesions and the radiation-induced free radicals which cause indirect damage of the DNA. In studies from UV irradiation it has been shown that transcribing regions of DNA are repaired more often than the non-transcribing regions. With reference to chromatin structure it has been observed that DNA-associated histone proteins have a protective effect against strand breaks caused by irradiation of tissues.

The cell membrane structure has also been considered as a key feature with regards to cell death following irradiation. Damage to the cell membrane from radiation has been observed to cause rapid cell death (apoptosis) and breaking down of the DNA.

Bacteria have also been observed to increase the expression of proteins that encourage DNA repair following irradiation and damage of the DNA macromolecule. Furthermore there has been evidence of genes being activated following exposure to low doses of ionizing radiation. Genes for growth factors, nuclear signal transducers and natural cytotoxins. These genes influence the biological response to radiation which may be repopulation, fibrosis, repair and cell killing. These events are known as inducible responses to radiation, and may help to explain the reaction and high sensitivity of cells to low doses of radiation.
Figure 1.3 depicts how, apart from DNA damage leading to cell death, Chromosome aberrations and mutations are also observed after irradiation. These are long lasting sub lethal effects and exist as genomic instabilities. So for many cell generations after irradiation there are problems seen after a considerable time period. [27]

The concept of the ‘bystander’ effect was introduced in 1988 (Mothersill and Seymor) [3]. The thought behind this concept is that there is a possibility for cell death and mutation to occur as a result of radiation damage to adjacent cells. So cells were dose deposition has not occurred will suffer from mutation and further damage. The plethora of factors involved in cell survival make the process of quantifying Tumour control probability and Normal tissue damage a complex one.

1.1.5 Cell Survival

All the aforementioned processes of cellular damage and cellular repair help to identify the status of the cell and whether it has retained its functionality and survived following its exposure to a dose of radiation. Cell survival curves (Figure 1.5) are used as a means to show the fraction of surviving cells subsequent to irradiation from a radiotherapy treatment.

Figure 1.5

Using cell survival curves one can obtain the surviving percentage of cells for a given dose value. The survival scale of the plot is logarithmic and this allows the small survival percentage of cells at high doses to be viewed. Moreover the random process of cell killing results in survival being an exponential function of dose. [27]

Cell survival is determined using colony forming assays, where the survival of cells is observed following irradiation. A cell suspension (Unattached floating cells in liquid culture medium [www.solvo.hu/glossary.html]) is used to obtain a number of cells to be plated and then these are exposed to radiation. Cell colonies are counted following exposure to radiation and from these the survival curves are deduced.

The radiosensitivity of cells will differ and hence so to will the shape of the survival curve. The processes behind cell kill and DNA damage can help explain the shape of these curves subsequent to mathematical analysis. Cell Survival curves are the basis on which radiobiological modelling is developed (see section 1.2).

1.1.6 Normal tissue response to radiation

Evaluating normal tissue response during irradiation provides an indication of the tolerance of the tissue to the dose of radiation. To quantify this certain clinical endpoints are used, for example in the case of the lung 5% Pneumonitis is used as
the level of tolerance. In our investigation of the lung tissue response to radiation the scoring system applied to assess the level of damage to the tissue is shown in table 1.

Normal Tissue Complications can be labeled as ‘Early’ or ‘Late’ effects depending on the speed of proliferation of the tissue in question. Early effects are seen in tissues that engage in rapid repair, tissues such as the skin. Here the effects are based on the rate of killing of the stem cells, which can self-renew and produce other cells, and the repair of clonogenic cells that survive. In contrast to this in late responding tissues there is a slow proliferation of cells and hence there is a substantial period before the onset of visible damage.

It is difficult to quantify early and late effects with maximum certainty because these effects or clinical endpoints are measured across a scale that encompasses a range of severities. It is often the case that in early responding tissues such as the skin, there is an onset of late effects such as fibrosis weeks after treatment that have developed from different interactions between cells following the early effects. This could be evidence of ‘bystander’ effects (see 1.1.5) occurring. Table 1 shows how different levels of damage for the lung, an intermediate to late responding tissue, are scaled. So there is no single tolerance for a tissue, and no zero effect.

The early and late responses exhibited by tissues become important in clinical applications and fractionated radiotherapy. Courses of fractionated therapy can be altered if early reactions of considerable severity are observed. This gives time for stem cells to repair and subsequently these will support the proliferating tissue towards survival.

A typical response is shown in figure 1.6 where the surviving fraction of cells against dose is shown. The delayed response for late responding tissues means that they are less prolific in the repair of DNA strand breaks and other cellular damage so there is a steeper fall in the surviving fraction at lower doses. Conversely for early responding tissues early repair provides more tolerance to dose and a larger surviving fraction is maintained until higher doses are reached. A more analytical examination of this curve is given in section 1.2

**Figure 1.6**

Alterations in fractionated therapy i.e. reducing the treatment time and intensifying the treatment with an increased dose rate, to account for the onset of early effects may result in the development of consequential late complications. Tissue restoration has not been prolific and the amount of stem cells left for repair has been reduced to a level that cannot help the tissue survive leading to chronic injury.
Conversely treatment times could be increased to prevent these chronic injuries but this does not come without a cost. An increase in the treatment time may result in late effects becoming more pronounced because although the early NTCP will be reduced with a less intense fractionation schedule the TCP will need to be maintained and to do this a consequent dose increase will have to exist for each fractionation which will affect healthy tissue in the long term.

The complexity of each tissue response incorporated with the complexity of each tumour and each specific patient anatomy, makes the managing of Normal Tissue Complications a composite process.

**The Lung**

The Lung is the most sensitive intermediate-to-late responding tissue. Irradiation of the lung can lead to induced disorders that vary in terms of the time scale of response. Acute Pneumonitis can occur at 2-6 months following treatment, and Fibrosis can develop over a period of months and years. Severe radiation pneumonitis during the first 6 months after irradiation can be life threatening.\(^1\)

Considered a ‘parallel’ organ the behaviour and functionality of the lung is such that it will continue to function even when moderately large parts of it are damaged or removed. Due to the structure of its ‘functional subunits’ (\(\text{Kallman et al 1992}\), FSU, Withers et al. 1988) see 1.1.7 the lung becomes a dose-limiting organ when large volumes of it are irradiated. The implications of this are more pronounced when using square field techniques compared to Intensely Modulated Radiotherapy Treatments (IMRT) which allows for only small parts to be irradiated. In certain lung disorders such as emphysema where both lungs are irradiated the response of the lung to radiation becomes more pronounced. Symptoms and effects of lung irradiation can be found in table 1.1 where Pneumonitis appears as the most severe effect.

As aforementioned stem cell survival is imperative to aid the proliferation of normal tissue cells following irradiation but it is not the only process that affects tissue response. The importance of cytokines, proteins released by cells of the immune system which act as intercellular mediators in the generation of an immune response ("cytokine." The American Heritage® Dictionary of the English Language, Fourth Edition. Houghton Mifflin Company, 2004.), was highlighted by Ruben et al 1995 \(^{27}\). The appearance of inflammatory cytokines after lung irradiation is said to contribute to the cause of radiation Pneumonitis. Moreover the production of fibroblasts, cells that make up connective tissue and provide structural support, is stimulated by fibrogenic cytokines which together with inflammatory cytokines support the development of radiation Pneumonitis. A future attempt to monitor and alter the rate of cytokine release following irradiation may prove successful in reducing normal tissue damage and severity of effects.

1.1.7 **Normal Tissue Structure and Function**

The effects of radiation on an organ can be classified into a three-level hierarchy: (3) Death of individual cells. (2) Damage of functional subunits. (1) Failure of organ function. Effects at a higher level directly result from effects at the level below. \(^9\)

Understanding the structure and function of normal tissue is essential to ensure an accurate modelling of dose-response. Tissues are composed of structural compartments and functional compartments and the cell populations in each of these will have a different response to irradiation.
In the structural compartment of tissue it is important that the clonogenic cells are able to repopulate considerably, after irradiation to maintain a level of survival and engage in repair of the tissue, and to not die out. For the functional compartments it is important that they are not destroyed on a mass scale such that organ function will cease.

The organization of the tissue and the sensitivity of the cells that the tissue is composed of will ultimately determine the response of an organ being irradiated. An accepted way of defining the structure of an organ has been adopted following work by (Withers et al 1988), where the tissue of organs is classified as a set of Functional Subunits (FSU's). This concept was introduced by Withers et al to help define tissue organisation and radiation response.

An FSU may be defined structurally e.g. a nephron, or functionally, as the largest unit of cells capable of being regenerated from a surviving clonogenic cell without loss of the specified function. Functional Subunits can be arranged in parallel or in series. If arranged in parallel the response of the associated organ or tissue is a graded response but if arranged in series the response is binary. The associated tolerance doses are a function of the number of target cells in an FSU and their radiosensitivity, and also the tissue organization and functional reserve which is the number of FSU's required for sufficient organ function. [26]

An important finding made in the work by Withers et al is related to the volume of the tissue irradiated. It was stipulated that an influence of treatment volume on tolerance doses is more likely to depend on tissue organisation and not on differences in cellular radiosensitivity.

Sigmoid dose response curves should have a lower threshold and be steeper the larger the treatment volume. The effect of increase in volume is greatest with changes in small volumes: once a large number of FSU’s are being irradiated, a further increase in volume has little effect on the position or slope of the probability curve for such complications. [26]

The caution when adopting the idea introduced by Withers et al is highlighted in a paper by Kallman et al 1992, that states “When defining a functional subunit one should keep in mind that the target cells of an organ are not only the functional cells but the tissue regenerating cells may be even more important. The division of an organ into functional subunits is therefore quite complex if the centres of function and regeneration do not coincide.” As discussed later on in this report this acts as a possible drawback in dose-response modelling of tissues. Furthermore studies by (Liao et al, 1995) showed that the functional subunits of the lung are possibly more widespread in the basal area compared to the apex making this area more radiosensitive. [4]

**The Volume Effect and Lung tissue**

The concept of the volume effect is observed when large volumes of organ tissue are irradiated. When large volumes of tissue are irradiated a decline is seen in the functional ability of an organ, where as the tissue sensitivity per unit volume is not affected. The radiosensitivity of each individual cell in a tissue is not increased if the irradiated volume increases but the overall functionality or clinical tolerance is strongly affected.

The lung like the kidney and other parallel structure organs is dose-limiting when large volumes of it are irradiated but its functionality is not weakened greatly if small areas are irradiated. So a threshold number of FSU have to be harmed following irradiation, of any magnitude, for function to weaken. The advantage of IMRT over
conventional radiotherapy is evident for organs with this pronounced volume effect. The severity of functional damage covers a wide scope, as seen in table 1, ranging from mild symptoms of dry cough and Dyspnea to severe respiratory inefficiency (Radiation Pneumonitis). So an assessment of dose distribution to the lung as a whole, as done in this investigation, is imperative in understanding the developed normal tissue complications.

For organs with a serial structure such as the spinal cord, the severity of functional damage does not cover a wide range and damage to a small number of FSU’s will cause the complete function of the organ to cease. One process however which occurs for tissues of this nature compared to parallel structured tissues, is that repopulation can occur from nearby cells repairing small volume damages from irradiation that occurred from small fields.

As identified by Kallman et al 1992, normal tissues cannot be described by a purely parallel structure. No organ is completely parallel or serial in structure and damage will always occur to some extent. The idea of FSU’s offers a constructive way of modelling the volume effects and responses of tissues following irradiation. This is discussed in greater detail in the methods section of the report.

In the case of the Lung the volume effect on functional damage has been investigated in mice, rats, dogs and pigs. In these studies the function of the lung was strongly dependant on the volume irradiated and for irradiated volumes of 50% and less there was no severe symptoms of pneumonitis. Although the function of the organ was affected by increased irradiated volumes the radiosensitivity of the cells showed no dependence on volume in the aforementioned studies.

Studies by Marks et al., 1997; Graham et al., 1999 showed that the total lung volume irradiated above 20Gy and above 30Gy, is a factor that can influence the probability of radiation pneumonitis occurring. This is further investigated in this report by looking closely at the dose distributions in the lungs after cancer treatment.

1.2 Modelling the biological effects

To model the biological effects and dose-response of tissue, mathematical models of cell kill are devised and these are then incorporated into the analysis of effects following irradiation. These models are based on the survival curves such as that shown in figure 1.5, and hence on how cell survival is linked to the dose.

1.2.1 Target theories

In Radiobiology cell kill is closely linked to the amount and the type of strand breaks imposed on a cells DNA. Subsequent to irradiation and whether damage is direct or indirect as discussed in 1.1.3 strand breaks will occur. As aforementioned it is predominantly the amount of DSB that are thought to influence the cells survival capability. If the incident radiation is characterized by a high LET then the probability of a DSB is increased and so to the probability of chromosome damage and cell death. Many SSB can occur but these can be repaired and cause a smaller effect. On the contrary a single DSB can lead to incurable effects for the cell.

The Target Theory has been adopted to describe how the damage to DNA may occur. It assumes that there are susceptible regions (targets) on the DNA macromolecule which help cell reproduction and that it is damage to these from radiation that governs the likelihood of survival. It can be thought of as the ‘heart’ of the DNA molecule.
The single-hit target theory is the idea that one single hit on a susceptible region will cause the cell function to cease. This can be applied to cell survival characteristics after high LET irradiation, and the survival curve produced is like that shown in figure 1.6 for the densely ionizing radiation. The exponential behaviour seen in survival is explained in section 1.1.4.

**Figure 1.7** [30]

A mathematical equation can be fitted to the survival curve produced as a result of irradiation. Cell kill is a random process and since the Poisson distribution ‘expresses the probability of a number of events occurring in a fixed period of time if these events occur with a known average rate, and are independent of the time since the last event’ (http://en.wikipedia.org/wiki/Poisson_distribution), it is used to analyse the probability of cell survival.

In the single-hit target theory it is assumed that when a tissue is irradiated there are lots of hits on different cells but that the probability of the next hit occurring in a known cell is very small.

\[ P(\text{survival}) = P(\text{no hits}) = \exp(-D/D_0) \]

In Equation 1, \( D_0 \) is the dose that results in one hit per target. A dose of \( D_0 \) means that the survival fraction drops to \( e^{-1} \), and if the dose is greater than \( D_0 \) then the cell will die. \( D/D_0 \) is the average number of hits per target, per cell for the single-target theory. The single-hit theory and the resulting survival curve are useful for describing the response at low doses of radiation for sensitive tissue.

Due to repair and repopulation processes, and the tissue regeneration seen in most tissues following irradiation, the straight survival curve is not an entirely accurate representation of cell response to dose. The more typical response is that of the continuously bending survival curves seen in the sparsely ionizing curve in figure 1.5 and in the curves shown in figure 1.6 and figure 1.7 (curve B). To explain these, a multi-target single hit theory has been devised. Here each cell has more than one susceptible target which causes its function to cease. One hit on a number \( n \) of susceptible targets is required for cell death to occur. Following from equation 1:

\[ P(\text{no hits on a target}) = \exp(-D/D_0) , \]

\[ P(\text{a target is hit}) = 1 - P(\text{no hits on a target}) = 1 - \exp(-D/D_0) \]

\[ P(\text{all targets } n \text{ are hit}) = [1- \exp(-D/D_0)]^n \]

\[ P(\text{survival}) = P(\text{not all targets are hit}) = 1 - [1- \exp(-D/D_0)]^n \]
The multi-target single hit theory can be used to describe the survival-dose relationship at higher doses. Repair which occurs at lower doses means that not all targets are damaged hence the cell kill does not occur.

The target hit theories are important to understand the radiation effects on cells. It is difficult however to locate targets on tissue cells and this has not yet been done. The only area that can be linked to the idea of targets is that of strand breaks and DNA, although one could also incorporate the effects outlined in 1.1.5.

Although the target theories can be applied to the curves shown in figure 1.4 they are both not a complete representation of the cell response. The single-target single-hit theory implies that no repair processes occur at the low doses, and the single-hit, multi-target theory implies that at low doses there is complete repair occurring. However low dose cell assays have shown that many cells exhibit Low Dose Hyper-radiosensitivity, so a significant amount of cell kill maybe occurring at low doses. So the probabilities of survival from the two single hit target theories, two independent events, have been multiplied to define what is known as the two-component model, and a new parameter D₁ has been introduced which is the dose required in the low dose region to reduce survival from 1 by e⁻¹. [27]

\[
P(\text{survival}) = \exp\left(-\frac{D}{D_0}\right) \times \left(1-(1-\exp[-\frac{D(1/D_0-1/D_1)])]^n\right)
\]

This model allows for cell killing at low doses also. The complexity of processes that occur in cells of a tissue once they are irradiated makes it difficult to completely characterise their response using a model, so no model will give the complete picture, however a good analysis of the cell survival can be made. One mathematical model that is used to define cell survival curves and serves as the foundation of radiobiological dose-response models is the Linear-quadratic model.

1.2.2 The Linear-quadratic model of cell kill

The Linear Quadratic (LQ) is the second order polynomial fitted to the survival curves of cells following irradiation. It is possible to incorporate radiobiological factors into this equation to explain cell kill and DNA damage:

\[
S(D) = e^{-(\alpha D + \beta D^2)} = \text{the fraction of cells surviving a dose } D.
\]

Compared to the models of target theory the linear quadratic model describes well, the radiation response of cells in the low dose region, up to 3 Gy. The LQ model describes survival curves that are continuously bending. The initial slope of the survival curve is described by the parameter α, a constant, and the parameter β, a constant, describes the quadratic component of the cell kill. α and β are known as parameters of curvature, and they can be explained biologically.

The key elements that ultimately define cell response to irradiation are the magnitude of damage and the efficiency of repair. The Theory of Dual Radiation Action (TDRA) (Kellerer and Rossi, 1972)²⁵ quantitatively predicts radiation injury in the sensitive site of a biological object, based on the detailed microscopic pattern of energy depositions.[²⁴] The TDRA identifies the linear component of the quadratic model \(e^{-(\alpha D)}\) as being due to single track events, and the quadratic term \(e^{-\beta D^2}\) as arising from two track events, where an event characterizes a sub-lethal lesion produced by a particle traversing through a cell.

A single track event arises from a single particle traveling through the cell and depositing its energy on the susceptible regions/targets such as the DNA strands,
causing a DSB or a SSB. These sub-lethal lesions would then combine to form a lethal lesion which would lead to the death of the cell.

A two track event arises from two different particles each depositing their energy to different susceptible targets of a cell. A combination of these sub-lethal lesions produced by each particle would create a lethal lesion which again would lead to cell death.

As described by Kellerer and Rossi, 1978, sublesions are produced depending on the pattern of energy transfers to the cell, and these sublesions can interact in pairs to produce lesions which in turn determine the observed effect i.e. the cell death or chromosome aberrations.

Lethal lesions are strongly dependant on the LET of the radiation and hence the dose. A linear quadratic form gives us the influence of dose on each lesion:

\[ -\ln(S) = \alpha D + \beta D^2 \]

where \(-\ln(S)\) is equal to the number of lethal lesions per cell, and is the natural logarithm of the surviving fraction of cells.

For fractionated survival Eq. 8 becomes:

\[ -\ln(S) = \alpha nd + \beta nd^2 \]

Where \(d = \) dose per fraction, and \(n=\) the number of fractions, so \(d = D/n\).

So the probability of the cell containing no lethal legions and thus surviving a given dose \(D\) is:

\[ P(S) = S(D) = e^{-(\alpha D + \beta D^2)} \]

This is the same expression seen in Eq. 7.

The ratio of \(\alpha/\beta\) gives the dose per fraction in Gy on the survival curve where the linear contribution to cell kill \(\alpha D = \beta D^2\) the quadratic contribution i.e. the dose per fraction where the number of single track events equals that of the two track events. This depicted in figure 1.7.

**Figure 1.8**
A high $\alpha/\beta$ ratio characterizes a dose response that is dominated by single track events from highly ionizing radiation, high LET. For radiation with a lower LET there is a greater likelihood of two track events which produce lesions that combine to form a lethal lesion leading to a smaller $\alpha/\beta$ ratio.

It is clear that the single track events will always occur following irradiation. If the dose rate delivered is low, then there will be enough time available for the tissue to repair between dose deliveries and so the linear term will dominate over the quadratic term, hence a high $\alpha/\beta$ ratio. This is a characteristic observed for early responding tissues. In Figure 1.5 the curve initially is dominated by the linear term and only begins to bend at high doses where the quadratic term becomes pronounced. Conversely for late responding tissues, the probability of events from two separate tracks combining is higher because of slow repair thus the quadratic term dominates and the curve bending occurs at lower doses.

Ratios of linear to quadratic terms for various organs from multifraction experiments are available and can be found in table 1 below. The organs are classified as early or late responding. As can be seen for the lung, it is classified as a late responding tissue with a relatively small $\alpha/\beta$ ratio ranging from 2 to 6 Gy.

### Table 2 $\alpha/\beta$ values

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Clinical End-point</th>
<th>$\alpha/\beta$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Erythema</td>
<td>8.8</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>Mucositis</td>
<td>8-15</td>
</tr>
<tr>
<td><strong>Late reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonitis, acute fibrosis</td>
<td>2-6</td>
</tr>
<tr>
<td>Bowel</td>
<td>Structure/perforation</td>
<td></td>
</tr>
<tr>
<td>Spinal cord (early and late)</td>
<td>Necrosis myelopathy</td>
<td>2</td>
</tr>
<tr>
<td><strong>Head and Neck</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>Late fibrosis, fistulae</td>
<td>3-4</td>
</tr>
<tr>
<td>Colon, rectum</td>
<td>Late fibrosis, fistulae</td>
<td>3-4</td>
</tr>
</tbody>
</table>

**Relative Biological Effectiveness**

An important characteristic of radiation, in the field of radiobiology, is its LET. The LET associated with radiation is responsible for the resulting biological effects observed in a tissue being irradiated. A higher value of LET results in an increase in biological damage. Relative Biological Effectiveness (RBE) compares the dose of a test radiation which has low LET (taken as 250 kVp X-rays) to the dose of a standard radiation to produce the same biological effect:

\[
RBE = \frac{\text{Dose from standard radiation to produce a given biological effect}}{\text{Dose from the test radiation to produce the same biological effect}}
\]

The RBE is not only dependant on the type of radiation. It is also dependant on the specific radiosensitivity of each tissue in question and each patient in question. Moreover it is dependant on the dose rate and the schedule of fractionation. The RBE varies with LET as shown in figure 1.8 below. An increase in LET is associated with an increase in RBE up to about 8 for LET = 200 KeV/μm. [30]
A drop in RBE is seen after a high LET is reached because here much of the energy deposition occurs more frequently on the same cell, so other cells may are not killed causing the biological effect to reduce. The observed increase in RBE with LET is the opposite of what is seen with the Oxygen Enhancement Ratio OER discussed in section 1.1.1 which decreases with LET increase.

