

**NPL REPORT IEA 1**

**ESTIMATING THE IMPACT OF IMPROVED DOSE CONTROL ON  
CLINICAL OUTCOMES IN RADIOTHERAPY**

**DR MIKE KING, EUGENIO RENEDO**

**OCTOBER 2019**



## Estimating the impact of improved dose control on clinical outcomes in radiotherapy

Dr Mike King; Eugenio Renedo  
Analysis and Evaluation, Strategy Directorate

### ABSTRACT

The following case study analyses one of the channels through which the National Physical Laboratory (NPL) contributes positively to cancer treatment by radiation therapy in the UK. It applies well-established radiobiological models to show the positive effect of radiotherapy dose audit for better accuracy in radiation dose delivery. Its objective is to estimate the number of prostate cancer patients who would have received an incorrect dose because of the radiation machine not being in specification had the dosimetry programme by NPL not been carried out. The study finds that the joint efforts of NPL and physicists in the radiotherapy community have led to a gradual increase in successful treatments. At the end of the 20-year period analysed, it is estimated that 15 additional prostate cancer patients were treated successfully each year.

© NPL Management Limited, 2019

ISSN 2633-4194

National Physical Laboratory  
Hampton Road, Teddington, Middlesex, TW11 0LW

Extracts from this report may be reproduced provided the source is acknowledged  
and the extract is not taken out of context.

Approved on behalf of NPLML by  
Fiona Auty, Head of Government Relations.

CONTENTS

- 1. EXECUTIVE SUMMARY .....1
- 2. RADIATION THERAPY FOR CANCER TREATMENT IN THE UK .....3
- 3. RADIOBOLOGICAL MODELLING .....4
  - A. TUMOUR CONTROL PROBABILITY: THE LINEAR QUADRATIC MODEL.....5
  - B. NORMAL TISSUE COMPLICATION PROBABILITY: THE LYMAN-KUTCHER-BURMAN MODEL .....7
- 4. RADIATION THERAPY IMPROVEMENTS IN PROSTATE CANCER TREATMENT.....10
- 5. CONCLUSION .....13
- 6. REFERENCES.....13



## PREFACE

This paper has been prepared by NPL's Analysis and Evaluation team to support the evidence NPL is submitting for the 2019 Comprehensive Spending Review. Hence, this document is mainly for analysts and policy makers at The Department for Business, Energy & Industrial Strategy. Its objective is to support the case that NPL is presenting to evidence the quality-of-life benefits generated by its public funding.

The goal of this report is to provide evidence of the importance of delivering accurate doses of radiation to cancer patients. The analysis focuses on one of the most widespread types of cancer among the UK population: prostate cancer. In order to show the impact of a reduction in the uncertainty of the dose administered to prostate cancer patients, two commonly used radiobiological models are combined to approximate the increase in the probability of both controlling the tumour and not causing significant side effects.

The logic model in the NMS evaluation framework provides a stylised representation of how NPL's activity leads to economic and social impacts in each of the themes featured in the NMS strategy (BEIS 2017). This report is focused on the second part of the logic model, showing outcomes and impacts derived from NPL's collaborative work with other organisations in the UK. The 'inputs', 'activities', and 'outputs' needed to achieve these outcomes is mainly beyond the scope of this paper. Also, it should be noted that the analysis only deals with NPL's collaborative work with the NHS. NPL's support to government departments or academic institutions, as well as, the private sector, does not feature in this case study.



## 1. EXECUTIVE SUMMARY

The National Physical Laboratory (NPL) provides the infrastructure and specialist knowledge that is the basis and the confirmation of accurate radiation dose delivery in the UK. Therefore, NPL helps to ensure the safe and effective delivery of radiotherapy in collaboration with radiation physicists and oncologists in hospitals. The goal of this work is to evidence the positive impact of accurate radiation delivery. The analysis focuses on one of the most widespread types of cancer among the UK population: prostate cancer.