### 1.2.3 Dose response and modelling

In radiobiology our main aim is to understand the biological effects of radiation on healthy and malignant tissue. To do this it is imperative to recognize all the influencing factors that characterize the dose-response relationship we observe. The most important of these is the aforementioned factor of cell survival following irradiation.

A dose-response relationship displays the probability of irradiation effects i.e. a response, on a scale of 0% to 100%, as a function of dose. Figure 1 shows a typical Dose-Response curve. The radiation effects observed for a tissue, increase with dose. The curves have a sigmoid shape showing that the observed effect approaches zero as the dose approaches zero and it approaches 100% as the dose increases to high levels. A measurement of response in each case is related to a specific effect, or clinical end-point.

A dose that results in a response of 100% is ultimately the dose at which an expected effect has reached its maximum severity. In the case of the lung, which is the organ observed in this investigation, the induced effect investigated, is that of radiation pneumonitis. An increase in dose is expected to cause the radiation effects of radiation pneumonitis to increase in severity. So looking at table 1 one can expect each scoring grade to cover a range of values on a dose-response curve. After very high doses we expect to see the effect of radiation pneumonitis at its maximum. It is important to note that there will always be a response or effect no matter how small a dose value is.

Dose-response curves will differ for each tissue type and each patient. Each tissue will vary in radiosensitivity. Through the use of dose-response curves we can compare patients from similar treatments in order to differentiate the variability that exists biologically in their response to radiation.

The steepness of a dose-response curve is important. It helps to quantify the change in response for every unit change in dose. It is known as the ‘γ-value’ or the normalized dose-response gradient. This helps to indicate the rate of responsiveness of a tissue being irradiated, and helps to measure the onset and rate of development
in the severity of radiation effects. The \( \gamma \)-value depends on the point on a dose-response curve at which it is evaluated. It is usually evaluated at the steepest point on the curve. In the case of the Poisson model described below it is evaluated at the 37\% response point.

The position of a dose-response curve on a scale of radiation is done by looking at a specific dose value that gives a certain level of tumour control or Normal Tissue Complication. For normal tissue response the value given is the D\(_{50}\) value, the radiation dose for 50\% response. This parameter together with the \( \gamma \)-value is used in dose-response modeling.

In figure 1.1 typical dose-response curves are shown for TCP and NTCP. Ideally we would like to increase the distance between these so that a unit increase in dose will cause a large increase in TCP and a small increase in NTCP. This concept is defined as the ‘therapeutic window’ or ‘therapeutic ratio’.

When new radiotherapy treatments are implemented a look at how they improve the therapeutic ratio is essential in giving an indication of the quality of the treatment. The therapeutic ratio is affected by factors such as dose rate; LET of irradiation, the treatment plan and the dose delivery techniques (IMRT, square field etc.). In an ideal situation one would see a steep TCP dose-response curve and a shallow NTCP dose-response curve, which would indicate an optimized treatment.
2. METHODS & MATERIALS

2.1 Patient group - Method of treatment

51 patients treated for inoperable stage III non-small cell lung cancer in the University Hospital of California, form the patient group analysed in this study. 3D dose distributions for each patient were available making the patient group eligible for this study. The clinical outcome for induced radiation pneumonitis was available for all but 5 of the patients so the patient set analysed consists of 46 patients in total.

A requisite for each patient in the study was for them to be able to tolerate external radiotherapy for a total dose up to 60 Gy based on a clinical evaluation. They should each have a histologically or cytologically confirmed primary, inoperable stage III non-small cell lung cancer (squamous cell carcinoma, adenocarcinoma, large cell or other), and a Karnofsky performance status \( \geq 50 \). The Karnofsky scale is shown below:

<table>
<thead>
<tr>
<th>Karnofsky Performance Status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal no complaints; no evidence of disease.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td>70</td>
<td>Care for self; unable to carry on normal activity or to do active work.</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs.</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance.</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death not imminent.</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary.</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Patients were excluded from the study if they had treatment with cytotoxic drugs within three months prior to entering the study and if they had a respiratory function FEV₁ (Forced Expiratory Volume in 1 second) <1 litre.

CT of the chest and pulmonary x-ray were used for the staging of the tumour. Bronchoscopy with biopsy or also fine needle aspiration cytology of the lung tumour was performed for verification of the malignancy. Patients were evaluated by ECG, spirometry (FEV₁, VC (Vital Capacity), CT of the chest and pulmonary x-ray.

Target Volumes were defined using the classification of ICRU 50 [ICRU Report 50]. The gross tumour volume (GTV) included the lung tumour and lymph node metastases as defined from diagnostic CT examination or via mediastinoscopy. The clinical target volume (CTV) was defined by adding a margin of 1.0 - 1.5 cm to the primary tumour. For the mediastinal metastases, a margin of 2.0 cm and 1.0 – 1.5 cm were added in the cranio caudal and lateral direction, respectively. The planning target volume (PTV) was defined as the CTV plus appropriate margins (usually 5-10 mm) for patient movements and set-up uncertainties. Organs at risk were the spinal cord and the healthy lung tissue.

A total dose of 60 Gy was prescribed to the ICRU reference point in the PTV, delivered in 33 fractions of 1.8 Gy/day, five days per week. The aim was to achieve
dose homogeneity of 57-63 Gy (95%-105%). The radiotherapy was intended to be delivered with no breaks, but if toxicity was observed one week of rest was allowed. The maximum allowed total dose to the spinal chord was 45 Gy. Not more than half of the normal total lung volume should receive a total dose above 20 Gy. The radiation treatment was delivered with 4-10 MV photons.

The field shaping was achieved using customised blocks cut individually for each specific case, or with a multi-leaf collimator (MLC). The patients were positioned in a supine position (lying down with the face up) with the head on a standard head rest and the arms above the head allowing for a multiple (3-5) field technique. The patients were simulated and treated whilst free breathing with no breathing instructions issued.

A CT-based 3D treatment plan was performed for the 51 patients included in the study. The treatment plans were produced with the Helax-TMS (Nucletron B.V., The Netherlands) treatment planning system using its pencil beam algorithm and with the correction for tissue inhomogeneities implemented.

**Dose Volume Histograms (DVH)**

3D treatment planning available in radiotherapy allows for important information to be obtained such as detailed dose-distributions and resulting Dose Volume Histograms (DVH). DVH’s provide very useful quantitative information as regards to the dose delivery in subvolumes of an organ. Data from DVH’s enables radiobiological models to be applied to assess the biological response, of healthy tissue, to radiation.

Data from DVH’s are used in this report for implementation and assessment of radiobiological models. Although useful, DVH data does come with many drawbacks. There is loss of spatial information on the dose-distribution, which can inaccurately present ‘hotspots’ in regions of tissue where there is not such a pronounced problem. Parts of the Planning Target Volume (PTV) maybe evaluated as healthy tissue. Moreover a DVH does not differentiate between functionally or anatomical regions of an organ, making it difficult to identify structures such as FSU’s. In the discussion part of this report a new concept introduced by, C-W Cheng, I J. Das 1999 the zDVH, a z-dependant dose volume histogram that enables spatial information to be retained, is discussed.

Calculations of NTCPs for each patient were performed using associated DVHs and the methods aforementioned in this report. A schematic of the calculation procedure which is neatly presented by (Kwa et al (1998)) is shown below:
Figure 2.1

3-D dose distribution

DVH of an Organ

DVH reduction into a single parameter (BEUD, EUD)

NTCP

An example of the received DVH data is shown in figure 2.2. For each patient the dose for each bin was provided with the associated volume. The percentage volume and percentage dose were calculated for each dose step for, the single lung case (lung minus PTV (Planning Target Volume), and treating the both lungs as a single organ. Calculations were performed using Microsoft Office Excel 2003.

Figure 2.2

After successful manipulation of the DVH data the procedure of NTCP calculation could be performed using each of the Dose-response models mentioned in the next section of the investigation. Figures 2.3 & 2.4 below show examples of the Excel environment in which the NTCP calculations were made:
Figure 2.3
2.2 Normal Tissue Complication Probability models.

The purpose of our investigation is to compare and assess the predictive strength of the most familiar normal tissue complication probability (NTCP) models, in predicting the incidence of radiation pneumonitis following radiotherapy treatment. Three NTCP models are assessed; (i) the relative seriality model, (ii) the LKB model and (iii) the parallel model, each with an associated set of parameters shown in table 3. These parameters have in each case been obtained through clinical experiment.

<table>
<thead>
<tr>
<th>Models</th>
<th>Parameter values</th>
<th>Parameter values</th>
<th>Parameter values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Seriality model</td>
<td>$D_{50}$ (Gy)</td>
<td>$\gamma$</td>
<td>$s$</td>
</tr>
<tr>
<td>Seppenwoolde et al (2003)</td>
<td>34</td>
<td>0.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Gagliardi et al (2000)</td>
<td>30.1</td>
<td>0.97</td>
<td>0.01</td>
</tr>
<tr>
<td>Mah et al (1987)</td>
<td>26</td>
<td>2</td>
<td>0.031</td>
</tr>
<tr>
<td>LKB model</td>
<td>$TD_{50}$</td>
<td>$m$</td>
<td>$n$</td>
</tr>
<tr>
<td>Burman et al (1991)</td>
<td>24.5</td>
<td>0.18</td>
<td>0.87</td>
</tr>
<tr>
<td>Seppenwoolde et al (2003)</td>
<td>30.8</td>
<td>0.37</td>
<td>0.99</td>
</tr>
<tr>
<td>Parallel model</td>
<td>$TD_{50}$</td>
<td>$m$</td>
<td>$n$</td>
</tr>
<tr>
<td>Seppenwoolde et al (2003)</td>
<td>31</td>
<td>0.32</td>
<td>0.67</td>
</tr>
</tbody>
</table>

2.2.1 The Relative Seriality model

Dose-response relationships for both tumours and Normal Tissues can be described by mathematical functions. The three most important which are used and implemented in radiobiological dose-response models are the probit, logit and Poisson models.

These mathematical models incorporate volume dependence of tissues and tumours allowing for an organ at risk, to be fully assessed as regards to the dose distribution during irradiation.
Each of the mathematical models incorporates the aforementioned parameters $\gamma$ and $D_{50}$, allowing for comparison. The Probit, logit and Poisson models respectively are shown below:

\[
P(D) = \frac{1}{2} \left[ 1 - \text{Erf} \left( \sqrt{\pi \gamma} \left( \frac{1 - D}{D_{50}} \right) \right) \right]
\]

\[
P(D) = \left[ 1 + \left( \frac{D_{50}}{D} \right)^{4\gamma} \right]^{-1}
\]

\[
P(D) = 2^{-\gamma \left( \frac{1 - \frac{D}{D_{50}}} \right)}
\]

Equation 14 is based on the Poisson statistical model of cell kill (see section 1.2.1), and is the only equation that has a radiobiological background. In equation 14 the value $D_{50}$ has been used to indicate the dose that leads to a 50% response, compared to the equations in section 1.2.1 where a value $D_0$ is used indicating the dose at which the survival has dropped to $e^{-1}$.

The other two models are purely mathematical and used to approximate the shape of the Poisson model, and the sigmoid shape of the dose-response curve, which has a radiobiological significance. An example is shown in figure 2.1(Kallman et al), where $D_{50} = 50\text{Gy}$ and $\gamma = 2.5\text{Gy}$.

Figure 2.5 \cite{3}
above equations need to be adapted to account for inhomogeneous dose distributions.

The concept of FSU’s is applied to calculate complications as a result of partial irradiation to an organ. The organ is said to be composed of a number of sensitive FSU’s. For tumours the model assumes that the tumour is a uniform and parallel structure, so the probability of controlling a fraction of the whole tumour volume, \( v = V/V_{ref} \), of known response \( P(1) \) for the reference volume \( V_{ref}(v=1) \) is given by:

\[
(15) \quad P(v) = [P(1)]^v
\]

For the Poisson statistical model of cell kill the dose and volume dependant equation becomes:

\[
(16) \quad P(D) = 2 \left[ e^{-\left(\frac{D}{D_{50}}\right) + k \ln v} \right]
\]

Equation 16 can be generalized to model the volume dependence for normal tissues, Eq.17. A constant \( k \) is inserted in front of the logarithmic term. This term is unity for tumours and negative for normal tissues. The negative value characterises the reduced risk when a smaller volume of tissue is irradiated (the volume effect). It is a similar effect to that seen in tumours when the clonogen number \( N_0 \) is increased.

\[
(17) \quad P(D) = 2 \left[ e^{-\left(\frac{D}{D_{50}}\right) + k \ln v} \right]
\]

\( P(D) \) is the probability of inducing normal tissue complication i.e. radiation pneumonitis for the lung following irradiation with a dose \( D \). \( D_{50} \) is the dose which gives a response probability of 50% and \( \gamma \) is the maximum normalized value of the dose-response gradient.

The linear quadratic Poisson model can be expressed in the following way:

\[
(18) \quad P(D) = \exp(-e^{\gamma - d / (\alpha / \beta) D}) \approx \exp(-e^{\gamma - (D / D_{50})(\alpha / \beta) \ln 2})
\]

Where the second equality, is used to calculate the response at each dose after correction for fractionation, and then can be used to compute the response of each volume element as described below.

Prior to computing the response of the lung in this investigation, the dose-distributions obtained were corrected for fractionation to allow for a comparison between patient treatments. The aim is to be able to compare each patient treatment and fractionation schedule making it isoeffective. \[27\] Schedules with different total doses and different dose per fraction are converted to equivalent schedules of 2Gy per fraction which would give the same biological effect (EQD\(_2\)). Each dose bin from the DVH was corrected separately, and the regional sensitivity of the lung was considered uniform. The following expression was used for correction based on the linear-quadratic (LQ) model:

\[
(19) \quad EQD_2 = D \frac{d + (\alpha / \beta)}{2 + (\alpha / \beta)} \quad [27]
\]

Where \( d \) is the dose per fraction, \( D \) the dose of each dose bin, and the \( \alpha / \beta \) ratio is considered to be 3.0 Gy for the lung.
An organ can be defined by a number of FSU. These are arranged to allow the organ to function in a specific way. The sub units in an organ can be represented as \( m \) subunits in series or \( n \) subunits in parallel. The response \( P_i \) of an individual subunit is described by equation \( 24 \), and the overall response \( P \) of an organ comprised of individual subunits is given by:

\[
\begin{align*}
(20) & \quad P = 1 - \prod_{i=1}^{m} (1 - P_i) \\
(21) & \quad P = 1 - \prod_{j=1}^{n} P_j
\end{align*}
\]

In most organs there is a mixture of parallel and serial organization of the subunits. The overall response is thus given by:

\[
(22) \quad P = \prod_{j=1}^{n} \left[ 1 - \prod_{i=1}^{m} (1 - P_{ij}) \right]
\]

If the sensitivity of each subunit is assumed to be identical and the absorbed dose distribution homogeneous then \( P_{ij} = P \Delta \) then:

\[
(23) \quad P = \left[ 1 - (1 - P_\Delta)^m \right]^n
\]

And

\[
(24) \quad P_\Delta = 1 - \left(1 - P^{1/n}\right)^{1/m}
\]

From these expressions it is possible to obtain the probability of complication to a fraction \( a:b \) of the whole organ \( P_{ab} \):

\[
(25) \quad P_{ab} = \left[ 1 - (1 - P_{\Delta})^a \right]^b = \left[ 1 - (1 - P^{1/n})^a \right]^b \cdot n^n.
\]

In the above expression the values of \( a \) and \( b \) are the relative fractions of the parallel and serial FSU's that are irradiated, and take values between 0 and 1.

Although most tissues are considered to have a mixture of serial and parallel organization, normal tissues are classified as either parallel or serial, depending on which form of structural organisation dominates. All tumours are considered as having a parallel distribution of subunits. The lung which is the organ analysed in this report is considered to be a parallel organ.

No tissue is considered to be completely parallel or serial even if it is labelled as parallel or serial because mathematically this poses problems which do not agree with the clinical observations. So a structure even if labelled as parallel is still assumed to contain a number of serial structures. To portray this mathematically a parameter \( 's' \) is used that describes the relative Seriality of the tissue, where a value of \( s=0 \) characterises a completely parallel structure and a value \( s=1 \) typifies a completely serial structure:

\[
(26) \quad s = \frac{m}{nm} = \frac{1}{n}
\]
Table 3 shows the values of $s$ for the lung used in the models investigated here. The response of a functional subunit $P_v$ then becomes:

$$P_v = \left(1 - \left(1 - P_s^v\right)\right)^{1/s}$$  \hfill (27)

where $P$ is the response given by equation 12. For a homogeneous dose distribution:

$$P = \left(1 - \left(1 - P_s^v\right)^{1/s}\right)^{1/s}$$  \hfill (28)

For a non-uniform dose distribution, we have the fractional volume of a volume element (voxel) $\Delta v = 1/M$ (the number of voxels of the organ). So equation 28 for the whole organ becomes:

$$P(D) = \left[1 - \prod_{i=1}^{M} \left(1 - P(D_i)^{1/L}\right)\right]^{1/s}$$  \hfill (29)

The whole organ response for a non-uniform dose distribution is described as a function of the dose $D_i$ in each structural component $i$. It is important to recognize that a voxel does not necessarily define an FSU but simply a volume element that receives a specific dose. Here $P(D)$ is the response of the organ (we will refer to the lung from now on) that has a reference volume and is irradiated to dose $D$. $\Delta V_i = \Delta V_i/V_{ref}$ is the fractional sub-volume of the organ that is irradiated compared to the reference volume which $D_{50}$ and $\gamma$ where calculated for. This value of $\Delta V_i$ is equivalent to each volume element obtained from the DVH. In our investigation the whole lung volume is the reference volume to which the model parameters $D_{50}$ and $\gamma$ were calculated.

Equation 29 is known as the Relative Seriality model. The empirical nature of this model gives it its credibility as a tool for looking at NTCP’s. Its predictive power for Normal Tissue complications was investigated in this report.

The Relative Seriality model gives us the complication probability for an inhomogeneous dose-distribution which is represented by a set of structural components $M$ with volume $\Delta v$ and corresponding dose $D_i$. This information can be extracted from Dose Volume Histograms (DVH) where each dose bin ($D_i$) in a DVH is a subvolume ($\Delta v$). These are known as differential DVHs.

In a model called the Critical Element model (Niemierko and Goitein 1990) an assumption was made that an organ consists of N critical elements which they labeled as FSUs. The difficulty however in defining a FSU accurately led to the development of the model whereby instead of an FSU the critical structures were defined as a set of subvolumes as incorporated in the Relative Seriality model. One can not accurately define a dose bin and associated subvolume as an FSU, as this requires considerable knowledge of each organs structure. So the critical element model (Niemierko et al) was developed further allowing for an NTCP to be calculated from a DVH (see below).

Due to the characteristic variability which exists in patient treatments, dose-distributions will be different also. To allow a comparison between patients in a population and their subsequent dose-distributions, the concept of a biologically effective uniform dose BEUD is used. It is the dose that causes exactly the same tumour or Normal tissue complication probability in the lung as the original dose-distribution. [31]
\[ BEUD = \frac{e^\gamma - \ln(-\ln(P(D)))}{e^\gamma - \ln(\ln 2)} \]

### 2.2.2 Theoretical NTCP Models

#### [A] The LKB model

The sigmoidal dose-response relationship obtained by empirical methods can be described by theoretical models which can estimate NTCP values for partial volume irradiation of an organ from a non-uniform dose distribution. The Probit and Logit models (Eq. 12 & Eq 13) are such models.

Lyman (1985) created a model based on a power law relationship between the tolerance doses for uniform whole or partial organ irradiation. Using the normal probability function or probit analysis, the NTCP is given as a function of the absorbed dose \(D\) in a partial organ volume \(V\) described by an error function:

\[
NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t(D)} e^{-\frac{x^2}{2}} dx
\]

where

\[
t(D) = \frac{1}{m} \left( \frac{D}{D_{50}(v)} - 1 \right)
\]

The upper part of the integral \(t\) is depends on the slope parameter \(m\), which is inversely related to the steepness of the dose response curve, and the \(D_{50}\) value which is the dose that leads to a 50% complication probability of a specific end-point (radiation pneumonitis for the lung). The main assumption of the Lyman model is that \(D_{50}\) is normally distributed among the population.

The volume dependence of the tissue tolerance for the partial volume irradiation is related to the reference volume \((V_{ref})\) using a simple power law relationship (eq.32) where the parameter \(n\) (the volume exponent) describes the volume dependence of the tolerance dose. The parameter \(n\) takes values between zero and 1. A value \(n \to 1\) is characteristic of a large volume effect, and a value \(n \to 0\) is characteristic of a small volume effect. An example of a value of \(n\) for the lung is \(\approx 0.87\) (Burman et al.1991) due to its 'parallel' structural organization and its pronounced volume effect.

\[
D_{50}(v) = D_{50}(V_{ref}) \left( \frac{V_{ref}}{v} \right)^n
\]

The initial model by Lyman (1985) applies to subvolumes receiving a uniform dose. This is rare in radiotherapy treatments, and so the model was extended to inhomogeneous irradiation using DVH reduction.

#### DVH reduction methods

Dose-volume histograms provide the dose distribution information of a non-uniform dose-delivery to a target volume. A multi-step DVH can be replaced by a single-step DVH with a uniform dose distribution. The DVH is reduced to a single value in dose-volume space and from this an NTCP can be calculated.
The inhomogeneous dose distribution is transformed into an equivalent uniform dose (EUD) of the whole organ with an isoeffective dose that causes the same complication probability as the original DVH. The same NTCP induced by the inhomogeneous dose-distribution is caused by an equivalent uniform dose distribution EUD. The upper part of the integral (eq.31) is a function of this Equivalent Uniform Dose. The concept of an EUD is useful when comparing dose response models and associated radiotherapy treatments. It is used in the same way as the aforementioned BEUD.