In order to show the impact of a reduction in the uncertainty of the dose administered to prostate cancer patients, two commonly used radiobiological models are combined to approximate the increase in the probability of both controlling the tumour and not causing significant side effects. The study finds that the joint efforts of NPL and radiation physicists and oncologists have led to 15 additional patients treated successfully each year.

Although the goal of this work is to illustrate the positive impact of this reduction in dose delivery uncertainty on patients treated in the UK, accounting for the benefits that this activity has had for all cancer patients treated with radiation is extremely complex because there are many specific variables that influence each type of cancer. Hence, this work only analyses the effect on prostate cancer. The objective is to show the intuition behind the mechanism through which this benefit for UK society has occurred, and not to provide a precise overall impact figure. It would be unwise and misleading to generalize the quantifications obtained for prostate cancer to other types of cancer.

Ultimately, this study provides a rationale of how better measurement generates value for the UK society through healthcare improvements. Moreover, this work could be considered as an application of a general mechanism through which NPL brings benefits to many sectors in the economy such as manufacturing or defence.

In any situation where the process of production and/or supply of a good requires the optimization of a physical quantity around a target value, better measurement can contribute to generate better results, which ultimately translate into efficiency gains. For example, temperature has a huge impact on the operation of complex mechanical apparatus such as aircraft engines. Heat generated when converting fuel to energy must be kept below a certain threshold through cooling systems, since any excess of heat could damage the engine. On the other hand, if the outside temperature is too low, cold may cause the engine to malfunction. This is because lubricants lose their viscosity creating friction and wear issues for moving parts. Therefore, better measurement of the temperature inside the engine can help manufacturers to develop safer and more durable engines.

**The paper is organised as follows:**

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Section 2</b> | This section presents some figures about the problem of cancer in the UK, how radiation therapy plays a fundamental role in its treatment, and the paramount contribution made by NPL and radiation physicists and oncologists to keep improving successful treatment rates.                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Section 3</b> | <p>This section details the two radiobiological models used as theoretical framework.</p> <ul style="list-style-type: none"><li>▪ The first model is the linear quadratic (LQ) tumour control probability (TCP) Poisson model, which approximates the probability of controlling the disease.</li><li>▪ The second model is the Lyman-Kutcher-Burman (LKB) normal tissue complication probability (NTCP) model, which describes the probability of unwittingly causing major side effects.</li></ul>                                                                                                                                                                       |
| <b>Section 4</b> | This section provides an estimate of the number of prostate cancer patients who have benefited from the greater calibration accuracy of radiation machines in the UK. To do so, the two radiobiological models are combined to generate a curve that shows the probability of controlling the tumour without the patient developing grade 2 rectal bleeding within 5 years. This curve is then used to approximate the number of patients for whom the improvement of the precision in the dose of radiation delivered has resulted in a satisfactory outcome that would have not occurred without the collaboration between NPL and radiation physicists in UK hospitals. |
| <b>Section 5</b> | Concludes the report.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

## 2. RADIATION THERAPY FOR CANCER TREATMENT IN THE UK

Cancer is one of the big challenges for the UK. One in two people born after 1960 will suffer from some type of cancer during their lifetime. More than 360,000 new cases of cancer are diagnosed each year in the UK (Cancer Research UK 2016). Cancer is projected to rise by 2% annually between 2014 and 2035, up to 742 cases per 100,000 people by 2035 (Smittenaar, et al. 2016).

Radiation therapy is one of the most effective treatments for cancer. In fact, 50% of all cancer patients would benefit from receiving radiation therapy as part of their cancer treatment (The Society of Radiographers 2019), whereas 40% currently receive it. The radiotherapy community (healthcare professionals, hospitals, the NHS and suppliers of radiation equipment among others) works conscientiously with the objective of continuously improving radiotherapeutic treatments. Consequently, the chances of survival and the quality of life of patients has increased significantly over the last decades.

Each member of the radiation therapy community has played an essential role in this successful journey for radiotherapy in the UK; and the National Measurement System (NMS) is no exception. Indeed, the safety and effectiveness of existing and new forms of radiotherapy relies on the NMS. The NMS, through the National Physical Laboratory (NPL), provides the measurement infrastructure and specialist knowledge that is the basis of accurate radiation dose. This helps to ensure the safe and effective delivery of radiotherapy in collaboration with UK radiation physicists and oncologists.

At the most basic level, radiotherapy can be thought to have the effect of killing human body cells. This includes both cancer cells and healthy ones. Hence, the success of radiotherapy depends critically on the certainty around the treatment. If the dose is not appropriate or it is not focused on the target volume, the cancer may continue to grow, and/or healthy tissue could be damaged producing life-changing side effects. In the clinical situation, there are several sources of uncertainty. These include the initial calibration and the maintenance of the radiation machines, as well as uncertainties around organ content, hydration levels and patient positioning during the radiation treatment.

NPL collaborates closely with the radiation therapy community to reduce all these sources of uncertainty by underpinning the calibration of each radiation machine in the UK, checking periodically the specification of the equipment, supporting the development of clinical codes of practice (Lillicrap, et al. 1990), as well as making measurements of end-to-end accuracy, from initial scans, through treatment planning, to treatment delivery.

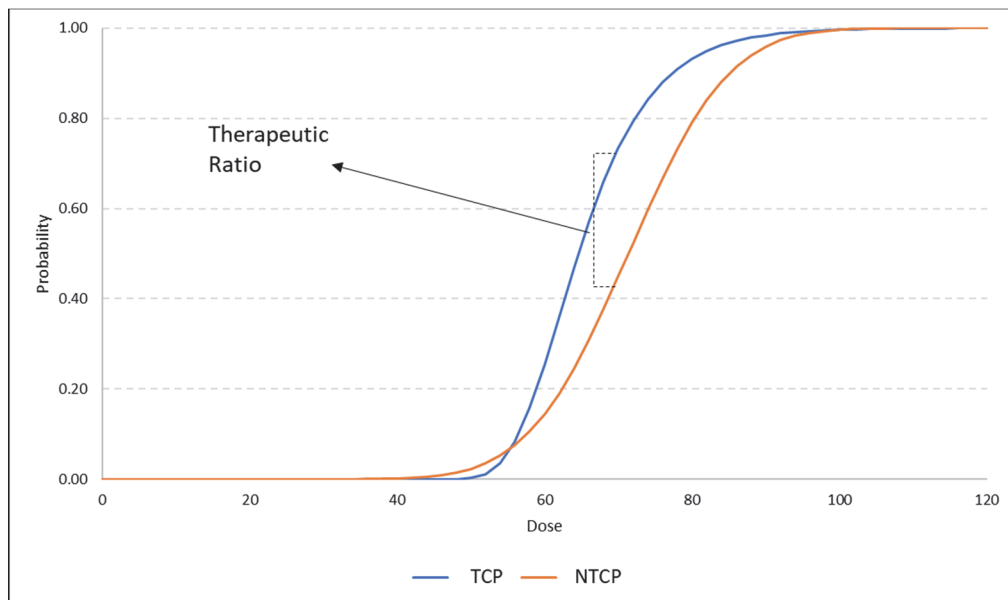
This collaboration between NPL and healthcare professionals has derived significant benefits for patients treated with radiation over recent times. One of the key areas where this collaboration has been successful is the calibration and audit of radiation machines in UK hospitals. In fact, NPL has conducted regular dosimetry audits over a 20-year period (Clark, et al. 2015) that show that the calibrated dose variation between radiotherapy centres has reduced over this time from 0.8% to 0.4% (Thomas, et al. 2017). NPL end-to-end treatment verification services have provided UK centres with confidence in the delivery of new techniques such as Stereotactic Ablative Body Radiotherapy (SABR) for Non-Small-Cell Lung Cancer and Stereotactic Cranial Radiosurgery (SRS) – a specialist form of radiotherapy that can be used to treat patients with intracranial conditions and for both benign and malignant brain tumours. These national audits have highlighted and resolved issues with inconsistencies in implementation that have resulted in significantly reduced variation in the dose delivered to the patient. This end-to-end testing has ensured that these new techniques have been implemented consistently thus raising standards nationally.