One of the main DVH reduction techniques applied in dose response modeling is a method by (Kutcher and Burman, 1989) known as the effective-volume method. The main idea behind this technique is that each subvolume irradiated follows the dose-response relationship of the whole organ irradiated, as described by the Lyman model.

Using a power-law relationship, all dose-volume pairs \((D_i,V_i)\) in a DVH are converted to a dose volume pair at a fixed reference dose e.g. the dose \(D_{\text{max}}\). So the original DVH is converted into a DVH with one dose bin at \(D_{\text{max}}\) with an effective volume \(V_{\text{eff}}\) (Kwa et al. 1998). This results in an effect that sees the organ being irradiated by a single dose.

\[
V_{\text{eff}} = \sum_i V_i \left( \frac{D_i}{D_{\text{max}}} \right)^\frac{1}{n}
\]

Using the power-law the dose-volume pair \((D_{\text{max}},V_{\text{eff}})\) can be used with the dose-volume pair \((\text{EUD},V_{\text{tot}})\) to obtain the EUD that irradiates the whole organ:

\[
\text{EUD}_{LKB} = \left[ \sum_i D_i \left( \frac{V_i}{V_{\text{tot}}} \right)^\frac{1}{n} \right]^n
\]

The reduction technique devised by (Kutcher and Burman 1989) combined together with the model by (Lyman 1985) gives rise to the LKB model, a model that is used to predict the Normal Tissue Complication Probability of an organ being irradiated. The EUD value Eq. (34) is used in Eq. (31) where the upper integral value \(t\) becomes:

\[
t(EUD) = \frac{1}{m} \left( \frac{\text{EUD}_{LKB}}{D_{50}(v)} - 1 \right)
\]

[B] The Parallel/Critical element model

In the critical element model an organ is modeled based on the assumptions that, it is made up of a number of structural elements, FSU’s, each of which responds independently. If one or more of these critical elements is damaged then a complication occurs.

An organ is modeled as consisting of \(N\) FSU’s and the probability of damage to a single FSU is equal to \(p\). This probability is a function of the dose \(D_i\) delivered to FSU.

FSU’s are considered small enough to neglect inhomogeneity of the dose distribution within them. The dose distribution to the whole organ is represented by the set of
$D_i$, which is presented as $\{D_i\}$. The probability of an FSU escaping damage is $1-p(D_i)$ and the complication probability for the whole organ is given by:

$$P(N,\{D_i\}) = 1 - \prod_{i=1}^{N}[1 - p(D_i)]$$ \[36\]

This equation accounts for an inhomogeneous dose-distribution and gives the relationship between the complication probability and the irradiated volume.

According to (Niemierko & Goeitein, 1991) earlier work by Schulthereis showed that for an inhomogeneous dose distribution defined by a number of $M$ subvolumes of volume $v_r$, within each of which the dose is considered uniform and equal to $D_r$, the complication probability can be described by:

$$P(\{v_r\},\{D_r\}) = 1 - \prod_{r=1}^{M}[1 - P(1,D)]$$ \[37\]

The subvolumes $\{v_r\}$ with corresponding doses $\{D_r\}$ can be extracted from a differential DVH where each bin of the DVH is a subvolume. It should be noted that each bin is a subvolume/voxel (volume element), not an FSU. So from the critical element model one can calculate an NTCP from a DVH.

Usually we are interested in partial volume irradiation, where a homogeneous dose-distribution is delivered to part of an organ. This is the idea behind the aforementioned concept of an Equivalent Uniform Dose EUD. For this case the above equation becomes where $\nu$ is a fraction of the reference volume (i.e. the volume of the whole organ being irradiated):

$$P(\nu,D) = 1 - [1 - P(1,D)]^\nu = P(\nu,EUD) = 1 - [1 - P(1,EUD)]^\nu$$ \[38\]

The critical element model does not provide any information as regards to the dose-response characteristics of an FSU or the whole organ $P(1,D)$ so it must be developed further by looking at the available information on dose-response relationships.

The parallel model or critical element model is developed, based on the sigmoidal dose-response relationship observed from empirical data, and $P(1,D)$ can be represented by a logistic-function such as that shown by Eq. 13 and Eq. 38.

$$P(D) = \left[1 + \left(\frac{D_{50}}{D}\right)^k\right]^{-1}$$ \[39\]

$P(D)$ is the probability that the dose $D$ inactivates an FSU during irradiation. $k$ is a parameter which describes the slope of a dose-response curve and the rate at which FSU damage occurs. The parameter $k = 4\gamma$ and in relation to the slope parameter $m$ mentioned above, $k \approx 1.6/m$. The above sigmoid dose-response function describes the probability of damaging a subunit at a given biologically equivalent dose.

Prior to reducing the DVH to a EUD, the concept of FSU’s and damage to FSU’s needs to be generalised, due to the difficulties met when trying to identify the true nature of an FSU and its structural organisation (see section 1.1.7). For this reason an ‘effect’ is defined instead of FSU kill. If a local dose-effect relation $E(D)$ is known, the average radiation effect on the whole organ is given by:
The average radiation effect $E_{av,\text{hom}}$ can be calculated easily for a homogeneous dose distribution across the whole organ, since there is one dose bin and one volume $V_{\text{tot}}$. So $E_{av,\text{hom}}=E(D)$. This single homogeneous dose can be replaced by the EUD obtained from DVH reduction of the original DVH which gave the average radiation effect $E_{av}$:

$$E_{av} \equiv E(EUD_{\text{parallel}})$$

The dose-effect relation $E(D)$ in Eq. 40, can be described by the logistic function Eq. 39, and consequently we can obtain an expression for the EUD$_{\text{parallel}}$:

$$EUD_{\text{parallel}} = D_{50}\left(\sum_i \frac{1}{1+(D_{50}/D_i)^k \frac{V_i}{V_{\text{tot}}}}\right)^{-1/ k}$$

Where $n = 1/k$.

The NTCP is given as a function of the absorbed dose $D$ in a partial organ volume $V$ described by the error function Eq. 31, where the upper part of the integral $t(D)$ now becomes, $t(EUD_{\text{parallel}})$. When $D_{50} \to \infty$ and $n = 1/k = 1$, then the EUD$_{\text{LKB}}$=$EUD_{\text{parallel}}$. \[1\]

2.3 Statistical Analysis

DVH data for each patient in the patient sample investigated was used to calculate the associated NTCP values, by applying the aforementioned models of dose-response, for each of the parameters shown in table 3.

Statistical analysis was used to explore the existing relationships that exist between the NTCP values, predicted by each model, and the clinical outcome score of Radiation Pneumonitis. The inclusion of extra associated predictor variables such as equivalent uniform dose (EUD), total dose, and Lung Volume, where also incorporated into the analysis to examine the extent of their effect on the clinical outcome. In addition to these, the dosimetric factors analysed included $V_{13}$, $V_{20}$, and $V_{30}$ for the percentage of lung volumes receiving $\geq 13\text{Gy}$, $\geq 20\text{Gy}$, and $\geq 30\text{Gy}$ respectively.

Analysis of the predictive power of the NTCP models was performed by applying statistical methods of correlation, regression, logistic regression, ANOVA (Analysis of Variance) and $\chi^2$ tests; each is briefly explained below. The analysis was performed using the software package SPSS 13.0 for Windows. A $p \leq 0.05$ was considered to be statistically significant. The analysis was applied for the whole lung and the single lung case.

Four important steps are performed to achieve the goal of statistical analysis:

1) Generate a hypothesis : [The higher an NTCP value = The higher clinical score]
2) Collect clinical data: [Dose-Volume Histograms]
3) Fit a statistical model to the data: [This will test predictions]
4) Assess statistical model: [Does it support the initial predictions]
We calculate the probability that the results obtained occurred by chance. As this decreases we are more confident that the experimental hypothesis is true. A probability value of $p \leq 0.05$ is taken as being statistically meaningful.

For each statistical method discussed below, a test statistic is calculated to evaluate the model:

\[
Test \ statistic = \frac{Variance \ explained \ by \ the \ model}{Variance \ not \ explained \ by \ the \ model}
\]

The higher the value of our test statistic the more confident we are that the model explains a sufficient amount of variation to explain what is truly occurring in the sample population. The direction of our test statistic can be positive or negative.

Finally, in our investigation we have a directional hypothesis i.e. the higher the value of the NTCP the higher the value of the clinical outcome/score of Radiation Pneumonitis. Our test becomes a one-tailed test in this situation.

**Statistical Methods-A brief explanation**

Although the statistical analysis was performed primarily using SPSS we felt it was important to present here, some of the underlying concepts of each statistical method employed.

**[A] Correlation**

The two important variables in this investigation are the Normal Tissue Complication Probability (NTCP) and the clinical outcome or score associated with each patient. Primarily we are interested to see what relationship exists between the two, if any does exist, and the strength of this relationship. A correlation is a measure of the linear relationship between variables. The variables can be related, positively, so a higher NTCP would result in a higher score, negatively where a higher NTCP results in a lower score, or not related at all.

A simple way to look at the association between two variables is to look at how they covary. First we look at the variance i.e. the average amount that the data vary from the mean. If one variable deviates from its mean, we want to see the other deviating from its mean in a similar way. \(^{[28]}\) So if an NTCP score is below its mean then we expect its associated clinical score to also be below the mean. To obtain the total difference observed for both variables we multiply each of their differences together so if both values are positive or negative we have a positive value indicating that they vary in the same direction. If one is positive above the mean and one is negative below the mean we have a negative value indicating that they are varying in opposite direction. The average sum of combined differences is known as covariance and it is a good way of assessing whether two variables are related. \(^{[28]}\)

One of the problems with using covariance is that it is dependant on the scales of measurement used, so it is not a standardized measure. A unit of measurement is needed into which any scale of measurement can be converted. The unit of measurement used is the standard deviation. The Standard deviation of a value is a measure of the average deviation from the mean. So if we divide any distance from the mean by the standard deviation we get the distance in standard deviation units. So for each case we divide the observed deviation by the standard deviation. To express the covariance in standard units of measurement we therefore divide by the standard deviation.
The standardized covariance is known as the *Pearson’s correlation coefficient* and takes a value between -1 and +1. A coefficient +1 is indicative of two perfectly correlated variables, a coefficient -1 is indicative of a perfect negative relationship, and 0 indicates that if one variable changes the other stays the same. The correlation coefficient is also used to measure the size of an effect, i.e. ±.1 is a small effect, ±.3 is a medium effect, and ±.5 a large effect.

It is important to note that the correlation coefficient gives no indication of the direction of *causality*. This means that correlation coefficients say nothing about which variable causes the other to change, they just indicate an existing relationship, if any.

One important use of the correlation coefficient is that it can be squared to give the coefficient of determination $R^2$. This is a measure of the amount of variability in one variable that is explained by the other. So if two variables were correlated e.g. $r=0.543$ then $R^2= 0.295$. This value of $R^2$ multiplied by 100 to give a percentage tells us how much variability in one variable is explained by the other and that one of the hypothetical variables accounts for, 29.5% of the variability, in the other.

A requirement for applying Pearson’s correlation coefficient is that the data is measured at the *interval* level. This requirement means that values are measured on a scale along the whole of which intervals are equal. This requirement is not met by all our data, because although NTCP values are interval data, the clinical outcome is measured on a scale of 0-4 and is measured at the *ordinal* level. However the concept of Pearson’s correlation coefficient can be incorporated to calculate Spearman’s correlation coefficient $r_s$, which is a non-parametric statistic. Spearman’s test works by first ranking the data and then applying Pearson’s equation to those ranks.

In the case of the clinical scores used in this investigation, we have data that are not interval, because each score on the LENT/SOMA scale encompasses a different range of severities. If data is measured at the ordinal level it is said to be non-parametric, and therefore Pearson’s correlation cannot be used, and Spearman’s correlation coefficient is used. To account for this the patient data was split into subgroups of ascending dose. Each patient and their associated scoring grade of pneumonitis belonged to one of the 9 subgroups.

Kendall’s tau is another non-parametric correlation and is used instead of Spearman’s correlation when there are many scores in a small data set that have the same rank. It is considered to be a statistic that provides a better estimate of the correlation in the population. In this investigation both are obtained for the data sets.

*Biseral and Point Biseral correlations*

Biseral and Point Biseral correlations are correlation coefficients that are used when one of the two variables explored, is dichotomous (i.e. categorical with only two categories). In this investigation the dichotomous variable, is having Radiation Pneumonitis, or not having Radiation Pneumonitis.

The difference between the use of the Biseral and Point Biseral correlations is dependant on whether the dichotomous variable is discrete or continuous. A discrete dichotomy is when there is no underlying continuum between the categories. So a patient has radiation pneumonitis or does not have radiation pneumonitis. A
continuous dichotomy is one for which a continuum does exist. So a patient can have lower severity of radiation induced side-effects, that do not amount to causing radiation pneumonitis, or they can have radiation pneumonitis but to different levels of severity. In this analysis we look at both measurements of correlation; patients with scores of 0, 1 and 2, are considered to not have radiation pneumonitis, and patients with a score of 3, or 4 are considered to have radiation pneumonitis.

[B] Regression \[28\]

Using the aforementioned method of correlation we can look at the relationship between two variables. In regression analysis we look at predicting one variable from the other. We attempt to predict an outcome from one or two predictor variables. So for this investigation we look to predict the outcome score from the main predictor variable, NTCP, and other associated variables such as EUD and irradiated volume of the lung.

In regression analysis a predictive model is fitted to the data and it is used to predict values of the dependent variable from one or more independent variables. In multiple regression analysis this idea is extended to include more predictor variables.

Any data can be predicted using the following general expression:

$$ (44) \quad \text{Outcome}_i = (\text{Model}_i) + \text{error}_i $$

In regression the model fitted is a linear model. The method of least squares is used to determine which line is the best fit to the data. The equation of the line that best fits the data is developed from the simple expression above and becomes:

$$ (45) \quad Y_i = (b_0 + b_1X_i) + \varepsilon_i $$

Where $Y_i$ is the outcome that we want to predict, $X_i$ is the $i$th patients value on the predictor variable, $b_1$ is the gradient of the straight line and $b_0$ is the intercept. The residual term $\varepsilon_i$ is the difference in the score predicted by the regression line and the actual score of the $i$th patient. We can obtain the gradient and intercept of the line and if this line is a good representative of the data we can input different values of a predictor variable to estimate an associate outcome. The value of $b_1$ (gradient) represents the change in the outcome that results from a unit change in the predictor. We want this value to be significantly different than zero, for our predictor variable to be considered important in predicting the outcome. SPSS calculates this value in the output and we can assess the model as required. The general expression (34) can be envisaged for this investigation, as follows:

$$ (46) \quad \text{Clinical Outcome} = (b_0 + b_1NTCP_i) + \varepsilon_i $$

Once a regression line is obtained and considered to be the 'line of best fit' an assessment is made about the goodness-of-fit of the model. This is important because we may have a line of best fit but in reality its fit to the data may not be very good. To do this the line of best fit is compared against the most basic model available, which is usually the mean. We calculate the fit of our model and that of the most basic one and look at how much difference exists between them (47). If there is a marked difference we can be confident that our model is a better one than the most basic.

$$ (47) \quad \text{deviation} = \sum (\text{observed} - \text{model})^2 $$

The sums of squares is calculated for both the basic model (the mean), this is known as the total sum of squares (SS$_T$), and the line of best fit (the regression line) which
is known as the residual sum of squares (SS$_R$). Once these are calculated, the model sums of squares are calculated (SS$_M$) from the difference between (SS$_T$) and (SS$_R$). This provides us with a value for the improvement in prediction that results from using the regression model instead of the mean. (FIELD)

The proportion of improvement due to the model ($R^2$) is obtained by dividing the sum of squares for the model (SS$_M$) by the total sum of squares (SS$_T$):

$$R^2 = \frac{SS_M}{SS_T}$$

This value of $R^2$ is the same as that seen in correlation and can be interpreted in the same way so by squaring this value a correlation coefficient can be obtained.

The sums of squares can also be used to assess the model using the F-test, which produces an F-ratio. This ratio is of the improvement due to the model, and is a ratio of the sum of squares of the model (SS$_M$), and the difference between the model and the observed data (SS$_R$). The mean sums of squares (MS) is taken for each and their ratio is a measure of how much the model has improved the prediction of the outcome compared to the level of inaccuracy of the model:

$$F = \frac{MS_M}{MS_R}$$

A good model should have a large F-ratio with a good significance value, so that a marked improvement can be observed due to the mode. This value is produced by the SPSS output for our data. The output reports an analysis of variance (ANOVA) which tells us whether the model results in a significantly good degree of prediction of the outcome variable. Finally an output from SPSS gives us the information as regards to the coefficients of the regression line which will tell us about the change in outcome as a result of a unit change in the predictor (See results section).

**Multiple Regression**

The methods of regression analysis can be extended to incorporate a number of predictors, not just a single predictor, and this is the logic behind multiple regression. Our expression for the equation of a line becomes:

$$Y_i = (b_0 + b_1X_1+b_2X_2+.....+b_nX_n) + \epsilon_i$$

In the case of multiple regression each predictor has an associated coefficient and the outcome is a combination of all predictors and their coefficients. A linear combination of predictors that correlate maximally with the outcome variable is what we want to find.

In order to be able to draw a conclusion about a population based on a sample analysis on which regression is performed one of the assumptions that must be true is that predictor variables must be quantitative (measured at the interval level) or categorical, and the outcome variable must be quantitative, continuous or unbounded. Our NTCP values are quantitative. It can be said that the clinical outcome scoring criteria is not measured at an interval level because of the differences in severity that each score encompasses. However for the purposes of part of this regression analysis, we have taken the outcome as being a measure ranging from 0 – 4. A more analytical explanation of assumptions on statistical data can be found in (Field.*Discovering Statistics using SPSS,*).
Using multiple regression we look at the effect of other predictor variables along with NTCP on predicting the outcome. Furthermore we look at incorporating categorical predictors in the regression model through the process of “dummy coding” \[28\], whereby the patient sample set is split into 9 groups of ascending dose (BEUD or EUD) and each outcome is related to a specific group, in order to observe any relationships between the equivalent dose which results in the NTCP value which we are using to predict a clinical outcome.

In the latter stages of analysis, logistic regression (see next section) has been applied where the outcome variable is considered as a dichotomous variable, whereby patients with a score of 2 or below are considered to not have radiation pneumonitis and patients of 3 or above are considered to have radiation pneumonitis. For the nature of the data that we have sampled in this investigation the method of Logistic Regression becomes a more accurate tool of analysis.

[C] Logistic Regression\[28\]

Logistic regression is a method that is very similar to multiple regression, with the difference that in Logistic regression the outcome variable being predicted is a categorical dichotomy and the predictor variables are continuous or categorical. So given some information we can predict which category a person belongs to. Once again with reference to our investigation we are looking to see if the variable NTCP is a good predictor of the clinical outcome or in this case the inception of radiation pneumonitis. So our continuous variable is NTCP and our dichotomous outcome variable is, either the patient has radiation pneumonitis or not.

With the general expression (44) in mind, in logistic regression instead of predicting the value of a variable \(Y\) from a predictor \(X\) or several predictors, we predict the probability of \(Y\) occurring given known values of \(X\).

\[
P(Y) = \frac{1}{1 + e^{-(b_0 + b_1X_1 + \cdots + b_kX_k)}}
\]

If we have more than one predictor variable the equation in the brackets becomes analogous to equation (50) above.

In linear regression an assumption made is that there is a linear relationship between variables. This is not possible with a dichotomous outcome variable so the form of the non linear relationship is transformed to a linear one using the above expression, whilst the relationship remains non-linear.

The logistic model predicts the probability of an event occurring for a given person \(P(Y_i)\) based on observations of whether or not the event did occur for that person, i.e. the actual outcome. So for each person in a sample \(Y\) will be 0 or 1 depending on whether the outcome did or didn’t occur, and the predicted value \(P(Y_i)\) will be between 0, no chance that the outcome will occur, and 1, the outcome will occur. Each predictor variable will have a coefficient associated with it. These coefficients need to be estimated by fitting models, based on available predictors, to the observed data. The chosen model is the one that when values are placed in it results in values for \(Y\) closest to the observed results. The estimations are done by a method called maximum-likelihood analysis. \[28\]

To assess the model like all statistical methods a test statistic is required. The observed and predicted values of the outcome are compared. This is done using a method called the log-likelihood, abbreviated as (LL). It is similar to the \(R^2\) value discussed in the aforementioned correlation and regression methods. This method is based on summing the probabilities associated with the predicted and actual
It tells us how much unexplained information there is after the model has been fitted, so large values of this test statistic indicate a poor fitting of the model to the data, and a large amount of unexplained observations.

The log-likelihoods of different models can be used to compare the models. Initially we compare the logistic regression model to a base model, like with the previous methods. This way we can assess the improvement of incorporating the variables in the model to predict the outcome. We cannot use the mean scores as a baseline model because we have a dichotomous variable with just 1’s and 0’s so we look at the frequencies of these 1’s and 0’s. In Logistic regression the baseline model is the model that gives us the best prediction when we don’t know anything other than the outcome values. This is achieved when only a constant is included. If we want to look at the improvement of the model due the added variables we use the following expression:

\[
\chi^2 = 2[LL(\text{New}) - LL(\text{Baseline})]
\]

The new model is taken and from it the baseline model is subtracted. The \( \chi^2 \) distribution has associated significance values which can be obtained to assess the improvement. The degrees of freedom for the chi-squared distribution are given by the number of parameters in the new model minus the number of parameters in the baseline model. The baseline model has only one parameter, the constant, whereas any new model has a number of parameters equal to the number of variables plus the constant.

To assess the individual contribution of each predictor in the model we look at the regression coefficients \( (b_1, b_2, b_3, \ldots, b_i) \). A statistic known as the Wald statistic is used to tell us whether the \( b \) coefficient for the predictor is significantly different from zero. This is produced by the SPSS output during analysis.

Finally, an important observation to record from the SPSS output is the value of \( \exp b \). This value indicates the change in odds resulting from a unit change in the predictor. It is the proportionate change in odds, where the odds are given by calculating the probability of an event occurring divided by the probability of that event not occurring. A value above 1 means that as the predictor increases the odds of the outcome increase.

An ideal situation in Logistic Regression is to have a dichotomous variable, a categorical predictor and a continuous predictor. For our investigation this can be applied to our data. We have an outcome of radiation pneumonitis that is dichotomous i.e. a patient has it or has not got it, we have a continuous predictor, in the NTCP values, and we have a categorical predictor which categorizes which patients received over 20Gy to over 25% of their lung volume, and which didn’t. We chose to investigate the dosimetric quantity \( V_{20} \) for this statistical method.