### 3. RADIOBIOLOGICAL MODELLING

Radiobiological modelling aims to predict the clinical effect of radiation therapy. Its goal is to explore the relation between variables associated with the treatment, such as the delivered dose or the size of the tumour, and the outcome variables, mainly cure and complication rates. Since the objective of any radiation therapy treatment is to cure the disease whilst minimising any side effect, radiobiological models have to account for both factors:

- The probability of controlling the tumour progression is known as *tumour control probability* (TCP).
- The probability of adverse effects affecting the surrounding normal tissue is known as *normal tissue complication probability* (NTCP).

Both factors can be represented by dose-response curves (generally sigmoid in shape) that describe the effect of different doses on the treatment outcome. The vertical difference between the TCP and the NTCP, known as the *therapeutic ratio* (TR), constitutes a measure of the likelihood of a satisfactory outcome of the treatment. A basic schematic of the modelling curves is given by the following figure:



In this work we utilise the commonly used linear quadratic (LQ) TCP model, and the Lyman-Kutcher-Burman (LKB) NTCP model.

## A. TUMOUR CONTROL PROBABILITY: THE LINEAR QUADRATIC MODEL

When radiation is delivered to the affected organ, *free radicals*<sup>1</sup> are produced in the cell nucleus. This leads to structural damage to the DNA, causing the cell to be unable to replicate successfully. This DNA damage has been shown to be the primary cause of radiation-induced cell death (Joiner and Van der Kogel 2016). A popular method to model the survival fraction of cells in the irradiated tissue is the *linear quadratic* (LQ) model (American Association of Physicists in Medicine 2012). The LQ model is a mechanistic biophysical model widely used in radiation therapy planning which quantifies the effects of radiation-induced damage at the cellular level (Dale and Jones 2007). The LQ model approximates the survival fraction of cells,  $S$ , by the following function of the dose delivered,  $D$ :

$$S = e^{(-\alpha D - \beta D^2)} \quad (1)$$

where  $\alpha$  and  $\beta$  are the coefficients of the linear and quadratic components respectively. However, in the clinical situation the dose is not delivered all at once. If we assume that the total dose is administered in  $n$  different sessions of equivalent doses,  $d$ , we get:

$$S = e^{(-\alpha d - \beta d^2)n} \quad (2)$$

As previously mentioned, radiation-induced cell death has been conclusively linked to DNA damage, specifically to DNA double-strand breaks<sup>2</sup> (DSB) (Sachs, Hlatky and Hahnfeldt 2001). In the previous formulation of the LQ model, the  $\alpha$  component is associated with single-strand breaks (SSBs) and the  $\beta$  component to DSBs. For higher doses, DSBs become more probable, and so the  $\beta$  component of the model becomes dominant. In any case, the process of cell survival is governed by the values of  $\alpha$  and  $\beta$  which depend on the type of cancer and the organ affected. For prostate cancer, which is the clinical case that we analyse in this work, these two parameters have been taken from Bolt (2018) ( $\alpha = 0.08 \text{ Gy}^{-1}$  and  $\beta = 0.04 \text{ Gy}^{-2}$ )<sup>3</sup>.

The LQ model finds the proportion of cells (both healthy and cancer cells) which survive the radiation treatment. However, just by itself, the LQ model tells us nothing about the tumour control probability (TCP). To model this probability, the vast majority of mechanistic models assume that the number of surviving clonogenic cells, i.e., cells capable of regrowing the tumour, follow the Poisson distribution<sup>4</sup> (Munro and Gilbert 1961):

$$P(k) = e^{-N_0} \frac{N_0^k}{k!} \quad (3)$$

where  $P(k)$  is the probability of  $k$  clonogenic cells remaining from the initial number of cancer cells irradiated,  $N_0$ .

---

1 A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron. As the formation of electron pairs is often energetically favourable, unpaired electrons are relatively uncommon in chemistry. Any chemical entity that carries an unpaired electron is usually rather reactive. Hence, free radicals can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants.

2 A double-strand DNA break occurs when both chains of the double helix structure are severed.

3 The gray, represented by the symbol 'Gy' is a derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.

4 The Poisson distribution is a discrete probability distribution that expresses the probability of a given number of events occurring in a fixed interval of time or space if these events occur with a known constant rate and independently of the time since the last event.

In addition, a unicellular hypothesis is invoked. This means that it is assumed that a single surviving clonogen is sufficient to regrow the tumour. Hence, we require for no clonogenic cells to survive the treatment, that is,  $k$  must be equal to zero in (3). Lastly, given that the average number of surviving clonogens is given by  $N_0 S$ , where  $S$  is given by (2), the probability of tumour control is then equal to the probability that no clonogens survive, which is obtained by substituting (2) in (3) and fixing  $k = 0$ :

$$TCP(d, n) = e^{-N_0 S} = e^{-N_0 e^{(-\alpha d - \beta d^2)n}} \quad (4)$$

where the total dose,  $D$  is given by the product of the number of sessions,  $n$ , times the fraction dose,  $d$ , ( $D = n \cdot d$ ).

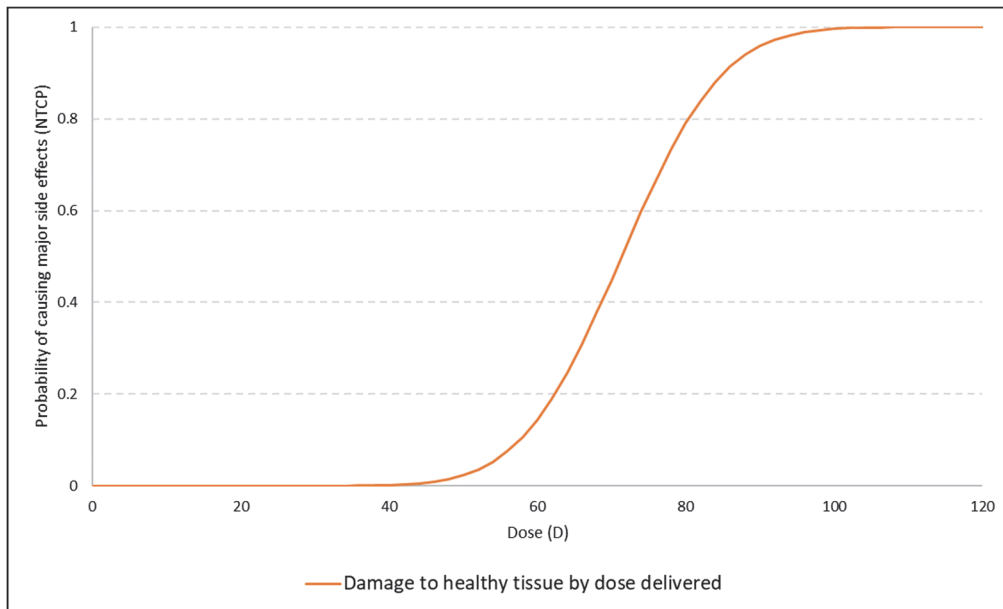
Note that the  $N_0$  will generally depend on the type of cancer modelled, and ultimately, it will depend on each specific clinical case. However, the radiobiological literature provides typical values for this parameter. We have used the one reported by Bolt (2018) ( $N_0 = 10,000$ ). Hence the TCP model used depends on three parameters whose values taken from (Bolt 2018) are reported in the following table:

| Parameter                                             | Symbol   | Value                  |
|-------------------------------------------------------|----------|------------------------|
| <b>Coefficient for single-strand DNA breaks (SSB)</b> | $\alpha$ | $0.08 \text{ Gy}^{-1}$ |
| <b>Coefficient for double-strand DNA breaks (DSB)</b> | $\beta$  | $0.04 \text{ Gy}^{-2}$ |
| <b>Initial number of clonogenic cells</b>             | $N_0$    | 10,000                 |