For analysis patients with a score of 0-2 are considered to not have radiation pneumonitis, and patients with 3 or above are considered to have radiation pneumonitis.

All the aforementioned test statistics and values are given in the SPSS output that following analysis. Examples are shown in the results section of this report.

[D] \( \chi^2 \) (Chi-squared test)

Another statistical tool used for analysis is the chi-squared test, which is a statistical test that allows for a relationship between two categorical variables to be assessed. Categorical data is data that does not have a continuum. In this investigation we
have a scoring grade to assess the severity of irradiation effects and consequently radiation pneumonitis. This scale is from 0-4 and can be developed such as to produce a resulting dichotomous variable. In our analysis we have performed tests where patients with a score of 0-2 are considered to not have radiation pneumonitis, and patients with 3 or above are considered to have radiation pneumonitis. Thus we have two categories in which patients can fall, (i) has radiation pneumonitis (ii) does not have radiation pneumonitis.

What we also know from our data is values for $V_{13}$, $V_{20}$, and $V_{30}$ for the percentage of lung volumes receiving $\geq 13\text{Gy}$, $\geq 20\text{Gy}$, and $\geq 30\text{Gy}$ respectively. These values can be used to split the patients into two categories. One example is having two groups, one that has $V_{20}$ values below 25% and one that has $V_{20}$ above 25%.

We can use the above mentioned categorical variables to see if there is a relationship between the induction of radiation pneumonitis and the $V_{20}$, $V_{13}$, and $V_{30}$ factors.

To look at the relationship between two categorical variables we analyze the frequencies, i.e. the number of cases that fall into each category. The chi-square statistic is a test statistic based on comparing the frequencies observed in certain categories, to frequencies you might expect to get in those categories by chance. The Pearson’s chi-square ($\chi^2$) is given by:

$$\chi^2 = \sum \frac{(\text{Observed}_{ij} - \text{Model}_{ij})^2}{\text{Model}_{ij}}$$

The data analysed is usually found in a contingency table as shown below:

<table>
<thead>
<tr>
<th>&gt;30% volume received 13Gy</th>
<th>RP</th>
<th>no RP</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>10</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>&lt;30% volume received 13Gy</td>
<td>12</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>28</strong></td>
<td><strong>18</strong></td>
<td><strong>46</strong></td>
</tr>
</tbody>
</table>

The observed data are the frequencies in the table, and to calculate the model data we calculate the expected values for each of the cells in the table using column and row totals:

$$\text{Model}_{ij} = E_{ij} = \frac{\text{RowTotal}_i \times \text{ColumnTotal}_j}{n}$$

Where $n$ is the number of observations, in our case 46. Once this is done we enter the value for each of the cells in the table into Eq. (53) and calculate the $\chi^2$ value for each. We then sum the values to obtain a value for the $\chi^2$ statistic. To obtain the significance value it is important to know the degrees of freedom which are calculated as $(r-1)(c-1)$, where $r$ is the number of rows, and $c$ the number of columns.

This information is calculated by SPSS and the statistic and its significance value are shown in the output. A likelihood ratio is also produced which is a statistic based on the maximum likelihood theory. [28] This is very similar to Pearson’s chi-square statistic, and is considered better when samples are small, such as the sample used in our investigation.

The SPSS output also produces a selection of other measures of strengths to assess the variables, and these are shown in the results section of the report. An important consideration for us is to ensure that the assumptions of the $\chi^2$ test are met. The two that are important, are (i) that each person contributes to only one cell of the
contingency table i.e. we can’t perform a repeated measures design,\(^{(28)}\)(ii) The expected frequencies should be greater than 5.

Also an important point raised in (Field. Discovering Statistics using SPSS,\(^{(2)}\)) is that small differences in cell frequencies can result in statistically significant associations between variables. This makes it important to look at row and column percentages to interpret effects that we get, because percentages will not depend on sample size like frequencies do.

χ\(^2\) analysis was performed as discussed by comparing the outcome, radiation pneumonitis or not, with the dosimetric quantities \(V_{13}\), \(V_{20}\), and \(V_{30}\). A measure of the effect size in each case was made by calculating the odds ratio, a ratio that is a ratio of the probabilities of an event occurring and an event not occurring. Although these factors are not incorporated into dose-response modelling they could prove to be useful predictors, and hence it may become possible to integrate them in dose-response modelling.

**[E] ANOVA**

One of our strategies for analysis is to split the patient sample into a set of subgroups of ascending dose and to then to statistically analyse the relationship between these subgroups and clinical score of radiation pneumonitis. Each of these subgroups can be considered as an independent variable, and a technique called Analysis of Variance (ANOVA) is applied to show how these independent variables interact with each other and what effects these interactions have on the dependent variable (the clinical outcome).

ANOVA tests the hypothesis that all group means are equal, something that we do not want to observe in our data. It works like a t-test but we cannot perform multiple t-tests due to the effect of errors that will arise. The ANOVA technique produces the F-ratio mentioned above which compares the amount of variance due to the model we have fitted with the amount of variance due to effects we are not interested in and that cannot be explained by our model.

The process of ANOVA is conceptually the same as that of regression and the difference lies in the type of relationship being explored. Historically states that "Researchers interested in controlled experiments adopted ANOVA whereas those looking for real-world relationships adopted multiple regression.”\(^{(28)}\)

To ensure our analysis met with the assumptions of ANOVA we had to ensure that homogeneity of variance exists between our subgroups. This is tested by a test statistic called the Levene statistic. Because our analysis was performed on 9 groups, 8 of the same size and 1 slightly larger there was not homogeneity of variance (a feature that occurs in many samples), but there is another statistic called Welch’s F, that accounts for this, giving a more realistic value of the F-ratio when the homogeneity of variance assumption is not met.

The F-ratio obtained from ANOVA will tell us whether the model fitted to the data accounts for any significant variation, but it will not tell us where the differences between groups lie.\(^{(28)}\) If an F-ratio is large enough and statistically significant it means that one or more of the differences between the means is significant.

In order to perform ANOVA we had to use our dummy coding which has been previously mentioned, and also use the idea of planned contrasts and associated weights \(^{(28)}\) which basically means that we tell SPSS which relationships to analyse between which group means, in an attempt to gain an overall insight into the overall relationship between the independent variables (the dose groups) and the dependant
variable (the clinical outcome score). Planned contrasts are used when you there is a specific hypothesis that you want to test, it is used as an analysis method for one-tailed tests. Contrasts are used to determine which groups differ and they work like t-tests work in regression analysis. (A more analytical explanation is given in Field. Discovering Statistics using SPSS.)

Using ANOVA we aimed to test whether an increase in BEUD or EUD and associated NTCP led to an increase in clinical outcome score.

2.4 Software development for NTCP calculations

An important part of this investigation was the development of a software tool, to perform calculations of NTCPs from associated patient DVHs for each of the dose-response models investigated. This was done in an attempt to provide an important tool for optimization of radiotherapy treatment planning.

The creation of the programme was primarily performed using Microsoft Visual Basic 6.0, and associated parts were constructed using Microsoft Office Excel. A schematic of the components is shown below in figure 2.2:

**Fig 2.2**

The patient therapy details form and the Patient NTCP Archive were created in Microsoft Excel. The concept of the development, stems from the idea that one can incorporate such a software tool in treatment planning, whereby patient data (from the Patient Therapy Details Form) extracted from a database can be loaded into the NTCP Calculation Pod© and NTCP calculations can be performed for each patient by the dose-response model selected. Results can then be stored in the Patient NTCP Archive and Medical Physicists along with Doctors and Oncologists can view the data and decide whether the treatment planning allows for maximum TCP and minimum NTCP.

The Visual Basic environment for the software creation is shown below. Figure 2.3 shows the environment for creating the form, and Figure 2.4 displays an example of the code. All associated code can be viewed in the Appendix A2.
Fig. 2.3

Fig. 2.4
3. RESULTS

Of the 46 patients used in this investigation 28 patients (61%) developed Radiation Pneumonitis (RP) grade 2 (mild/no RP) or above. 18 patients (39%) scored 1 (very mild/no RP) and below. In our statistical analysis when treating the Radiation Pneumonitis as a dichotomous variable, we stated that patients with a score of 2 or above had RP and patients below 2 had no RP, however we also analysed the patients by specifying that patients with a score of 3 or above had RP and patients below 3 had no RP, so two scenarios were investigated. Taking into consideration the latter scenario, 13 patients (28%) developed RP grade 3 (RP) or above. 33 patients (72%) developed RP grade 2 (mild/no RP) or below.

For each dose-response model, and associated parameter, NTCPs were calculated for each patient, and the values were plotted against BEUD, and EUD, where required to allow for comparison between patients. Furthermore these results were plotted together with the theoretical curve produced by arbitrary dose values for each model, to allow for an assessment to be made of the modelling. This procedure was performed for both the single lung case (fig.3.1) and treating the lungs as a single organ (fig.3.2) (Paired lungs).

Fig. 3.1 the plots portray the patient group for each model, and associated parameter sets from table 3, for the single lung case. Every symbol represents a patient who has been treated for lung cancer. Patients that developed radiation pneumonitis score 3 or above are represented with crosses and patients that scored lower than 3 with circles. The theoretical NTCP curve for each model is shown by the black curve.
Dose-Response Curve of a single lung - ptv:
Relative Seriality model (Gagliardi et al)

Dose-Response curve of a single lung - ptv:
Relative Seriality Model (Mah et al)

Dose-Response Curve of a single lung - ptv:
LKB-model (Seppenwoolde et al)
Dose-Response Curve of a single lung - ptv:
LKB-model (Burman et al)

Dose-Response Curve of a single lung - ptv:
Parallel-model (Seppenwoolde et al)
Fig. 3.2 the plots portray the patient group for each model, and associated parameter sets from table 3, for the paired lungs case. Every symbol represents a patient who has been treated for lung cancer. Patients that developed radiation pneumonitis score 3 or above are represented with crosses and patients that scored lower than 3 with circles. The theoretical NTCP curve for each model is shown by the black curve.
Dose-Response curve of the lungs considered as a single organ:
Relative Seriality Model (Mah et al)

Dose-Response Curve of the lungs considered as a single organ:
LKB-model (Burman et al)

Dose-Response Curve of the lungs considered as a single organ:
LKB-model (Seepenwoolde et al)
An initial look at the dose-response curves for both the single lung case and the paired lung case reveals that most calculated patient responses are clustered in the low regions of NTCP. Patients with grade 3 pneumonitis or higher are also found to have low predicted NTCP values placing them in the lower regions of the dose response curve.

In terms of the steepness of the curve, and the normalized dose-response gradient $\gamma$, this is highest for the parameter set Mah et al (1991) and its equivalent for the LKB model $m$ which is the reciprocal value of the gradient is lowest for Burman et al (1987) parameters. These parameters are indicators of the absolute change in response probability following a relative change in the dose.

Models using these parameter sets will therefore have a higher range of response probabilities over a range of dose, compared to parameter sets with lower $\gamma$ and higher $m$ values. For parameter sets Gagliardi et al (2000) and Seppenwoolde et al (2003) the steepness parameters are almost half the size in magnitude compared to the Mah et al (1991) parameter set and the Burman et al (1987) parameter set. This leads to shallower dose response curves with a smaller change in response for every unit change in dose. It should be noted that $\gamma$ is evaluated just above the 37% response point.

Looking at the distribution of the patients on the theoretical dose-response curve we can see that for models using the parameter sets with steeper dose-response gradients the patients are spread across a wider range of response probabilities. These parameter sets give rise to more sensitive response to changes in BEUD and EUD.

When NTCPs were calculated for the lungs as a paired organ the values were lower than those for the single lung case, indicating a potential underestimation of response. More patients were clustered around the low NTCP regions up to .3, and only for the Parallel model was there a greater spread of response values.

A mean cumulative or differential dose volume histogram (DDVH) was calculated for the patient group analysed (fig 3.3). It should be appreciated that lung volumes differ substantially between patients, and no two patient lung volumes are the same. This could give rise to a more pronounced volume effect in some patients than others something we discuss in the next section of the investigation.
**Fig. 3.3** A Mean Dose Volume Histogram (DVH) which depicts the percentage dose that is received for the mean lung volume calculated from all patients in the patient sample.

It is evident that the lower percentages of dose are delivered to the larger percentage of the lung volume, and that only small volumes of the lung receive the maximum percentage dose or more. For most patients the total dose was typically 60 Gy, so up to about 30% of the dose 18 Gy was delivered to a significantly large portion of the lung. In our analysis we investigate the aforementioned dosimetric quantities $V_{13}$, $V_{20}$, and $V_{30}$. Figure 3.4 shows bar charts of these dosimetric quantities for each patient, arranged in ascending order and indicates which of these was diagnosed with RP grade $\geq 3$.

**Fig. 3.4** Bar charts depicting the $V_{13}$, $V_{20}$, and $V_{30}$ dosimetric quantities for each patient in our data set. The bars shaded with patterns represent those patients that developed RP grade $\geq 3$. 
A preliminary look at the data indicates no clear relationship between the percentage of volume receiving a certain specific dose and the resulting clinical outcome of radiation pneumonitis, with some diagnosed patients having low $V_{13}, V_{20}$, and $V_{30}$ and others high values for these parameters. Using the results subsequent to statistical analysis, we aim to quantify any existing relationship and assess its significance.

**Statistical Analysis**

**CORRELATION**

SPSS Output 1.1 shows an example of the output for a Spearman’s correlation and Kendall’s tau, between the variables NTCP and Clinical Score. In each case a table is displayed that gives the correlation coefficient between the two variables.

For the Single lung case the best Spearman’s correlation coefficient was (-.191) with a significance value (.102), for the Relative Seriality model using the parameter set Mah et al (1987). The significance value here is greater than .05 and closer to .1 significance level, so we can conclude that there is not a significant relationship between the subgroups of patient NTCP values and the Clinical score, because we have selected $p<.05$ as the significance level. If we look at the correlation itself it is
negative so we can conclude from this analysis method that if the NTCP value increases there is not a corresponding increase in clinical score. We can look at the $R^2$ coefficient of determination which tells us that $-.191^2 = .0365$. If this value is converted into a percentage we can say that NTCP accounts for 3.65% variability in the clinical outcome score.

**SPSS Output 1.1**

<table>
<thead>
<tr>
<th>Correlations</th>
<th>NTCP_RS_M_S</th>
<th>Score_RS_M_S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendall's tau_b</td>
<td>1.000</td>
<td>-.148</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>.</td>
<td>1.01</td>
</tr>
<tr>
<td>N</td>
<td>46</td>
<td>46</td>
</tr>
</tbody>
</table>

The best Kendall’s tau correlation coefficient was also true for the Relative Seriality model using parameters by Mah et al (1987). A value (-.149) was found with a significance value (.101). Kendall’s statistic is smaller than Spearman’s and this is usually the case, but the significance value is lower than the equivalent for Spearman’s. However the value is still larger than the 0.05 significance value. As mentioned earlier in this report Kendall’s statistic provides a more accurate picture of what correlation would exist in the population.

For the paired lung case the best Spearman’s and Kendall’s correlation coefficients, were again for the Relative Seriality model with Mah et al (1987) parameters. Spearman’s correlation was (-.209) with a significance value (.081) and Kendall’s tau was (-.170) with a significance value (.073). The significance values are improved from the single lung case, however they are both still above the .05 significance level, and in each case the $R^2$ value is small indicating that a small variability in the outcome score is accounted for by change in NTCP, and that even this small change is likely to occur by chance.

The second part of correlation analysis was performed considering the outcome variable as a dichotomous one, i.e. the patient developed RP or did not develop RP. The analysis was performed on two levels, one where patients with scores of 2 and above, were considered to have RP, and also when patients with scores 3 and above, were considered to have RP. An example of the output is shown in SPSS Output 1.2. The output produces only the point-Biseral correlation coefficient and the Biseral coefficient can be calculated from it.
SPSS Output 1.2

<table>
<thead>
<tr>
<th>Clinical_Score</th>
<th>Pearson Correlation</th>
<th>Sig. (1-tailed)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTCP_PL_LKB_Burn</td>
<td>Pearson Correlation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the first scenario (scores 2 or above = RP) the best point-Biseral correlation for the single lung case was calculated as (.198) with a significance value (.094) for the Relative Seriality model with Mah et al (1987) parameters. The resulting Biseral coefficient was found to be (.2511) which is an improved value which is as a result of considering the dichotomous variable as having an underlying continuum. For the paired lung case the best correlation was extremely low (.043) with a non significant value (.388) for the LKB model with Seppenwoolde et al (2003) parameters.

For the second scenario (scores 3 or above = RP) the best point-Biseral correlation was found to be (.208) with a significance value (.083) and a Biseral correlation (.276), for the LKB model with Burman et al (1991) parameters. This was higher than the p<.05 significance level.

In each case it is obvious that an improved correlation is observed when the dichotomous variable RP is considered to have an underlying continuum.

REGRESSION

Preliminary regression analysis

The first part of the analysis was performed using regression and multiple regression to look at whether we can predict the outcome variable (clinical score) from a number of predictor variables, primarily NTCP, and then other associated variables such as lung volume, and total dose. The first regression analysis was performed looking at the relationship for all scores and NTCP values, we then looked at the relationship of NTCP values related to the high scores (3 and 4) and then we looked at the relationship of NTCP values related to low scores (0, 1 and 2).

The important components/results from a typical output from SPSS following regression analysis is shown below (SPSS output 1.3).

SPSS output 1.3

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
<th>Durbin-Watson</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.558</td>
<td>.128</td>
<td>.100</td>
<td>.722</td>
<td>.128</td>
<td>4.547</td>
<td>1</td>
<td>31</td>
<td>.041</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>.707</td>
<td>.137</td>
<td>.048</td>
<td>.743</td>
<td>.009</td>
<td>.155</td>
<td>2</td>
<td>29</td>
<td>.857</td>
<td>.335</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), NTCP Burman LKB Paired Lungs
b. Predictors: (Constant), NTCP Burman LKB Paired Lungs, Total Dose received by patient, Total Lung Volume Paired Lungs
c. Dependent Variable: Clinical Outcome
The first part of the output describes the overall model used in our regression analysis. Model 1 refers to the initial analysis where only the NTCP values of each patient are used as a predictor variable. Model 2 refers to when an extra two predictors are added to the model, total dose, and lung volume. The dependent variable is displayed as being the clinical outcome.

The column labeled \( R \) gives the values of the multiple correlation coefficient between the predictors and the outcome and essentially these are the same as those explained above in the correlation analysis. \( R^2 \) is also given which explains how much variability in the outcome is caused by the predictors.

For the above case shown in the output, the value of \( R^2 \) has only increased by a small amount suggesting that the additional predictor variables have not considerably increased the amount of variability in the outcome. NTCP accounts for 12.8% of variation in clinical outcome, and with the additional variables this value increases to 13.7%. This means that the two additional variables have only contributed to 0.9% increase in variability of the outcome, a very small amount, which leads us to believe that the NTCP value is the main contributor to a change in the outcome.

The adjusted \( R^2 \) value tells us how well our model generalizes with the real population. The closer this value is to \( R^2 \) the better. For the above case the value has dropped 2.8% which means if we were analyzing the population as a whole there would be 2.8% less variance explained in the outcome from NTCP. The F-ratio tests the significance of the \( R^2 \) value, and for model 1 this value is (4.547) with a significance value (.041) a value less than the p=.05 significance level leading us to the conclusion that the result is not a chance finding. The same result is seen in the
ANOVA output, so we can be confident that the model is significantly better at predicting the outcome than using the mean as the best guess.

The final part of SPSS output 1.3 gives us information about the $b$ coefficients described previously shown in the methods section. They tell us about the relationship between the clinical outcome and each of the predictors. The negative value indicates a negative relationship between NTCP and Clinical outcome, for the analysis of low scores, using the LKB model with Burman et al (1991) parameters for the paired lungs case.

The $t$-test checks if the coefficients are significantly different from zero and in this case for NTCP the significance of the $t$-test is .041 which is below the $p=.05$ significance level. The standardized $b$-coefficients are provided, to allow for a direct comparison between variables if they are recorded on different scales of measurement. They tell us the number of standard deviations that the outcome will change as a result of the one standard deviation change in the predictor. So for the above example as NTCP increases by one standard deviation the clinical outcome decreases by .358 standard deviations.

Finally confidence intervals are provided that tell us if 100 sample were collected we would be 95% confident that the $b$-values would be approximately the same in each case. Good models have tight confidence models that suggest the $b$-values in the sample are close to what they are in the population. A bad model will have confidence intervals that cross zero, which means that the predictor in some samples will have a positive relationship with the outcome and in others a negative relationship. For the above example the intervals do not cross zero so we can be confident that the model is acceptable.

When all scores are considered the best model was found to be for model 1, the LKB model with Burman et al (1991) parameters, for the single lung, with an F-ratio (1.986) and a significance value (.166) which is above the $p=.05$ significance level. Despite this the confidence intervals in this case crossed zero indicating a bad model and the significance value indicates that any relationship was purely by chance.

When just high scores are considered the best model was found to be for model 1, the Parallel model with Seppenwoolde et al (2003) parameters, for the paired lungs case, with an F-ratio (8.009) and a significance value (.016) well below the $p=.05$ significance level. Standardized beta coefficients were positive so an increase in NTCP constitutes an increase in Clinical outcome in the high score domain. Moreover the confidence intervals did not cross zero indicating a good model.

Finally when just low scores are considered the best two models were found to be, for model 1, the LKB model with Burman et al (1991) parameters for the paired lungs case, with an F-ratio (4.547) and a significance value (.041) below the $p=.05$ significance level (see SPSS output 1.3), and the Relative Seriality model with Mah et al (1987) parameters for the paired lungs case, with an F-ratio (4.723) and a significance value (.038). In both cases the confidence intervals did not cross zero, but the relationship was found to be negative between NTCP and the outcome.

Results from model 2 were ignored because they provided little significance to the outcome, and F-ratio’s were below 1, which is not desirable because it means that there is more unexplained variation than explained variation.