## B. NORMAL TISSUE COMPLICATION PROBABILITY: THE LYMAN-KUTCHER-BURMAN MODEL

The goal of any radiation therapy treatment is to deliver a homogenous and accurate dose to the target volume alone. However, this is almost never achievable, and thus, healthy surrounding tissue is often exposed to lower doses of radiation. The Lyman-Kutcher-Burman (LKB) model (Lyman 1985) (Kutcher and Burman 1989) describes the complication probabilities for uniformly irradiated whole or partial organ volumes.

In order to grasp the intuition behind the LKB NTCP model, we should ponder the relation between the dose delivered and the damage caused to healthy tissue. In abstract terms, this relationship is qualitatively equivalent to the analogy of an object falling from a certain height and the probability that it gets damaged. Common sense tells us that this relation cannot be linear; in fact, we expect a sigmoid relation. A fall from a small height does not involve any risk. As the height becomes higher the chances of suffering irreparable damage gradually increase. Above certain height, serious harm is almost certain. The same kind of relation is expected between the probability of causing major damage and the radiation dose delivered to the patient:



At low doses it is very unlikely that any damage to healthy tissue is produced by the radiation treatment. However, as the dose is increased the probability of a major complication occurring goes up; but it cannot go up indefinitely. Beyond a certain value, it asymptotes rapidly to one, that is, above certain dose, the damage to surrounding healthy tissue is almost certain.

To model this expected behaviour, the LKB model makes use of the normal distribution to represent an empirical sigmoid dependence of the NTCP. If we consider the probability density function (PDF) of the standard normal distribution,  $\varphi(z)$ , and the corresponding cumulative distribution function (CDF),  $\Phi(z)$ , then the cumulative distribution function of the generic NTCP curve of the LKB model can be expressed as:

$$NTCP(z) = \Phi\left(\frac{z - A}{B}\right) \quad (5)$$

Hence, starting from the functional form of the normal distribution CDF, the LKB model requires parameters  $A$  and  $B$  to be determined experimentally. This has been repeatedly addressed by the radiobiological literature.

Based on this intuition provided by the normal distribution, the LKB model adopts the following form:

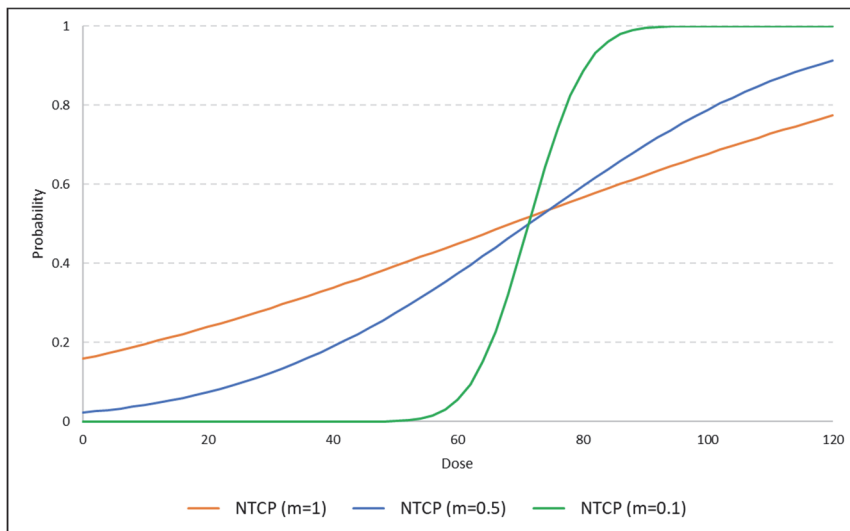
$$1 - NTCP(D, V) = \int_{-\infty}^{t(D, V)} e^{-\frac{x^2}{2}} dx = \frac{1}{2} \left[ 1 - \operatorname{erf} \left( \frac{t(D, V)}{\sqrt{2}} \right) \right] \quad (6)$$