*Regression analysis performed on Sub-groups*
In the second part of regression analysis we used the sub-groups of patients arranged in ascending dose as predictors in the regression model. An attempt is made at finding the relationship between dose groups with associated NTCP values, and the clinical outcome score. A baseline group was selected (the lowest dose group) against which the other groups were compared to see if the ascending dose and consequent NTCP, had an effect on clinical outcome.

The example below is of the SPSS output for the Relative Seriality model, with Seppenwoolde parameters for the single lung case:

**SPSS output 1.4**

![SPSS output screenshot]

The output produced is the same as that seen in the previous regression analysis and each value and test statistic is interpreted in the same way.

The model statistics which provides the $R^2$ value tells us, that for this case 32.1% of the variance in the change in clinical outcome can be explained by the dose group in which a patient is in. To check if this amount is significant we can look at the F-ratio also provided by ANOVA which has a significance value (.051) very close to the $p=.05$ significance level so we can be confident that the 32.1% of variance that can be explained is a significant amount.
A look at the coefficients shows that the first ‘dummy’ variable (lowDose vs 2\textsuperscript{nd} group) shows the difference between the change in outcome score for the baseline group and the 2\textsuperscript{nd} lowest dose group. We have used dummy variables here which represent groups of patients as 0’s and 1’s, and we know that $b$ coefficients describe a change in the outcome due to a change in the predictor. So in this case a unit change in the predictor is the change from 0 to 1. So it shows the change in the clinical outcome score that results from the change in the dummy variable from 0 to 1, so the change in clinical outcome if a patient is in the low dose group (baseline) compared to a patient in the 2\textsuperscript{nd} lowest group.

Like in the previous analysis the t-statistic tests to see if the difference between groups is 0. If this value is significant then the group in question is significantly different from the baseline category. In the example above it is evident that some $b$ coefficients are negative and others positive, with the most significant value (.063) occurring for the 8\textsuperscript{th} lowest dose group so a high dose group. The negative value means that there was a significant decrease in the clinical outcome score when comparing the baseline group to this group. This particular group for this example contained some of the lowest clinical outcome scores, so it is understandable that a negative relationship exists and quite a significant one too, although not below the $p=.05$ significance level.

By looking at the aforementioned test statistics, we deduced that the best model for the Single lung case is the Relative Seriality model with Seppenwoolde et al (2003) parameters, as shown in SPSS output 1.4. For the single lung case the 8\textsuperscript{th} lowest dose group (2\textsuperscript{nd} highest) was the most significant effect but this was due to no patients scoring above 2 in this group.

For the Paired lung case the best model is the Parallel model with Seppenwoolde et al (2003) parameters, producing an F-ratio (1.832) with a significance value (0.102). Despite this value being above the $p=.05$ significance level, it should be noted that the significance values for the 3\textsuperscript{rd} group, the 4\textsuperscript{th} group, and the 6\textsuperscript{th} group, against the baseline group, where (.017), (.036) and (.070) respectively. These values of high significance were for negative $b$ coefficients, suggesting that there was a higher clinical score for patients in the lowest groups compared to the higher dose groups. This is characteristic for the Parallel model where many patients predicted to have low NTCP values were diagnosed with grade 3 pneumonitis or higher. The data from the subgroups of patients can be found in the Appendix.

**LOGISTIC REGRESSION**

For logistic regression we analysed the patient data by looking at if the NTCP values and dosimetric parameter $V_{20}$ can act as predictor variables to predict a dichotomous outcome variable, in this case having or not having radiation pneumonitis.

An example of the SPSS output for this statistical analysis is shown in SPSS output 1.5 below:
The first part of the output gives the log-likelihood statistic which assesses the overall fit of the model. This becomes an important statistic when looking at the model after the variables have been included.

The second part of the output gives the information for the model when no predictors are included, and only the constant exists, (see Eq. 40). This represents the fit of the model when the most basic model is fitted to the data, and every patient is assigned to a single category of the outcome variable. SPSS predicts that every
patient belongs to the category where most observed cases exist. For this example
33 patients had no RP, and 13 had RP. So if SPSS predicts that every patient has no
RP then this prediction will be correct 33 times out of 46 so 71.7%. If SPSS was to
predict that the every patient had RP it would only be correct 13 times out of 46 so
28.3%, so it is best to make the former prediction that everyone does not have RP.

For the above example the value of the constant is given as -.932. The next table
labeled Variables not in the Equation gives the $\chi^2$ statistic which tells us if the
coefficients for the variables not in the model are significantly different from zero,
and if we were to add them whether they would contribute greatly to the outcome.
When the significance of the chi-squared distribution is greater than the $p=.05$
significance level the program concludes that the addition of the variables would not
be sufficient in providing a significant contribution to the outcome. The column
labeled score provides a Roa’s efficiency score statistic (Field) that informs us about
the strength of each variable. In this example the parameter $V_{20}$ has the highest
score and lowest significance value (.425) but this is a lot larger than the .05
significance level, so the analysis will terminate because the variables appear to have
no significance other than that down to chance.

**SPSS output 1.6**

<table>
<thead>
<tr>
<th>Omnibus Tests of Model Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square</td>
</tr>
<tr>
<td>Step 1 Step</td>
</tr>
<tr>
<td>Block</td>
</tr>
<tr>
<td>Model</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

* Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

<table>
<thead>
<tr>
<th>Hosmer and Lemeshow Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>NTCP_RS_S by V20(1)</td>
</tr>
<tr>
<td>NTCP_RS_S</td>
</tr>
<tr>
<td>Constant</td>
</tr>
</tbody>
</table>

* Variable(s) entered on step 1: V20, NTCP_RS_S * V20, NTCP_RS_S.

SPSS output 1.6 shows how the analysis continues for the above example for the
Relative Seriality model NTCPs with Seppenwoolde et al (2003) parameters. The
first table in the output tells us about the overall fit of the model, by using the log-
likelihood statistic which is multiplied by -2 to give the chi-squared distribution which
can be used to check if the events occurred by chance or not.
In the table labeled model summary we have the log likelihood statistic once the variables have been included. This value should be less than the initial value from SPSS output 1.5, indicating an improvement in the model by adding the predictors. However the difference is very small and an assessment of how significant the improvement is, can be given by the chi-squared statistic. The value of the chi-square statistic is not significant (.449) so the effect of including the variables has not changed the outcome any more substantially than when the constant was used. The R square values indicated are analogues of the R square values used in the previous methods, indicating the amount of variability described by the extra variables, which in this case is very small (Cox & Snell R-square = 0.033).

In the final table, the $b$ coefficients are given and the Wald statistic and its significance, which tells us if the coefficients are significantly different from zero. Furthermore the value exp($b$) is given which is a proportionate measure of the odds. A value above 1 means that as the predictor increases the odds of the outcome increase, and this is true for the NTCP value and $V_{20}$. Aside from the significance value associated with the Wald statistic for the constant, for the above example the parameter $V_{20}$ has the highest $b$ coefficient, Wald statistic, and significance (.258) compared to the NTCP values.

For the single lung case the best model was found to be the Relative Seriality model, with Seppenwoolde et al (2003) parameters its output which has been described above.

For the paired lungs case the best model was found to be the Relative Seriality model, with Mah et al (1987) parameters. For this model the addition of the extra predictor variables caused the value of the -2Log likelihood reduce from 54.813 to 48.611, indicating that the model predicts the outcome variable more accurately with the quantities NTCP and $V_{20}$. The chi-squared statistic which quantifies this change has a value of 6.355 and a significance value (.096), not below the .05 significance level but not very much higher than it. Cox & Snell R-square = .129 indicating that the variables account for at least 12.9% of the variability in the outcome. Finally for the NTCP value and the $V_{20}$ parameter, the value of the $b$ coefficient, the Wald statistic, its significance value and the exp ($b$) are, (5.905), (2.955), (.086), (366.933), and (1.488), (3.157), (.076), (4.426) respectively.

It is evident for this case that the NTCP values from this model and the $V_{20}$ parameter have both contributed to a reasonable level in the variability of the outcome.

For all other models in this Logistic Regression analysis, the -2log likelihood reduced in each case when the variables were introduced but the reduction was very small, and insignificant. Moreover in each of these cases no variable contributed to a greater effect than just having the constant in the model.

**CHI-SQUARE ANALYSIS ($\chi^2$)**

Chi-square analysis was performed to assess whether the dosimetric factors $V_{13}$, $V_{20}$, and $V_{30}$ influence the clinical outcome for a patient. This was done for two cases, (i) when a patient was considered to have developed RP if they had a scoring grade 2 or above and (ii) when a patient was considered to have developed RP if they had a scoring grade of 3 or above. An example of the SPSS output from a type (i) case analysing $V_{20}$ is shown below:

**SPSS output 1.7**
### What percentage of the lung volume was irradiated * Did They get Radiation Pneumonitis

#### Crosstabulation

<table>
<thead>
<tr>
<th>What percentage of the lung volume was irradiated</th>
<th>Did They get Radiation Pneumonitis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP</td>
<td>NoRP</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>Count</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>% within What percentage of the lung volume was irradiated</td>
<td>58.6%</td>
</tr>
<tr>
<td></td>
<td>% within Did They get Radiation Pneumonitis</td>
<td>60.7%</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>37.0%</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>Count</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>% within What percentage of the lung volume was irradiated</td>
<td>64.7%</td>
</tr>
<tr>
<td></td>
<td>% within Did They get Radiation Pneumonitis</td>
<td>39.3%</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>23.9%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>28.0</td>
</tr>
<tr>
<td></td>
<td>% within What percentage of the lung volume was irradiated</td>
<td>60.9%</td>
</tr>
<tr>
<td></td>
<td>% within Did They get Radiation Pneumonitis</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>% of Total</td>
<td>60.9%</td>
</tr>
</tbody>
</table>

#### Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
<th>Exact Sig. (1-sided)</th>
<th>Point Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>.167</td>
<td>1</td>
<td>.683</td>
<td>.761</td>
<td>.465</td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.009</td>
<td>1</td>
<td>924</td>
<td>.761</td>
<td>.465</td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>.168</td>
<td>1</td>
<td>.682</td>
<td>.761</td>
<td>.465</td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td>.163</td>
<td>1</td>
<td>686</td>
<td>.761</td>
<td>.465</td>
<td></td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>.163</td>
<td>1</td>
<td>686</td>
<td>.761</td>
<td>.465</td>
<td>.228</td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

a. Computed only for a 2x2 table
b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.65.
c. The standardized statistic is -.404.
The first table in SPSS output 1.7 is called a cross tabulation table and is similar to the contingency table described in the methods section of the report. It shows which cases fall in each category. 29 patients (63%) had over 20% of their lung volume receiving 20 Gy, and of these 17 (58.6%) developed RP and 12 (41.4%) did not. A total of 17 patients (37%) had less than 20% of their lung volume receiving 20 Gy, and of these 11 (64.7%) developed RP and 6 (35.3%) did not. Looking closely at the row ‘% within Did They get Radiation Pneumonitis’ we can see that of the patients that developed RP 60.7% had greater than 20% of their lung volume receiving 20 Gy, and 39.3% had less than 20% of their lung volume irradiated. So as a simple first summary of the results when a patient receives 20 Gy to more than 20% of their lung volume they are more likely to develop radiation pneumonitis. The final thing that we can confirm by looking at this table is that the assumption which requires expected frequencies to be greater than 5 in a chi-square test has been met in this analysis.

The next part of the output, provides the chi-square statistic and other analogous statistics. The Pearson chi-square statistic, tests whether the two variables are independent. If the significance value of this test statistic is below the p=.05 significance level we can reject the hypothesis that the two variables are independent and accept the hypothesis that a relationship exists between them. The value of the chi-square statistic is .167 and its significance value is a (.683). Indicating that when 20% of volume irradiated by 20 Gy there is no significant effect on the outcome. In small samples like the patient sample used here the Likelihood ration is preferred as a statistic of measure and here it is similar (.168) to the chi-square value with a similar significance value (.682).

The final table of the output shows some statistical tests that measure the strength of the association between the variables. These measures modify the chi-square statistic to take into account the sample size and degrees of freedom, giving the test statistic a value between 0 and 1[28], with a value of 1 indicating the strongest possible association between the variables, and 0 indicating absolutely no association. The values of these test statistics in this example are small (.060) and not significant, so the association strength between the variables is very weak.

Using the chi-squared analysis method, for the first case scenario (when a patient was considered to have developed RP if they had a scoring grade 2 or above) the best association between the dosimetric factors $V_{13}$, $V_{20}$, and $V_{30}$ and the clinical outcome was found to be the case described above, SPSS output 1.7. It is interesting to note that although simple analysis of the crosstabulation table led us to believe that the chances of developing RP were heavily dependant on more than 20% of the lung receiving 20 Gy, the statistical analysis shows a weak association.

Using the chi-squared analysis method, for the second case scenario (when a patient was considered to have developed RP if they had a scoring grade of 3 or above) the best association between the dosimetric factors $V_{13}$, $V_{20}$, and $V_{30}$ and the clinical

---

### Symmetric Measures

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Approx. Sig.</th>
<th>Exact Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal by Phi</td>
<td>-0.60</td>
<td>.583</td>
<td>.761</td>
</tr>
<tr>
<td>Nominal Cramer’s V</td>
<td>.60</td>
<td>.583</td>
<td>.761</td>
</tr>
<tr>
<td>Contingency Coefficient</td>
<td>.60</td>
<td>.583</td>
<td>.761</td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.
outcome was found to be between $V_{30}$ and the clinical outcome. The Likelihood ratio value was 2.160 and its significance value .142 which is above the $p=.05$ significance level but is considerably lower than all other cases. Moreover the Phi statistic value is .214 with a significance value of .142. For this significance value we can say that the effect or association is between .1(small) and .3(medium), but we can not be confident that a true association has been identified.

**ANOVA**

One way ANOVA was run to determine the different effects of the subgroups of patients on the clinical outcome, in an attempt to establish any existing effects and relationships, between the dose and associated NTCP values, and the clinical outcome. SPSS output 1.8 shows an example output from our results for the Relative Seriality model with Seppenwoolde et al (2003) parameters, for the single lung case.

**SPSS output 1.8**

<table>
<thead>
<tr>
<th>Score</th>
<th>N</th>
<th>Mean</th>
<th>Std Deviation</th>
<th>Std Error</th>
<th>95% Confidence Interval for Mean</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>lowest dose group</td>
<td>5</td>
<td>2.600</td>
<td>.7071</td>
<td>.3182</td>
<td>1.1220</td>
<td>2.8780</td>
<td>1.00</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>2nd lowest dose group</td>
<td>5</td>
<td>2.200</td>
<td>.8369</td>
<td>.37417</td>
<td>1.1811</td>
<td>3.2399</td>
<td>1.00</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>3rd lowest dose group</td>
<td>5</td>
<td>1.200</td>
<td>1.1234</td>
<td>.58310</td>
<td>.4199</td>
<td>2.8189</td>
<td>.00</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>4th lowest dose group</td>
<td>5</td>
<td>1.600</td>
<td>.8443</td>
<td>.40000</td>
<td>.4884</td>
<td>2.7105</td>
<td>1.00</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>5th lowest dose group</td>
<td>5</td>
<td>2.600</td>
<td>1.1401</td>
<td>.59999</td>
<td>1.1843</td>
<td>4.0157</td>
<td>1.00</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td>6th lowest dose group</td>
<td>5</td>
<td>2.000</td>
<td>.3350</td>
<td>.37417</td>
<td>1.7811</td>
<td>3.3339</td>
<td>2.00</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td>7th lowest dose group</td>
<td>5</td>
<td>1.400</td>
<td>.8443</td>
<td>.40000</td>
<td>.2854</td>
<td>2.5105</td>
<td>.00</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>8th lowest dose group</td>
<td>5</td>
<td>2.600</td>
<td>.8389</td>
<td>.37417</td>
<td>.2399</td>
<td>1.6389</td>
<td>.00</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>highest dose group</td>
<td>6</td>
<td>.6657</td>
<td>1.2110</td>
<td>.5977</td>
<td>2.2375</td>
<td>.00</td>
<td>4.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>1.8043</td>
<td>1.0872</td>
<td>.1537</td>
<td>1.4813</td>
<td>2.1274</td>
<td>.00</td>
<td>4.00</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Levene Statistic</th>
<th>df1</th>
<th>df2</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test of Homogeneity of Variances</td>
<td>.892</td>
<td>8</td>
<td>37</td>
<td>.533</td>
</tr>
</tbody>
</table>

**ANOVA**

<table>
<thead>
<tr>
<th>Score</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups (Combined)</td>
<td>17.106</td>
<td>6</td>
<td>2.136</td>
<td>2.190</td>
<td>.051</td>
</tr>
<tr>
<td>Linear Term</td>
<td>1.549</td>
<td>1</td>
<td>1.549</td>
<td>1.362</td>
<td>.274</td>
</tr>
<tr>
<td>Unweighted</td>
<td>1.285</td>
<td>1</td>
<td>1.285</td>
<td>1.320</td>
<td>.227</td>
</tr>
<tr>
<td>Weighted</td>
<td>15.611</td>
<td>7</td>
<td>2.258</td>
<td>2.831</td>
<td>.061</td>
</tr>
<tr>
<td>Deviation</td>
<td>1.064</td>
<td>1</td>
<td>1.064</td>
<td>1.110</td>
<td>.289</td>
</tr>
<tr>
<td>Unweighted</td>
<td>8.300</td>
<td>1</td>
<td>8.300</td>
<td>.903</td>
<td>.335</td>
</tr>
<tr>
<td>Weighted</td>
<td>14.881</td>
<td>6</td>
<td>2.480</td>
<td>2.540</td>
<td>.037</td>
</tr>
<tr>
<td>Deviation</td>
<td>36.133</td>
<td>37</td>
<td>.977</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53.239</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The first table from the output provides the descriptive statistics from the patient data. The important values from this are the mean with its associated standard error, and the confidence intervals which show the values within which the true value mean would lie if a population was analysed instead of a sample. So if we take the 5th lowest dose group as an example, and took lots of samples from a population of patients, the means of the samples would have a standard deviation of .5099.

The second table of the output provides the Levene statistic which tests if the variances of the 9 groups are significantly different. One of the main assumptions of ANOVA is that there is homogeneity of variance between each of the groups and if the Levene statistic is significant below the p=.05 significance level, we know that this assumption has been violated. For the above output the value the Levene statistic is .892 and is not significant (.533) therefore we can assume homogeneity of variance conditions have been met.

The main ANOVA summary table is shown in the 3rd table of the output. The table has two important components, the 'between group effects', due to the model, and the 'within group effects' due to unsystematic variation in the sample data. The between group effect is displayed for trends of a linear and quadratic nature. These are analysis of trends, and for this investigation we expect a linear trend whereby the group means increase proportionally. We have included the quadratic trend also to see if there are situations where the clinical outcome increases with dose and then falls off again, perhaps indicating that the predictive power of the models is stronger at low values of NTCP than higher values. This is something we discuss in the next section of the report. The between group effect which is labeled Combined is the overall experimental effect.
The F-ratio tests whether the group means are equal. If they were all to be equal then we would not expect a change in outcome with increasing BEUD or EUD and corresponding NTCP. The F-ratio tells us that the means of the groups are not equal. For the above case the F-ratio is 2.190 with a significance value of (.051) very close to the p=.05 significance level. So we can conclude that the F-ratio has not occurred by chance and that there is a significant effect of dose on the clinical score. The important point here is that it is still unknown what the effect of this dose is and which groups differed.

Once a significant effect has been identified, the analysis of the aforementioned trends can be looked at. The linear component tests if the means increase across the groups in a linear way. The row labeled weighted gives an F-ratio for the linear trend of 1.326 with a significance value of .257. For the quadratic trend the F-ratio is below 1 with a non-significant value, and this indicates that the pattern of means is not represented by a curve.

The next table provides the statistics that are analogous to the Levene statistic and these are not required in this example because we already have a Levene statistic that is not significant so we know that our variances are homogeneous.

The final two tables show the contrast coefficients which tell us which comparisons were made and the table labeled Contrast Tests shows the results of the comparisons between groups. The comparisons made are indicated by the plus and minus signs, so the first comparison is between the lowest dose group and each other group. The next comparison is between the 2nd lowest dose group and the highest dose group, the next between the 3rd lowest dose group and the 2nd highest dose group and so on in sequence.

The Contrast Tests table shows the statistics of each contrast. Depending on whether the homogeneity of variances has been met, the results are read from the top part of the table or the bottom part. The value of each contrast is given by taking the group mean, multiplying it by the weight of the contrast of interest and then summing the values together. For the first case the contrast takes a negative value as the weight of the contrast was -8.

SPSS calculates a t-statistic by dividing the contrast value by the standard error (Field), and then this value is analysed using critical values of the t-distribution. SPSS gives the significance value of the contrast and this is the 2-tailed value. We tested a one-tailed hypothesis that the clinical outcome would increase in relation to the ascending groups above the baseline group, so the significance value should be divided by 2. This is true for our other contrasts too.

Taking contrast 1 as an example we could say that increasing dose increased the clinical outcome, if the significance value relatively close to or below the p=.05 significance level. However for this contrast the significance value is not low enough at .323. The lowest significance value (.1895) for a contrast in this example is for the 2nd contrast which compares the second lowest dose group to the highest dose group. However again this is not significant enough to confidently conclude that an increase in dose leads to an increase in corresponding clinical outcome.

For the Single lung case the best model deduced from ANOVA was the, Relative Seriality model with Seppenwoolde et al (2003) parameters, as discussed above with an F-ratio of 2.190 with a significance value of (.051) very close to the p=.05 significance level. So we can conclude that the F-ratio has not occurred by chance and that there is a significant effect of dose. Looking at the contrasts this effect seems to come mainly from contrast number 1, which is a comparison of the baseline group with all the groups, contrast number 2, which compares the second
lowest group with the highest dose group and contrast group number 3 which compares the 3rd lowest dose group with the 2nd highest dose group. Although the significance of these values suggests that they are likely to have occurred by chance.

For the single lung case the Relative Seriality model with Mah et al (1987) parameters also produced some interesting results with an F-ratio of 1.765 and a significance of .116 (SPSS output 1.9) for the overall effect of the experiment.

**SPSS output 1.9**

<table>
<thead>
<tr>
<th>Score</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>14.708</td>
<td>8</td>
<td>1.838</td>
<td>1.765</td>
<td>.116</td>
</tr>
<tr>
<td>Linear Term</td>
<td>1.954</td>
<td>1</td>
<td>1.954</td>
<td>1.876</td>
<td>.179</td>
</tr>
<tr>
<td>Weighted Deviation</td>
<td>1.858</td>
<td>1</td>
<td>1.858</td>
<td>1.784</td>
<td>.190</td>
</tr>
<tr>
<td>Quadratic Term</td>
<td>12.848</td>
<td>7</td>
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<td>.497</td>
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<td>37</td>
<td>1.041</td>
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<th>Std Error</th>
<th>t</th>
<th>df</th>
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</table>

Moreover for this case the contrasts with the most significant values proved to be contrasts 1, 4, and 5 (SPSS output 1.9), indicating that the effect of dose increase on clinical outcome was stronger between the intermediate dose groups.

For the Paired lung case the best model deduced from ANOVA was the, Parallel model with Seppenwoolde et al (2003) parameters:
Due to the significance of the Levene statistic we need to look at the second half of the Contrast Tests table.

The combined experimental effect is defined by the F-ratio 1.832 with a significance value of .102, but the most significant contribution seems to arise from the quadratic trend, which produces an F-ratio of 5.733, with a highly significant value of .022, well below the p=.05 significance level. This behaviour indicates that the clinical score fluctuates with increasing dose values. Thus one could hypothesize that the Parallel model is better at predicting low NTCP values and then there is a drop in predictive power relative to the eventual clinical outcome. The highest significance values are for contrasts 1 and 3, which are .008, and .021 respectively both below the p=.05 significance level.
Software implementation for NTCP calculations

In figure 2.2 we saw the three components that the software tool development would be comprised of. Figure 3.5 shows the layout of the patient therapy details form, created using Excel.

**Fig. 3.5** The patient therapy details form.

The form comes with a series of fields yellow in colour. The Medical Physicist or a associated medical personnel, is required to fill in the form with the following details, hospital/Clinic name, Organ classification, Patient number, Total Dose of therapy, and the number of fractionations for the therapy. Although in this investigation the Organ at risk being investigated is the lung, we have developed the program such that a user can include details of other organs of interest that he or she would like to perform NTCP analysis on. It should be noted that the form can accommodate for multiple patient profiles, so a group of patients can be assessed collectively.

The *'Patient Therapy Details Form'* is the first important component of the software tool. It is imperative that it is filled in correctly and associated instructions are issued with the software during installation.
The second and most important component is the program itself, the NTCP calculation Pod, which is depicted in figure 3.6 below:

**Fig. 3.5** The NTCP calculation Pod.

The program begins with the user, loading the required *Patient Therapy Details Form* which they have obtained from the hospital they work in or another establishment. This form as explained above, may contain, information from one patient or a group of patients.

The program then requires the user to select a dose-response model on which the NTCP calculation will be performed. For the next stage the user must enter the values for the parameters that are required for the model they have selected. Incorrect input or failure to enter parameters will not enable the program to run and a warning will be given that informs the user that they must fill in the correct fields. The next stage requires that the user selects an organ classification, to indicate which organ is being analysed. This is important for storage of the correct information in the results archive. Once all the required selections and inputs have been made the user confirms that they are happy with the selected conditions and the following screen is shown figure 3.6 which gives the user the option to run the analysis:
Once the analysis is run the final screen figure 3.7 is depicted which informs the user that they can access the results data stored in the archive file:
The program user can then access the archive file which is the final component of the software tool developed for this investigation and this can be seen in figure 3.8 below:
The results Archive stores the information from the analyses performed using the dose-response models to calculate the NTCP for a given therapy. The medical Physicist can quickly view the therapy details, total dose, and no. of fractionations, and the resulting NTCP value for the organ class selected. The archive stores information results from all three models investigated in this report and can be adapted to include any extra models for future development. For a more detailed look at the treatment and associated calculation steps of NTCP the user can access the patient therapy detail forms after the program is run.
4. DISCUSSION

An evaluation of the predictive power of Normal Tissue Complication Probability (NTCP) dose-response models has been performed in this investigation in an attempt to assess the ability that these models have in accurately quantifying tissue complications subsequent to radiotherapy treatments for inoperable stage III non-small cell lung cancer. These predictions were compared with true results of the clinical outcome in patients receiving treatment. Radiation Pneumonitis was the observed clinical outcome, and an attempt was made to assess how well the severities of complications that cause this condition relate to the predicted NTCP values produced by the dose-response models.

In total data from 46 patients was analysed in this investigation. 28 patients (61%) developed Radiation Pneumonitis (RP) grade 2 (mild/no RP) or above and 18 patients (39%) scored 1 (very mild/no RP) and below. For the analysis when treating the Radiation Pneumonitis as a dichotomous variable, we stated that patients with a score of 2 or above had RP and patients below 2 had no RP, however we also analysed the patients by specifying that patients with a score of 3 or above had RP and patients below 3 had no RP, so two scenarios were investigated. Taking into consideration the latter scenario, 13 patients (28%) developed RP grade 3 (RP) or above. 33 patients (72%) developed RP grade 2 (mild/no RP) or below.

NTCP calculations were performed using DVH data from each treatment, by use of the three most common dose-response models for NTCPs, the Relative Seriality model, the LKB model and the Parallel model, for a varying set of parameters shown in table 3.

A preliminary look at the results of NTCP for each patient plotted on the theoretical curves for each model and parameter set, revealed that when parameters of steepness were higher the calculated response probabilities became spread across a wider range of dose. This was most evident for the models using the Mah et al (1991) and Burman et al (1987) parameter sets which were the Relative Seriality model and the LKB model. For these models and parameters the patients were not clustered in the low NTCP regions .3 and below, and were spread across the scale. Furthermore patients that had developed radiation pneumonitis grade 3 or higher were positioned higher up the NTCP scale above .4 up to .6. The Parallel model with Seppenwoolde et al (2003) also exhibited a slightly larger spread of predicted NTCP values than its rival models for the single lung case, with the initial theoretical curve increasing steadily from zero before the steep part. The theoretical curve for the LKB model with Seppenwoolde et al (2003) parameters also exhibited this behaviour of steady increase at low doses and low NTCP values.

When the lung was considered to function as a paired organ, low values were predicted for NTCPs, and thus even patients labeled as having developed RP grade 3 or above were positioned in low regions of the NTCP scale. Exceptions existed for the models using the Mah et al (1991) and Burman et al (1987) parameters were as described above the patients were spread further across the NTCP scale. Moreover the Parallel model with Seppenwoolde et al (2003) parameters was also seen to express this behaviour for the paired lung case.

Clinical dose response curves for TCP and NTCP are usually less steep than those calculated for model situations. This is caused by heterogeneity, e.g. for normal tissues, genetically determined radiosensitivity, co-existing disease of the irradiated tissues, pharmaceutical drugs (e.g. chemotherapy), or smoking may affect radiation response. [10] The more heterogeneous a sample population is the less steep the dose-response curve. In general heterogeneities observed in normal tissues are
more comparable between patients, where as those observed in tumours less so, so curves for NTCP are steeper than those of TCP.\textsuperscript{[10]}

With this in mind although we observed a larger spread across the NTCP scale for models using larger values of $\gamma$, this may not be characteristic to the true nature of clinically produced dose-response curves, which are known to be of a shallower nature. Thus we could conclude from this preliminary information that parameter sets such as those of Gagliardi et al (2000) and Seppenwoolde et al (2003) should be more accepted, because the shallower nature of the theoretical curves produced with these, is closer to those that are clinically observed, and thus the potential acceptance of predictions of NTCP values made using these models would be more easily accepted.

The conditions under which these parameter sets are determined is an important consideration when comparing the models because these will vary from set to set and this is discussed in the latter parts of this section.

An initial look at the bar charts of the dosimetric quantities $V_{13}, V_{20},$ and $V_{30}$, depicting the value of each quantity for each patient and their diagnosis of Lung complication, does not allow for a relationship to be deduced easily. Our initial statistical analysis on these quantities and their association with the clinical outcome did not reveal any significant association or strong effect.

Using the chi-squared analysis method, for the first case scenario (when a patient was considered to have developed RP if they had a scoring grade 2 or above) the best association between the dosimetric factors $V_{13}, V_{20},$ and $V_{30}$ and the clinical outcome was found to be for the $V_{20}$ quantity. The value of the chi-square statistic is .167 and its significance value is a (.683). This indicates that when 20% or more of lung volume is irradiated by 20 Gy there is no significant effect that we can say with confidence has not occurred by chance, on the outcome.

Using the chi-squared analysis method, for the second case scenario (when a patient was considered to have developed RP if they had a scoring grade of 3 or above) the best association between the dosimetric factors $V_{13}, V_{20},$ and $V_{30}$ and the clinical outcome was found to be between $V_{30}$ and the clinical outcome. The Likelihood ratio value was 2.160 and its significance value .142 which is above the p=.05 significance level but is considerably lower than all other cases. For this significance value we can say that the effect or association is between .1 (small) and .3 (medium), but we cannot be confident that a true association has been identified.

It should be noted that for the chi-square analysis the reason we chose to assess the dosimetric quantities in relation to the value of 20% for the percentage of lung volume irradiated by them, was to ensure that the assumption of expected frequencies, which are required to be above 5 in each case, is met. Splitting the sample population using other volume criteria violated this assumption. Moreover there have been studies that relate the incidence of radiation pneumonitis for patients that have >30\% of their lung irradiated with >25Gy \textsuperscript{[1]}, so this investigation was used to find a similar relationship between >20\% and >13Gy, >20Gy and >30Gy.

\textit{Evaluation of the quality of the predictions made by the models}

Through the use of statistical analysis an attempt was made to assess the predictive power of the dose-response models. For each model an assessment was made on the collective influence made by the calculated NTCP values and associated variables, as predictors of the actual clinical outcome.
Results from correlation analysis show that Relative Seriality model using the parameter set Mah et al (1987) provided the best significance value of the Spearman’s and Kendall’s correlation coefficients. A Kendall tau correlation value of (-.149) was found with a significance value (.101), above the p=.05 significance level. The correlation indicated suggests that an increase in NTCP value does not correspond to an increase in clinical outcome, but a decrease, however the significance value is not low enough to conclude that this has not occurred purely by chance. NTCP was found to account for 3.65% variability in the clinical outcome score.

For the paired lung case the best Spearman’s and Kendall’s correlation coefficients, were again for the Relative Seriality model with Mah et al (1987) parameters. Significance values are improved compared to the single lung case, however they are both still above the .05 significance level, and in each case the R² value is small indicating that a small variability in the outcome score is accounted for by change in NTCP, and that even this small change is likely to occur by chance.

Results from treating the RP as a dichotomous variable, revealed that for the first scenario (Patients with score ≥2 have RP) the Biseral coefficient (.2511) significance (.094) was highest for the results using the Relative Seriality model with Mah et al (1987) parameters. For the second scenario (Patients with score ≥3 have RP) the Biseral coefficient (.276) significance (.083) was highest for the LKB model with Burman et al (1991) parameters. These significance values that are produced as a result of considering radiation pneumonitis as a dichotomous variable with an underlying continuum, i.e. having a scoring grade 0 or 1, are considerable better when looking at the correlation statistics than when the scoring scale is continuous. There were no significant results of correlation for the paired lung case.

Simple regression analysis to assess NTCP as a predictor variable and also to assess the influence of other variables (total dose, lung volume), revealed that when assessing all scores, the best model was the LKB model with Burman et al (1991) parameters, F-ratio (1.986), significance value (.166). This significance value indicates that any predicting done by the NTCP variable was purely by chance when all scores were assessed. Significant results were found for the paired lung case when looking at low and high scores separately.

When just high scores are considered the best model was found to be the Parallel model with Seppenwoolde et al (2003) parameters, F-ratio (8.009), significance value (.016) well below the p=.05 significance level with positive standardized coefficients indicating that an increase in NTCP resulted in an increase in clinical outcome.

When just low scores are considered the best two models were found to be the LKB model with Burman et al (1991) parameters, for the paired lungs case, F-ratio (4.547), significance value (.041), below the p=.05 significance level, and the Relative Seriality model with Mah et al (1987) parameters for the paired lungs case, F-ratio (4.723), significance value (.038). In both cases the confidence intervals did not cross zero, but the b coefficients for NTCP were found to be negative indicating that a standard unit increase in NTCP would cause a standard unit decrease in clinical outcome.

It should be noted that the results from analysis on low and high scores, can not be confidently addressed because of the small amount of data for each case, low and high score. Furthermore, the influence of additional variables on the outcome did not explain sufficient variability for this test.
Regression analysis on sub-groups of ascending dose revealed that the best model for the Single lung case is the Relative Seriality model with Seppenwoolde et al (2003) parameters, F-ratio (2.190), significance (.051), very close to the p=.05 significance level.

For the Paired lung case the best model is the Parallel model with Seppenwoolde et al (2003) parameters, F-ratio (1.832), significance value (0.102). Despite this value being above the p=.05 significance level, the significance values for the 3rd group, the 4th group, and the 6th group, against the baseline group, where (.017), (.036) and (.070) respectively. These values of high significance were for negative b coefficients, suggesting that there was a higher clinical score for patients in the lowest groups compared to the higher dose groups. This is characteristic for the Parallel model where many patients predicted to have low NTCP values were diagnosed with grade 3 pneumonitis or higher.

Logistic regression analysis revealed any relationship between variables NTCP and V20 with the clinical outcome. For the single lung case the best model was found to be the Relative Seriality model, with Seppenwoolde et al (2003) parameters, although the significance value of the test statistic, do suggest that any variation is likely to be by chance.\( \chi^2 \) sig. (.449) When the variables NTCP and V20 were added no significant change in the -2Log Likelihood occurred, however of the two variables V20 had the largest b coefficient (1.390) significance (.258). Again however although these were the lowest significance values for all the models, they still tell us that any effects are likely to have occurred by chance.

For the paired lungs case the best model was found to be the Relative Seriality model, with Mah et al (1987) parameters. For this model the addition of the extra predictor variables caused the value of the -2Log likelihood reduce from 54.813 to 48.611, indicating that the model predicts the outcome variable more accurately with the quantities NTCP and V20. The chi-squared statistic had a value of 6.355, significance (.096), not below the .05 significance level but not very much higher than it. The variables were found to account for at least 12.9% of the variability in the outcome. It is evident for the paired lung case that the NTCP values from this model and the V20 parameter have both contributed to a reasonable level in the variability of the outcome.

For all other models in this Logistic Regression analysis, the -2log likelihood reduced in each case when the variables were introduced but the reduction was very small, and insignificant. Moreover in each of these cases no variable contributed to a greater effect than just having the constant in the model.

The final statistical method used was the ANOVA method, to look for relationships between patient subgroups of ascending dose and the associated change of clinical outcome.

For the Single lung case the best model deduced from ANOVA was the, Relative Seriality model with Seppenwoolde et al (2003) parameters, F-ratio of 2.190 with a significance value of (.051) very close to the p=.05 significance level. So we can conclude that the F-ratio has not occurred by chance and that there is a significant effect of dose. Contrasts effects seems to come mainly from contrast number 1, which is a comparison of the baseline group with all the groups, contrast number 2, which compares the second lowest group with the highest dose group and contrast group number 3 which compares the 3rd lowest dose group with the 2nd highest dose group. Although the significance of these values suggests that they are likely to have occurred by chance.
For the single lung case the Relative Seriality model with Mah \textit{et al} (1987) parameters F-ratio 1.765, significance of .116 also suggests a reasonably significant effect. Close to the p=.1 significance level. Contrasts with the most significant values proved to be contrasts 1, 4, and 5, indicating that the effect of dose increase on clinical outcome was stronger between the intermediate dose groups.

For the Paired lung case the best model deduced from ANOVA was the, Parallel model with Seppenwoolde \textit{et al} (2003) parameters, F-ratio 1.832, significance .102, with the most significant contribution coming from the quadratic trend, which produces an F-ratio of 5.733, significance .022, well below the p=.05 significance level. This behaviour indicates that the clinical score fluctuates with increasing dose values. Thus one could hypothesize that the Parallel model is better at predicting low NTCP values and then there is a drop in predictive power relative to the eventual clinical outcome. The highest significance values are for contrasts 1 and 3, which are .008, and .021 respectively both below the p=.05 significance level. This together with results from regression seems to suggest that the Parallel model with Seppenwoolde \textit{et al} (2003) parameters for the paired lungs case has a high predictive power at low and high scores but not at intermediate scores. Figure 3.2 for the Parallel model in the paired lungs case shows that patients have been classified around low and high NTCP values with few at intermediate values.

\textit{Parameter discrepancies}

The statistical analysis performed on the patient data, reveal that the dose-response model with the best predictive strength appears to be the Relative Seriality model. This was true in most cases for the single lung analysis, predominantly when the Seppenwoolde \textit{et al} (2003) parameter set was applied. In addition to this the parameter set Mah \textit{et al} (1987) used with this model proved to predict well in the Biseral correlation analysis and the ANOVA analysis for patient subgroups. This particular model and parameter set also predicted encouraging results for the paired lung case when looking at the influence of predictors such as the NTCP and $V_{20}$, in Logistic regression. For the paired lung results the Parallel model with Seppenwoolde \textit{et al} (2003) parameters provided the most significant results especially for low NTCP values predicting the clinical outcome. The Seppenwoolde \textit{et al} (2003) parameter set is identified as the best one in this investigation for the conditions and analysis performed.

It is evident that the influence of the different parameter sets on the models is significant. A look at how these parameter sets were derived reveals the reasons why some may be better at predicting more accurately. Seppenwoolde \textit{et al} (2003) parameters are calculated from dose distributions used mainly for lung cancer irradiation [2], in comparison to Burman \textit{et al} (1991) parameters which are not based on actual data. In addition to this Gagliardi (2000) parameters are also derived from experiments using 5 field techniques. It becomes important therefore when assessing models that the parameter sets used, are studied, before concluding about the predictive power of each model. Parameter fits are descriptive of the patient population, treatment techniques and fractionation schedule used. [11]

An important concept that requires consideration when comparing dose-response models, highlighted by Tsougos \textit{et al} 2005, is that of the biologically effective uniform dose BEUD and the equivalent uniform dose, used to compare patient samples on theoretical curves. In models where a DVH reduction technique is used the DVH is converted to a single point to produce an EUD which is used then to calculate NTCP. [2] Conversely for the BEUD case the NTCP is calculated from the 3D dose distribution and then from this value the BEUD is calculated. The EUD concept
is based on the survival of tissue cells following irradiation, and the BEUD concept on the tissue response probability following irradiation. The two concepts are treated being analogous but this may create drawbacks in the analysis of the dose effects for different models.

**Was the statistical analysis accurate?**

For the statistical analysis an attempt was made to select the most valid statistical methods that would best analyze the data. Our sample size of 46 patients can be considered quite small for this type of study. For regression analysis which is the basis of most statistical methods, to test the overall effect of a model the minimum sample size recommended is $50 + 8k$ where $k$ is the number of predictors.\[28\]  

When looking at the relationships in this investigation between the single predictor and the outcome this value is not much higher than our sample, but introducing extra variables in the analysis we have performed would produce more significant results in a bigger sample size. An example of this can be if we consider the variation of lung volumes in patients receiving treatment. Every patient has a different lung volume, and in some cases the differences are large. A larger sample would allow for deeper analysis based on lung volumes, and the position of the lung irradiated, by enabling groups to be assessed and more detailed overall effects to be obtained from extra predictor variables.

This is likely to have acted as a drawback in our statistical analysis. However any significant results are not ineffectual and can be used to support existing studies and pave the way for new studies.

**Can models be applied with confidence?**

Many studies have been conducted evaluating the predictive power of NTCP dose-response models on the clinical outcome of radiation pneumonitis following lung cancer treatments. Significant results have been found within patient populations through the use of the models. It appears that the main influencing factors which surround these dose-response models are the parameter sets which govern their predictive success. In essence it is the parameter sets which are being compared and not the models, as it is these that provide the model with its predictive strength, so it becomes difficult to say with confidence which model is the best one. The ultimate aim could be not to discover which model has the best accuracy and predictive strength, but to know which model can be adapted for each specific situation, to produce the best accuracy in predicting the clinical outcome. Furthermore parameter sets need to be optimized to improve their description of radiobiological effects.

Every model appears to have its strengths and weaknesses, which may lie in mathematical techniques used, assumptions made or quantity of parameters included. The aim of this investigation and other investigations concerning dose-response modeling is to highlight the strengths and weaknesses within the predicted variations and Endeavour to improve the models and integrate their application into the clinical environment as an important tool for optimizing radiotherapy. These models need to be vital in treatment planning not useful if therapy is to be optimized; for this to occur, the clinical personnel need to be confident in the outcome model prediction.

Deasy *et al* (2001) propose a framework of estimating and conveying uncertainties in outcome predictions. Source errors in outcome predictions are divided into four categories, (1) *Model errors*, due to mathematical set up of the model and the
situations it is designed for, (2) Parameter uncertainties, due to unlimited patient data that is potentially available, (3) Biological noise that arises because models are based on complex biological phenomena. Also that what appears as random biological noise may become understood after further studies and analytical procedures, and (4) Measurement error, is the difference between calculated endpoints and actual values. These four important levels of uncertainty highlight the fact that for the models to be applied confidently in clinical situations, we must be aware of the model characteristics and more importantly the errors that surround its implementation.

Current challenges

Tumour positions, tumour behaviour, patient response and treatment techniques, are all different from patient to patient. The aim in radiotherapy is to characterize this variability in the best possible way to ensure optimized treatment.

Kallman et al 1992, highlighted the important point that tumour response and composition ultimately effect the dose delivery, and hence the NTCP that can occur. One patient may have a tumour in the same position as another patient, but tumour type and behaviour will differ, and as a consequence so to will the dose delivery, making the Tumour control probability and NTCP different despite the same position.

Treatment techniques will differ between patients and clinical establishments, so there is a considerable difficulty in achieving uniformity within treatments. The problem with this existing non-uniformity between treatments is also transferred to the radiobiological analysis performed by the dose-response models, making it difficult to find a single best solution. The aforementioned problem of parameter sets is also a challenge. A parameter set will be obtained in a clinical situation from a certain sample of the population but this set may not have the equivalent accuracy for a different patient sample.

One of the main issues for reporting damage to Normal tissues is the scoring criteria used. Tsougos et al 2005, address the issue of scoring grades and highlight the fact that chosen scoring grades used to assess clinical endpoints give rise to uncertainty in predictions made from applied models and parameter sets.

The clinical scores in this report have been based on the RTOG/EORTC and LENT/SOMA scoring criteria. Scoring systems are under continual evolution with the aim of improving them further. [27] The aim is to have a scoring system that can be used accurately over a diverse population of patients. For parts of the statistical analysis in this report the tissue complication of radiation pneumonitis was addressed as being a dichotomous variable, i.e. either a patient has or has not got RP. This was done in an attempt to reduce any uncertainties that develop in the scoring scales, from misclassification.

The RTOG/EORTC system is clinically rather than radiobiologically orientated [27] which means underlying biological effects may be missed in the initial outcome diagnosis. Normal tissue complications are also affected by treatment-related factors and patient-related factors. [27] Aside from the aforementioned treatment related factors such as dose per fraction, total dose and other dose-volume parameters, patients that have undergone surgery or chemotherapy need to be considered when used in analysis studies. Also patient-related factors such as smoking and breathing difficulties will also affect the way severity scoring for radiation pneumonitis is used to classify patients. By getting more accurate RP scoring we can establish NTCP limits for certain severities and be confident about assigning patients to potential severities in our predictions.
One other important factor in patient variability is the clinical follow up procedure which takes place in order to give patients a clinical outcome score. This procedure allows for discrepancies to occur because some patients develop late complication effects beyond the time at which they are assessed and given a score. This will almost certainly lead to uncertainties of the predicted clinical outcome, when using the dose-response models.

Future Developments and suggestions

In order to allow the confident and accurate implementation of NTCP dose-response models in radiotherapy, NTCP values predicted by models need to be accurately related to severity scales of clinical endpoints. The aim is to be able to say for example that, ‘patients who lie within the NTCP values 0.4 – 0.6 are highly likely to develop grade 2 pneumonitis and patients who lie within the 0.1 – 0.2 NTCP levels are unlikely to develop radiation pneumonitis’ based on an accurate scoring procedure. All the aforementioned factors involved in dose-response modeling make this a challenging task.

One suggestion is that like with TCP models which incorporate characteristics of, tumour proliferation time, hypoxia, cell density, NTCP models could incorporate parameters with more biological characteristics included, such as low dose hypersensitivity characteristics. With existing treatment variability and tumour response characteristics differing from patient to patient perhaps a hybrid model could be created whereby in the case of an NTCP model a parameter relevant to tumour response could be included, thus TCP could be related to NTCP during modeling. If higher doses and delivery methods are needed to eradicate a tumour then this will have an effect on the NTCP and if this can be represented by a parameter, perhaps the models could improve in their predictive accuracy.

Finally the integration of the Spatial Dose-Volume Histogram (zDVH) proposed by Cheng and Das 1999 [12], could be adapted to maintain the spatial resolution that is lost in DVH reduction techniques. Spatial variation and size and magnitude of high and low-dose regions can be visualized with a zDVH. [12] The zDVH which is a 2D analogue of a 3D DVH can provide dose-volume and spatial information that may be vital for the correlation of long-term radiation effects. [12] If this method could be integrated into NTCP modeling it could help to improve the predictive strength of the existing models.

NTCP Calculation Pod: Implementation of the software

The creation of the NTCP calculation software is directed towards the future prospect of being able to integrate such a software program in Treatment Planning, allowing for the integration of radiobiological analysis.

The Patient Therapy Details form is created with the aspiration of “maintaining a uniform process for data recording and improve efficiency in the acquisition of NTCP results for Radiotherapy treatment planning.” Such a procedure for data recording can meet with the requirements of the Radiotherapy Network DICOM RT Standard, to improve the efficiency of treatments.

The NTCP calculation Pod is easy to use, has clear input fields and there is an ability to extend the program with a new model and new parameters as new developments evolve. The program can act as a quick tool for evaluating the quality of therapy for each patient, using radiobiological models with reference to the therapeutic ratio and the NTCP value.
Patient information can be stored on a database and for treatment planning this information can be used, to optimize treatments making them Patient Specific or ‘tailor made’ i.e. characterize variability.

Radiobiology applications in treatment planning can allow us to better understand the biological effects on tumours and healthy tissue following irradiation. If we can gain an insight into the NTCP’s for individual treatments then we can reach the main goal of cancer therapy which is to improve/increase the ‘Therapeutic ratio’.

A possibility or vision for the future would be to couple the NTCP-Calculation Pod or a similar software tool, with a parameter optimization tool such as MLE (Maximum Likelihood Estimation program), and a statistical analysis program, for a complete optimized evaluation of treatment plans. If statistical analysis is performed and errors eliminated where possible, to confirm the reliability of the model predictions, it is hoped that this vision can be achieved.
An evaluation of the predictive strength of Normal Tissue Complication Probability (NTCP) dose-response models, for acute Pneumonitis in patients treated with conformal radiation therapy for non-small cell lung cancer was performed in this study. The most common radiobiological dose-response models were assessed, the Relative Seriality model, the LKB model, and the Parallel model, each with varying parameter sets.

The predictive strength of models was assessed by statistically analyzing the relationship between the NTCP results produced, and the true clinical outcome score, based on RTOG/EORTC, LENT/SOMA scoring protocols.

Some pleasing results were found to suggest that these NTCP models could be used to positively predict associated clinical outcomes post radiation therapy, with the best overall model based on the 46 patient sample, being the Relative Seriality model with Seppenwoolde et al (2003) parameters. The best results were achieved when considering the onset of radiation pneumonitis as a dichotomous variable, and the patient sample was split into subgroups.

No significant effect was found for the dosimetric quantities $V_{13}$, $V_{20}$, and $V_{30}$, in relation to the clinical outcome, with the quantity $V_{20}$ having been investigated more readily. Furthermore the inclusion of these quantities in statistical models of assessment along with the NTCP predictor variable did not affect the variability of the outcome in a significant way.

Through this study it has been recognized that radiobiological modeling is a complex process based on complex biological phenomena with associated noise. Making accurate predictions using these models, with confidence is challenging, yet the potential for further development and analysis is evident, as the importance of such a radiobiological approach can only be useful in the goal of treatment planning optimization.

Parameter sets used with each model proved to play a significant part in the ability of models to accurately predict the onset of radiation pneumonitis, with parameter sets obtained by real experiment (Seppenwoolde et al (2003)) seeming to be the most welcome. The difficulty that lies in saying with confidence which model is the best, stems from the parameter sets used to implement the models, and it is the development and more accurate application of these that will enable a good model to function with high predictive ability.

Suggestions have been made for the possibility of including tumour response and behavioral characteristics, within a model that can be considered to be a hybrid of NTCP and TCP, because the eradication processes of a tumour will have a direct effect on NTCP.

The development and creation of an NTCP calculation software tool became an important part of this investigation, with the vision behind such a program being to improve efficiency of patient data collection and processing in the realm of radiobiological analysis. The hope is that such a software tool can be integrated with a treatment planning system to offer radiobiological analysis for each patient, and help to achieve the goal of optimizing radiotherapy treatment, maximizing TCP and minimizing NTCP.
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APPENDIX A.

NTCP values, and BEUD & EUD values calculated for each model, and associated clinical outcome score for each patient. Also shown are the subgroups used for statistical analysis.

Relative-Seriality, Seppenwoolde, Single Lung

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APPENDIX B.

Visual Basic code for the NTCP calculation Pod software tool.

Dim xlApp As Excel.Application
Dim xlwbook As Excel.Workbook
Dim xlsheet As Excel.Worksheet
Dim Res1 As Integer

Option Explicit
  Dim FileSelected As String
  Dim RunProgram As String

Private Sub cmd_arch_Click()
' Dim RunProgram As String
' Dim Result As Integer
  Shell "c:\Program Files\Microsoft Office\OFFICE11\EXCEL.exe C:\Program Files\NTCP-Calculation_Pod\Archive.xls", vbMaximizedFocus
Unload Me

'Shell " OPEN C:\Program Files\NTCP-Calculation_Pod\Archive.xls", vbMaximizedFocus
'runExe = Shell(path & "Archive.xls", vbMaximizedFocus)
'RunProgram = "C:\Program Files\Microsoft Office\OFFICE11\excel.exe"
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
'Result = Shell(RunProgram & "C:\Drivers", vbNormalFocus)
End Sub

Private Sub Dir1_Change()
  File1.FileName = Dir1.Path
End Sub

Private Sub Drive1_Change()
  Dir1.Path = Drive1.Drive
End Sub

Private Sub Form_Load()
  txt_plw.Visible = False
  cmd.Visible = False
  lst_types.AddItem "Text files (XLS)"
  lst_types.ListIndex = 0
  If lst_types.ListIndex = 0 Then
    File1.Pattern = ".*.xls"
  End If
End Sub

Private Sub lst_types_Click()
  If lst_types.ListIndex = 0 Then
    File1.Pattern = ".*.xls"
  End If
End Sub

Private Sub Command1_Click() 'File1_DblClick()
  If File1.FileName = "" Then
    MsgBox ("Select a file to run")
    Exit Sub
  End If
  FileSelected = File1.Path
  If Right(FileSelected, 1) = "" Then
    FileSelected = FileSelected & File1.FileName
  Else
    FileSelected = FileSelected & "\" & File1.FileName
End If

Res1 = MsgBox("Welcome to the NTCP-CalculationPod", vbInformation)

Frame4.Visible = True
Frame8.Visible = True
txt_hospital.Visible = True
txt_OrganClass.Visible = True

'Private Sub Form_Load()
Set xlApp = New Excel.Application
Set xlwb = xlApp.Workbooks.Open(FileSelected) '("C:\Documents and
Settings\Yiannis\Desktop\Hospital PatientData Forms\PatientTherapyDetailsForm.xls")
Set xlsheet = xlwb.ActiveSheet 'Sheets.Item(1)

If AddIns("Analysis ToolPak").Installed = False Then
  AddIns("Analysis ToolPak").Installed = True
End If

txt_hospital.Text = xlsheet.Cells(2, 1)
txt_patient.Text = xlsheet.Cells(11, 1)
txt_OrganClass.Text = xlsheet.Cells(4, 1)

'DETAILS ABOUT THE OPTIONS AND TICK BOXES
opt_RelativeSeriality.Value = False
opt_LKB.Value = False
opt_Parallel.Value = False
opt_SingleLung = False
opt_PairedLungs = False
opt_breast = False
opt_HeadNeck = False
opt_Prostate = False
opt_AVM = False
lb_msg.Caption = ""

End Sub
Private Sub cb_confirm_Click()
  Dim ParameterSet As String, OrganClass As String
  Dim MRs, MLkb, MParl, MOther
  Dim Current As Worksheet
  Dim Resp, Resp1, Resp2, Resp3, Resp4, Resp5, Resp6, Resp7, Resp8, Resp9, Resp10 As Integer

  '******************************************************************
  Val (txt_D50)
  Val (txt_n)
  Val (txt_m)
  Val (txt_patient)
  Val (txt_s)
  Val (txt_gma)
  '******************************************************************

  'ENSURING THAT A MODEL IS SELECTED'

End Sub
'If opt_RelativeSeriality.Value = False Then
'If opt_LKB.Value = False Then
'If opt_Parallel.Value = False Then
'If opt_Other.Value = False Then
'MsgBox ("You must select a model")
'End If
'End If
'End If
'End If

If opt_RelativeSeriality.Value = True Then
    MRs = "Relative Seriality"
End If

If opt_LKB.Value = True Then
    MLkb = " LKB"
End If

If opt_Parallel.Value = True Then
    MParl = " Parallel"
End If

If opt_Other.Value = True Then
    MOther = " Other"
End If

''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''
'VERIFYING THAT THE USER HAS ENTERED THE CORRECT PARAMETERS FOR THE SELECTED DOSE-
RESPONSE MODEL'
''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''

If opt_RelativeSeriality.Value = True Then
    If Val(txt_gma) = False Then
        Resp2 = MsgBox("You must enter a value for 'Gamma'", vbExclamation)
    End If
End If

If opt_RelativeSeriality.Value = True Then
    If Val(txt_s) = False Then
        Resp3 = MsgBox("You must enter a value for the seriality parameter 's'", vbExclamation)
    End If
End If

If opt_RelativeSeriality.Value = True Then
    If Val(txt_D50) = False Then
        Resp4 = MsgBox("You must enter a value for 'D50'", vbExclamation)
    End If
End If

If opt_LKB.Value = True Then
    If Val(txt_n) = False Then
        Resp5 = MsgBox("You must enter a value for 'n'", vbExclamation)
    End If
End If

If opt_LKB.Value = True Then
    If Val(txt_m) = False Then
        Resp6 = MsgBox("You must select a value for 'm'", vbExclamation)
    End If
End If

If opt_LKB.Value = True Then
    If Val(txt_D50) = False Then
        Resp7 = MsgBox("You must enter a value for 'D50'", vbExclamation)
    End If
End If
If opt_Parallel.Value = True Then
    If Val(txt_n) = False Then
        Resp8 = MsgBox("You must enter a value for 'n'", vbExclamation)
    End If
End If
If opt_Parallel.Value = True Then
    If Val(txt_m) = False Then
        Resp9 = MsgBox("You must select a value for 'm'", vbExclamation)
    End If
End If
If opt_Parallel.Value = True Then
    If Val(txt_D50) = False Then
        Resp10 = MsgBox("You must enter a value for 'D50'", vbExclamation)
    End If
End If
If opt_Parallel.Value = True Then
    If Val(txt_D50) = True Then
        If Val(txt_n) = True Then
            If Val(txt_m) = True Then
                End If
            End If
        End If
    End If
End If
If opt_PairedLungs.Value = False Then
    If opt_PairedLungs.Value = False Then
        If opt_breast = False Then
            If opt_HeadNeck = False Then
                If opt_Prostate = False Then
                    If opt_AVM = False Then
                        Resp1 = MsgBox("You must select the Organ Classification", vbExclamation)
                    End If
                End If
            End If
        End If
    End If
End If
If opt_PairedLungs.Value = True Then
    OrganClass = "Single Lung"
ElseIf opt_PairedLungs.Value = True Then
    OrganClass = "Paired Lungs"
ElseIf opt_breast = True Then
    OrganClass = "Breast"
ElseIf opt_HeadNeck = True Then
    OrganClass = "Head & Neck"
ElseIf opt_Prostate = True Then
    OrganClass = "Prostate"
ElseIf opt_AVM = True Then
    OrganClass = "AVM"
End If
End If
pic2.Visible = False
If opt_RelativeSeriality.Value = True Then
    cmd.Visible = True
    lb_msg.Caption = "You selected the Radiobiological Model: " & MRs & MLkb & MParl _
    & " For the Organ Class: " & OrganClass & Chr(13)
ElseIf opt_LKB.Value = True Then
    cmd.Visible = True
    lb_msg.Caption = "You selected the Radiobiological Model: " & MRs & MLkb & MParl _
End If
ElseIf opt_Parallel.Value = True Then
    cmd.Visible = True
    lb_msg.Caption = "You selected the Radiobiological Model: " & MRs & MLkb & MParl _
    & " For the Organ Class: " & OrganClass & Chr(13)
ElseIf opt_Other.Value = True Then
    cmd.Visible = True
    lb_msg.Caption = "You selected the Radiobiological Model: " & MRs & MLkb & MParl _
    & " For the Organ Class: " & OrganClass & Chr(13)
Else
    Resp = MsgBox("You must select a model", vbOKOnly + vbExclamation, "Confirmation")
End If
End Sub

Private Sub cmd_Click()
'Declaring Current as a worksheet object variable
Dim Current As Worksheet
Dim Response As Integer
Dim Response1 As Integer
'Dim Result As Integer

Response = MsgBox("Would you like to continue with the selected conditions and parameters?", vbYesNo + vbQuestion, "Confirmation")
If Response = vbNo Then
    MsgBox "Please select the desired conditions and parameters."
End If
If Response = vbYes Then
'Case vbOK
'End Select
    Frame10.Visible = False
    Drive1.Visible = False
    Dir1.Visible = False
    File1.Visible = False
    Command1.Visible = False
    Picture1.Visible = False
    Frame2.Visible = False
cb_confirm.Visible = False
    Frame3.Visible = False
    Frame1.Visible = False
    Frame7.Visible = False
    opt_PairedLungs.Visible = False
    opt_breast.Visible = False
    opt_HeadNeck.Visible = False
    opt_Prostate.Visible = False
    opt_AVM.Visible = False
    opt_RelativeSeriality.Visible = False
    opt_LKB.Visible = False
    opt_Parallel.Visible = False
    opt_Other.Visible = False
    Label1.Visible = False
    Label2.Visible = False
    Label3.Visible = False
    Label5.Visible = False
    Label6.Visible = False
txt_s.Visible = False
txt_gma.Visible = False
txt_D50.Visible = False
txt_n.Visible = False
txt_m.Visible = False
'CALCULATING THE NTCP FOR THE RELATIVE SERIALITY MODEL

' Loop through all of the worksheets in the active workbook.
If opt_RelativeSeriality.Value = True Then
For Each Current In Worksheets
Current.Activate

'CALCULATING THE PERCENTAGE OF VOLUME RECEIVING THE DOSE STATED.
Range("G10").Select
ActiveCell.Formula = "=(D10/$D$10)*100"
ActiveCell.FormulaR1C1 = "=(RC[-1]/R2C2)*100"
Selection.AutoFill Destination:=Range("G10:G249"), Type:=xlFillDefault
Range("G10").End(xlDown).Select

'CALCULATING THE DOSE RECEIVED BY EACH PERCENTAGE OF VOLUME.
Range("H10").Select
ActiveCell.Formula = "=(C10*$A$13)/100"
ActiveCell.FormulaR1C1 = "=(RC[-3]*R6C11)/100"
Selection.AutoFill Destination:=Range("H10:H249"), Type:=xlFillDefault
Range("H10").End(xlDown).Select

'CALCULATING dvi
'dvi = dVi/Vref is the fractional subvolume (or voxel) of the organ
'that is irradiated compared to the reference volume for which the
'values of D50 and GAMMA were calculated
Range("I10").Select
ActiveCell.Formula = "=(G10-G11)/100"
ActiveCell.FormulaR1C1 = "=(RC[-2]-R[1]C[-2])/100"
Selection.AutoFill Destination:=Range("I10:I249"), Type:=xlFillDefault
Range("I10").End(xlDown).Select
Range("A352").Select
ActiveCell.Value = Val(txt_D50)

'CALCULATING THE CORRECTED DOSE FOR FRACTIONATION
Range("J10").Select
ActiveCell.Formula = "=C10*(1+(C10/$A$15/3))/(5/3)"
ActiveCell.FormulaR1C1 = "=RC[-2]*(1+(RC[-2]/R8C11/3))/(5/3)"
Selection.AutoFill Destination:=Range("J10:J249"), Type:=xlFillDefault
Range("J10").End(xlDown).Select
Range("A351").Select
ActiveCell.Value = Val(txt_gma)

'CALCULATING P(Di) THE PROBABILITY OF INDUCING NORMAL TISSUE COMPLICATION FOR EACH VOXEL
Range("K10").Select
ActiveCell.Formula = "=EXP(-EXP((EXP(1)*$A$351)-($J10/$A$352)*(EXP(1)*$A$351-LN(LN(2)))))
Selection.AutoFill Destination:=Range("K10:K249"), Type:=xlFillDefault
Range("K10").End(xlDown).Select
Range("A350").Select
ActiveCell.Value = Val(txt_s)

'CALCULATING THE RESPONSE
Range("L10").Select
ActiveCell.Formula = "=(1-K10*$A$350)^I10"
Selection.AutoFill Destination:=Range("L10:L249"), Type:=xlFillDefault
Range("L10").End(xlDown).Select
'CALCULATING THE NTCP (NORMAL TISSUE COMPLICATION PROBABILITY)
Range("A253").Select
    ActiveCell.Formula = "=(1-Product(L10:L249))^(1/($A$350))"

'CALCULATING THE BEUD (Biological Effective Uniform Dose)
Range("c255").Select
    ActiveCell.Formula = "=$A$352*(EXP(1)*$A$351-LN(-LN($A$253)))/(EXP(1)*$A$351-LN(LN(2)))"

Next

Workbooks.Open FileName:= "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
ActiveSheet.Unprotect
ActiveWorkbook.Save
ActiveWindow.Close

Sheets.Add
"Sheets("Sheet1").Select
"ActiveSheet.Move
"    'Moves active sheet to end of active workbook.
"Sheets("Sheet1").Name = "Archive-RS"
"Range("A1").Select
"ActiveCell.FormulaR1C1 = "Hospital"
"Range("B1").Select
"ActiveCell.FormulaR1C1 = "Patient No."
"Range("C1").Select
"ActiveCell.FormulaR1C1 = "Lung Classification"
"Range("D1").Select
"ActiveCell.FormulaR1C1 = "Total Dose"
"Range("E1").Select
"ActiveCell.FormulaR1C1 = "No. of fractionations"
"Range("F1").Select
"ActiveCell.FormulaR1C1 = "NTCP - Relative Seriality"

For Each Current In Worksheets
    Current.Activate

'HOSPITAL
Range("A2").Select
Selection.Copy
Workbooks.Open FileName:= "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("A2").Select
Do Until IsEmpty(ActiveCell)
    ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close

Next
For Each Current In Worksheets
Current.Activate

'PATIENT NO.

Range("A11").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("B2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'LUNG CLASSIFICATION

Range("A4").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("C2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'TOTAL DOSE

Range("A13").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("D2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'NO. OF FRACTIONATIONS
Range("A15").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("E2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
Current.Activate
'NTCP - RELATIVE SERIALITY
Range("A253").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("F2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
Current.Activate
'BEUD - RELATIVE SERIALITY
Range("C255").Select
Selection.Copy
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("G2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
Workbooks.Open FileName:= _
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Relative Seriality").Select
Range("A1:F300").Sort Key1:=Range("F2"), Order1:=xlAscending, Header:= _
xlGuess, OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom, _
DataOption1:=xlSortNormal
ActiveSheet.Protect DrawingObjects:=True, Contents:=True, Scenarios:=True
ActiveWorkbook.Save
ActiveWindow.Close
AddIns("Analysis ToolPak").Installed = False
txt_plw.Visible = False
cmd.Visible = False
pic.Visible = False
pic3.Visible = True
lb_msg.Visible = False
Frame9.Visible = False
cmd_arch.Visible = True
Picture2.Visible = False
xlwbook.Save
Set xlsheet = Nothing
xlwbook.Close
Set xlwbook = Nothing
xlApp.Quit
Set xlApp = Nothing
Response1 = MsgBox("NTCP results can be viewed in the file 'Archive.xls'. The file can be accessed by clicking on the green button below.", vbOKOnly + vbInformation, "Confirmation")
'If Response1 = vbYes Then
  RunProgram = "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
  Result = Shell(RunProgram, vbNormalFocus)
'End If
'Shell("C:\Program Files\NTCP-Calculation_Pod\Archive.xls", vbNormalFocus)
'End If
'MsgBox "NTCP results are stored for viewing in the file 'Archive.xls'", vbOKOnly + vbInformation
'MsgBox "A more detailed view of the data can be found in the file 'PatientTherapyDetailsForm.xls'", vbOKOnly + vbInformation
"Workbooks.Open FileName:="C:\Documents and Settings\Yiannis\Desktop\Adaptation\Archive1.xls"
"Workbooks("Archive1.xls").Worksheets("Sheet1").Activate
'Looping through the archive to place in a new set of results
'HOSPITAL NAME
"Range("a1")\Select
'Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
'Loop
"ActiveCell.Value = txt_hospital.Text

PATIENT NUMBER

"Range("B1")\Select
'Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
'Loop
"ActiveCell.Value = txt_patient.Text

RADIOBIOLOGICAL MODEL

"Range("C1")\Select
'Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
"If ck_RelativeSeriality.Value = 1 Then
   ActiveCell.Value = "Relative Seriality"
"ElseIf ck_LKB.Value = 1 Then
   ActiveCell.Value = "LKB"
"ElseIf ck_Parallel.Value = 1 Then
   ActiveCell.Value = "Parallel"
"End If

'PARAMETER SET

'Range("D1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'If opt_Seepenwoolde.Value = True Then
   ActiveCell.Value = "Seepenwoolde et al"
 'ElseIf opt_Gagliardi.Value = True Then
 '   ActiveCell.Value = "Gagliardi et al"
 'ElseIf opt_Mah.Value = True Then
 '   ActiveCell.Value = "Mah et al"
 'ElseIf opt_New.Value = True Then
 '   ActiveCell.Value = "New"
'End If

'LUNG CLASSIFICATION

"Range("D1").Select
"Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
"If opt_SingleLung.Value = True Then
   ActiveCell.Value = "Single Lung"
"ElseIf opt_PairedLungs.Value = True Then
   ActiveCell.Value = "Paired Lungs"
"End If

'Normal Tissue Complication Probability (NTCP) value

"Range("E1").Select
"Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
ActiveCell.Value = Val(txt_NTCP)

'Workbooks.Close

ElseIf opt_LKB.Value = True Then

.................................................................

'CALCULATING THE NTCP FOR THE LKB MODEL

.................................................................

For Each Current In Worksheets
Current.Activate

'CALCULATING THE PERCENTAGE OF VOLUME RECEIVING THE DOSE STATED.
Range("G10").Select
ActiveCell.Formula = "=(D10/$D$10)*100"
'ActiveCell.FormulaR1C1 = "=(RC[-1]/R2C2)*100"
Selection.AutoFill Destination:=Range("G10:G249"), Type:=xlFillDefault
Range("G10").End(xlDown).Select
CALCULATING THE DOSE RECEIVED BY EACH PERCENTAGE OF VOLUME.

Range("H10").Select
ActiveCell.Formula = ".=(C10*$A$13)/100"
ActiveCell.FormulaR1C1 = ".=(RC[-3]*R6C11)/100"
Selection.AutoFill Destination:=Range("H10:H249"), Type:=xlFillDefault
Range("H10").End(xlDown).Select

CALCULATING dvi

dvi = dVi/Vref is the fractional subvolume (or voxel) of the organ
that is irradiated compared to the reference volume for which the
values of D50 and GAMMA were calculated

Range("I10").Select
ActiveCell.Formula = ".=(G10-G11)/100"
ActiveCell.FormulaR1C1 = ".=(RC[-2]-R[1]C[-2])/100"
Selection.AutoFill Destination:=Range("I10:I249"), Type:=xlFillDefault
Range("I10").End(xlDown).Select

CALCULATING THE CORRECTED DOSE FOR FRACTIONATION

Range("J10").Select
ActiveCell.Formula = ".=C10*(1+(C10/$A$15/3))/(5/3)"
ActiveCell.FormulaR1C1 = ".=RC[-2]*(1+(RC[-2]/R8C11/3))/(5/3)"
Selection.AutoFill Destination:=Range("J10:J249"), Type:=xlFillDefault
Range("J10").End(xlDown).Select

CALCULATING Vi/Vtot

Range("M10").Select
ActiveCell.Formula = ".=(G10/100)"
Selection.AutoFill Destination:=Range("M10:M249"), Type:=xlFillDefault
Range("M10").End(xlDown).Select
ActiveCell.Value = Val(txt_D50)

CALCULATING viDi^1/n

Range("N10").Select
ActiveCell.Formula = ".=(110/$M$10)*((J10^((1/$A$353)))"n
Selection.AutoFill Destination:=Range("N10:N249"), Type:=xlFillDefault
Range("N10").End(xlDown).Select
ActiveCell.Value = Val(txt_n)

CALCULATING EUD

Range("C257").Select
ActiveCell.Formula = "SUM(N10:N300)^$A$353"

CALCULATING t

Range("E255").Select
ActiveCell.Formula = "=(C$257-$A$352)/($A$354*$A$352)"
ActiveCell.Copy
ActiveCell.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False

'Erf function

If Range("E255"),.Value < 0 Then
Range("E257").Select
ActiveCell.Formula = "=0.5*(1+ERF(-E255/SQRT(2)))"
Else
Range("E257").Select
ActiveCell.Formula = "=0.5*(1+ERF((E255)/SQRT(2)))"
End If
'CALCULATING ERF FUNCTION
"Range("E257")".Select
"If Range("E255")".Value < 0 Then
"" ActiveCell.Formula = "+.5*(1+ERF(-E255/SQRT(2)))"
"Else
"" ActiveCell.Formula = "+.5*(1+ERF((E255)/SQRT(2)))"
"End If

'CALCULATING NTCP
Range("A256")".Select
If Range("E255")".Value < 0 Then
 ActiveCell.Formula = "+1-E257"
Else
 ActiveCell.Formula = "=E257"
End If

Next

Workbooks.Open FileName:= 
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB")".Select
ActiveSheet.Unprotect
ActiveWorkbook.Save
ActiveWindow.Close

For Each Current In Worksheets
Current.Activate

'HOSPITAL
Range("A2")".Select
Selection.Copy
Workbooks.Open FileName:= 
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB")".Select
Range("A2")".Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'PATIENT NO.
Range("A11")".Select
Selection.Copy
Workbooks.Open FileName:= 
"C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB")".Select
Range("B2")".Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
   :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
Current.Activate

'LUNG CLASSIFICATION

Range("A4").Select
Selection.Copy
Workbooks.Open FileName:="C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB").Select
Range("C2").Select
Do Until IsEmpty(ActiveCell)
   ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
   :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
Current.Activate

'TOTAL DOSE

Range("A13").Select
Selection.Copy
Workbooks.Open FileName:="C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB").Select
Range("D2").Select
Do Until IsEmpty(ActiveCell)
   ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
   :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
Current.Activate

'NO. OF FRACTIONATIONS

Range("A15").Select
Selection.Copy
Workbooks.Open FileName:="C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-LKB").Select
Range("E2").Select
Do Until IsEmpty(ActiveCell)
   ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'NTCP - LKB

Range("A256").Select
Selection.Copy
Workbooks.Open FileName:= "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Worksheets("NTCP-LKB").Select
Range("F2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
Current.Activate

'EUD - LKB

Range("C257").Select
Selection.Copy
Workbooks.Open FileName:= "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Worksheets("NTCP-LKB").Select
Range("G2").Select
Do Until IsEmpty(ActiveCell)
ActiveCell.Offset(1, 0).Select
Loop
ActiveWorkbook.Save
ActiveWindow.Close

Next

Workbooks.Open FileName:= "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Worksheets("NTCP-LKB").Select
Range("A1").Select
   Range("A1:F300").Sort Key1:=Range("F2"), Order1:=xlAscending, Header:= _
   xlGuess, OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom, _
   DataOption1:=xlSortNormal
ActiveSheet.Protect DrawingObjects:=True, Contents:=True, Scenarios:=True
ActiveWorkbook.Save
ActiveWindow.Close

AddIns("Analysis ToolPak").Installed = False

txt_plw.Visible = False
cmd.Visible = False
pic.Visible = False
pic3.Visible = True
lb_msg.Visible = False
Frame9.Visible = False
cmd_arch.Visible = True
Picture2.Visible = False

xlwbook.Save
Set xlsheet = Nothing
xlwbook.Close
Set xlwbook = Nothing
xlApp.Quit
Set xlApp = Nothing

Response1 = MsgBox("NTCP results can be viewed in the file 'Archive.xls'. The file can be accessed by clicking on the green button below.", vbOKOnly + vbInformation, "Confirmation")

' MsgBox "NTCP results are stored for viewing in the file 'Archive.xls'", vbOKOnly + vbInformation
'MsgBox "A more detailed view of the data can be found in the file 'PatientTherapyDetailsForm.xls'", vbOKOnly + vbInformation

"Workbooks.Open FileName:=""C:\Documents and Settings\Yiannis\Desktop\Adaptation\Archive1.xls"

"Workbooks("Archive1.xls").Worksheets("Sheet1").Activate

' Looping through the archive to place in a new set of results

'HOSPITAL NAME

"Range("a1").Select
"Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
"ActiveCell.Value = txt_hospital.Text

'PATIENT NUMBER

"Range("B1").Select
"Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
"ActiveCell.Value = "+A11"

'RADIOBIOLOGICAL MODEL

"Range("C1").Select
"Do Until IsEmpty(ActiveCell)
"ActiveCell.Offset(1, 0).Select
"Loop
"If ck_RelativeSeriality.Value = 1 Then
"   ActiveCell.Value = "Relative Seriality"
"ElseIf ck_LKB.Value = 1 Then
"   ActiveCell.Value = "+LKB"
"ElseIf ck_Parallel.Value = 1 Then
"   ActiveCell.Value = "Parallel"
"End If

'PARAMETER SET

'Range("D1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'If opt_Seepeenwoolde.Value = True Then
"   ActiveCell.Value = "Seepeenwoolde et al"
ElseIf opt_Gagliardi.Value = True Then
  ActiveCell.Value = "Gagliardi et al"
ElseIf opt_Mah.Value = True Then
  ActiveCell.Value = "Mah et al"
ElseIf opt_New.Value = True Then
  ActiveCell.Value = "New"
End If

LUNG CLASSIFICATION

Range("D1").Select
Do Until IsEmpty(ActiveCell)
  ActiveCell.Offset(1, 0).Select
  Loop

If opt_SingleLung.Value = True Then
  ActiveCell.Value = "Single Lung"
ElseIf opt_PairedLungs.Value = True Then
  ActiveCell.Value = "Paired Lungs"
End If

Normal Tissue Complication Probability (NTCP) value

Range("E1").Select
Do Until IsEmpty(ActiveCell)
  ActiveCell.Offset(1, 0).Select
  Loop
  ActiveCell.Value = "+=A259"

Workbooks.Close
ElseIf opt_Parallel.Value = True Then

\'CALCULATING THE NTCP FOR THE PARALLEL MODEL\'

For Each Current In Worksheets
  Current.Activate
  \'CALCULATING THE PERCENTAGE OF VOLUME RECEIVING THE DOSE STATED.\'
  Range("G10").Select
  ActiveCell.Formula = "+(D10/$D$10)*100"
  ActiveCell.FormulaR1C1 = "+(RC[-1]/R2C2)*100"
  Selection.AutoFill Destination:=Range("G10:G249"), Type:=xlFillDefault
  Range("G10").End(xlDown).Select

  \'CALCULATING THE DOSE RECEIVED BY EACH PERCENTAGE OF VOLUME.\'
  Range("H10").Select
  ActiveCell.Formula = "+(C10*$A$13)/100"
  ActiveCell.FormulaR1C1 = "+(RC[-3]*R6C11)/100"
  Selection.AutoFill Destination:=Range("H10:H249"), Type:=xlFillDefault
  Range("H10").End(xlDown).Select

  \'CALCULATING dvi\'
  dvi = dVi/Vref is the fractional subvolume (or voxel) of the organ
  that is irradiated compared to the reference volume for which the
  values of D50 and GAMMA were calculated
  Range("I10").Select
  ActiveCell.Formula = "+(G10-G11)/100"
  ActiveCell.FormulaR1C1 = "+(RC[-2]-R[1]C[-2])/100"
  Selection.AutoFill Destination:=Range("I10:I249"), Type:=xlFillDefault
  Range("I10").End(xlDown).Select
  Range("A352").Select
  ActiveCell.Value = Val(txt_D50)
CALCULATING THE CORRECTED DOSE FOR FRACTIONATION

Range("J10").Select
ActiveCell.Formula = "+C10*(1+(C10/$A$15/3))/(5/3)"
ActiveCell.FormulaR1C1 = "=RC[-2]*(1+(RC[-2]/R8C11/3))/(5/3)"
Selection.AutoFill Destination:=Range("J10:J249"), Type:=xlFillDefault
Range("J10").End(xlDown).Select

CALCULATING Vi/Vtot
Range("M10").Select
ActiveCell.Formula = "+(G10/100)"
Selection.AutoFill Destination:=Range("M10:M249"), Type:=xlFillDefault
Range("M10").End(xlDown).Select
ActiveCell.Value = Val(txt_n)

CALCULATING D50/Di
Range("O10").Select
ActiveCell.Formula = "+IF(J10=0,0,$A$352/J10)"
Selection.AutoFill Destination:=Range("O10:O249"), Type:=xlFillDefault
Range("O10").End(xlDown).Select
ActiveCell.Value = Val(txt_m)

CALCULATING (1/(1+(D50/Di)*(1/n)))*dvi/Vtot
Range("P10").Select
ActiveCell.Formula = "+(1/(1+(O10)*(1/$A$353)))*I10"
Selection.AutoFill Destination:=Range("P10:P249"), Type:=xlFillDefault
Range("P10").End(xlDown).Select

CALCULATION STEP 1
Range("G255").Select
ActiveCell.Formula = "+SUM(P10:P249)"

CALCULATION STEP 2
Range("G257").Select
ActiveCell.Formula = "+G255^-1"

CALCULATION STEP 3
Range("G259").Select
ActiveCell.Formula = "+G257-1"

CALCULATION STEP 4
Range("G261").Select
ActiveCell.Formula = "+G259^((1/(1/$A$353)))"

CALCULATING EUD
Range("C259").Select
ActiveCell.Formula = "+A352*G261"

CALCULATING t
Range("D255").Select
ActiveCell.Formula = "=(C$259-$A$352)/($A$354*$A$352)"
ActiveCell.Copy

ERF function
If Range("D255").Value < 0 Then
Range("D257").Select
ActiveCell.Formula = "+0.5*(1+ERF(-D255/SQRT(2)))"
Else
Range("D257").Select
ActiveCell.Formula = "+0.5*(1+ERF((D255)/SQRT(2)))"
End If

CALCULATING ERF FUNCTION
Range("D257").Select
If Range("D255").Value < 0 Then
  ActiveCell.Formula = "=0.5*(1+ERF(-D255/SQRT(2)))"
Else
  ActiveCell.Formula = "=0.5*(1+ERF((D255)/SQRT(2)))"
End If

'CALCULATING NTCP
Range("A259").Select
If Range("D255").Value < 0 Then
  ActiveCell.Formula = "=1-D257"
Else
  ActiveCell.Formula = "=D257"
End If

If Range("A259").Value > 0.5 Then
  MsgBox "High Normal Tissue Complication Probability", vbOKOnly + vbInformation
ElseIf Range("A259").Value < 0.5 Then
  MsgBox "Low Normal Tissue Complication Probability", vbOKOnly + vbInformation
End If

Next

Workbooks.Open FileName:= _
  "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
ActiveSheet.Unprotect
ActiveWorkbook.Save
ActiveWindow.Close

For Each Current In Worksheets
  Current.Activate

'HOSPITAL
Range("A2").Select
Selection.Copy
Workbooks.Open FileName:= _
  "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
Range("A2").Select
Do Until IsEmpty(ActiveCell)
  ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
  :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close

Next

For Each Current In Worksheets
  Current.Activate

'PATIENT NO.
Range("A11").Select
Selection.Copy
Workbooks.Open FileName:= _
  "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
Range("B2").Select
Do Until IsEmpty(ActiveCell)
    ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
    :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next
For Each Current In Worksheets
    Current.Activate
    'LUNG CLASSIFICATION
    Range("A4").Select
    Selection.Copy
    Workbooks.Open FileName:= _
        "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
    Sheets("NTCP-Parallel").Select
    Range("C2").Select
    Do Until IsEmpty(ActiveCell)
        ActiveCell.Offset(1, 0).Select
    Loop
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
    ActiveWorkbook.Save
    ActiveWindow.Close
Next
For Each Current In Worksheets
    Current.Activate
    'TOTAL DOSE
    Range("A13").Select
    Selection.Copy
    Workbooks.Open FileName:= _
        "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
    Sheets("NTCP-Parallel").Select
    Range("D2").Select
    Do Until IsEmpty(ActiveCell)
        ActiveCell.Offset(1, 0).Select
    Loop
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
    ActiveWorkbook.Save
    ActiveWindow.Close
Next
For Each Current In Worksheets
    Current.Activate
    'NO. OF FRACTIONATIONS
    Range("A15").Select
    Selection.Copy
    Workbooks.Open FileName:= _
        "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
    Sheets("NTCP-Parallel").Select
    Range("E2").Select
    Do Until IsEmpty(ActiveCell)
        ActiveCell.Offset(1, 0).Select
Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
:=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next

For Each Current In Worksheets
Current.Activate

'NTCP - PARALLEL

Range("A259").Select
Selection.Copy
Workbooks.Open FileName:= _
   "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
Range("F2").Select
Do Until IsEmpty(ActiveCell)
   ActiveCell.Offset(1, 0).Select
   Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
   :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next

For Each Current In Worksheets
Current.Activate

'EUD - PARALLEL

Range("C259").Select
Selection.Copy
Workbooks.Open FileName:= _
   "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
Range("G2").Select
Do Until IsEmpty(ActiveCell)
   ActiveCell.Offset(1, 0).Select
   Loop
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
   :=False, Transpose:=False
ActiveWorkbook.Save
ActiveWindow.Close
Next

Workbooks.Open FileName:= _
   "C:\Program Files\NTCP-Calculation_Pod\Archive.xls"
Sheets("NTCP-Parallel").Select
Range("A1:G300").Sort Key1:={Range("F2"), Order1:=xlAscending, Header:= _
   xlGuess, OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom, _
   DataOption1:=xlSortNormal
ActiveSheet.Protect DrawingObjects:=True, Contents:=True, Scenarios:=True
ActiveWorkbook.Save
ActiveWindow.Close

AddIns("Analysis ToolPak").Installed = False

txt_plw.Visible = False
cmd.Visible = False
pic.Visible = False
Response1 = MsgBox("NTCP results can be viewed in the file 'Archive.xls'. The file can be accessed by clicking on the green button below.", vbOKOnly + vbInformation, "Confirmation")

'MsgBox "NTCP results are stored for viewing in the file 'Archive.xls'", vbOKOnly + vbInformation
'MsgBox "A more detailed view of the data can be found in the file 'PatientTherapyDetailsForm.xls'", vbOKOnly + vbInformation

"Workbooks.Open FileName:=""C:\Documents and Settings\Yiannis\Desktop\Adaptation\Archive1.xls"

"Workbooks("Archive1.xls").Worksheets("Sheet1").Activate

'Looping through the archive to place in a new set of results

'HOSPITAL NAME

"Range("a1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'ActiveCell.Value = txt_hospital.Text

'PATIENT NUMBER

"Range("B1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'ActiveCell.Value = txt_patient.Text

'RADIOBIOLOGICAL MODEL

"Range("C1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'If ck_RelativeSeriality.Value = 1 Then
'  ActiveCell.Value = "Relative Seriality"
'ElseIf ck_LKB.Value = 1 Then
'  ActiveCell.Value = "LKB"
'ElseIf ck_Parallel.Value = 1 Then
'  ActiveCell.Value = "Parallel"
'End If

'PARAMETER SET

'Range("D1").Select
'Do Until IsEmpty(ActiveCell)
'ActiveCell.Offset(1, 0).Select
'Loop
'If opt_Seenenwoolde.Value = True Then
ActiveCell.Value = "Seepenwoolde et al"
ElseIf opt_Gagliardi.Value = True Then
  ActiveCell.Value = "Gagliardi et al"
ElseIf opt_Mah.Value = True Then
  ActiveCell.Value = "Mah et al"
ElseIf opt_New.Value = True Then
  ActiveCell.Value = "New"
End If

' LUNG CLASSIFICATION

Range("D1").Select
Do Until IsEmpty(ActiveCell)
  ActiveCell.Offset(1, 0).Select
  Loop

If opt_SingleLung.Value = True Then
  ActiveCell.Value = "Single Lung"
ElseIf opt_PairedLungs.Value = True Then
  ActiveCell.Value = "Paired Lungs"
End If

' Normal Tissue Complication Probability (NTCP) value

Range("E1").Select
Do Until IsEmpty(ActiveCell)
  ActiveCell.Offset(1, 0).Select
  Loop
  ActiveCell.Value = Val(txt_NTCP)
End If
End If
End Sub

Private Sub cb_exit_Click()
If pic3.Visible = True Then
  Unload Me
ElseIf txt_hospital.Text = "" Then
  Unload Me
Else

  AddIns("Analysis ToolPak").Installed = False
  xlwbook.Save
  DoEvents
  Set ExcelWorksheet = Nothing
  xlwbook.Close
  Set xlwbook = Nothing
  xlApp.Quit
  Set xlApp = Nothing
  Unload Me
ElseIf pic3.Visible = True Then
  Unload Me
ElseIf txt_hospital.Text = "" Then
  Unload Me
Else
  AddIns("Analysis ToolPak").Installed = False
  xlwbook.Save
  DoEvents
  Set ExcelWorksheet = Nothing
  xlwbook.Close
  Set xlwbook = Nothing
  xlApp.Quit
  Set xlApp = Nothing
  Unload Me
End If
End Sub

'Shell "C:\Program Files\Internet Explorer\IEEXPLORE.EXE", vbNormalFocus