Three key elements of this equation should be noted:

- The previous equation shows the probability of the treatment **not** producing normal tissue complications. Therefore,  $1 - NTCP(D, V)$  is computed.
- Equation (6) includes the element  $\operatorname{erf}(\cdot)$ , that is, the error function<sup>5</sup>. This expression results from integrating the normal distribution.
- The dependence of the model on dose,  $D$ , and the proportion of the total organ volume irradiated,  $V$ , is embedded in the upper limit of the integral,  $t(D, V)$ . This function is commonly used in radiobiological modelling and is given by:

$$t(D, V) = \frac{D - \frac{D_{50}}{V^n}}{\frac{D_{50}}{V^n} \cdot m} \quad (7)$$

Based on this formulation we can see that if  $m = 1$  and  $n = 0$ , then the upper limit of the integral is nothing less than the percentage deviation of the dose delivered with respect to the parameter  $D_{50}$ , which denotes the uniform dose given to the entire organ that results in a 50% complication risk. However, it would make sense for these two parameters to differ from those values. Firstly, it should be noted that the parameter  $m$  controls the steepness of the curve. If  $m = 1$ , then the sigmoid shape we expect vanishes. The following picture simulates the shape of the  $1 - NTCP(D, V)$  curve for different values of  $m$ :



<sup>5</sup> The error function is a special mathematical function of sigmoid shape that occurs often in probability and statistics. It is defined as:

$$\operatorname{erf}(x) = \frac{1}{\sqrt{\pi}} \int_{-x}^x e^{-t^2} dt = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt.$$

In statistics, for nonnegative values of  $x$ , the error function has the following interpretation: for a random variable  $Y$  that is normally distributed with mean 0 and variance 0.5,  $\operatorname{erf}(x)$  describes the probability of  $Y$  falling in the range  $[-x, x]$ .

The value of the parameter  $m$  is determined empirically and depends on the site of the tumour. For our analysis for prostate cancer we will consider a specific side effect: grade 2 rectal bleeding within 5 years. For this major complication, parameter  $m$  has been taken from Bolt (2018) ( $m = 0.15$ ). This value enables the curve to exhibit the sigmoid behaviour expected.

On the other hand, given that  $V$  represents the proportion of the organ volume which is irradiated, the parameter  $n$  defines the magnitude of the *volume effect* ( $n$  lies between 0 and 1 with larger values corresponding to a larger volume effect). This effect can be defined as the relation between the tolerated dose and the organ volume irradiated. The equation shows how the maximum dose that does not generate complications increases as the irradiated volume decreases.

The magnitude of the volume effect depends largely on the underlying anatomic biological structure of the organ, and this is what parameter  $n$  captures. Often organs are classified as *serial* or *parallel* organs.

- In the former, damage to one part of the organ will have a direct effect on the overall performance of the organ. An example of a serial organ is the spinal cord, since damage of even a small section can cause the inability to nerve signal transportation, affecting many parts of the body that connect to this nerve.
- Conversely, a parallel organ may better tolerate damage to a certain area, so it can still perform its function. The lung is a good example of a parallel organ, since damage to a non-critically large volume of the organ can normally be compensated for by the remainder of the lung.

The prostate shows a low volume effect, that is, it is closer to be a pure serial organ. The value of  $n$  and  $V$  have also been taken from Bolt (2018) ( $n = 0.13$ ,  $V = 0.73$ ).

Finally, it should also be noted that the term  $D_{50}/V^n$  describes the position of the sigmoid curve along the dose axis equation (6). As previously mentioned,  $D_{50}$  represents the uniform dose given to the entire organ that results in a 50% complication risk. The value of this parameter for clinical cases of prostate cancer has also been taken from Bolt (2018) ( $D_{50} = 68.5 \text{ Gy}$ ).

Hence, the LKB NTCP model depends on four parameters. All parameter values taken from Bolt (2018) for grade 2 rectal bleeding within 5 years in prostate cancer are reported in the following table:

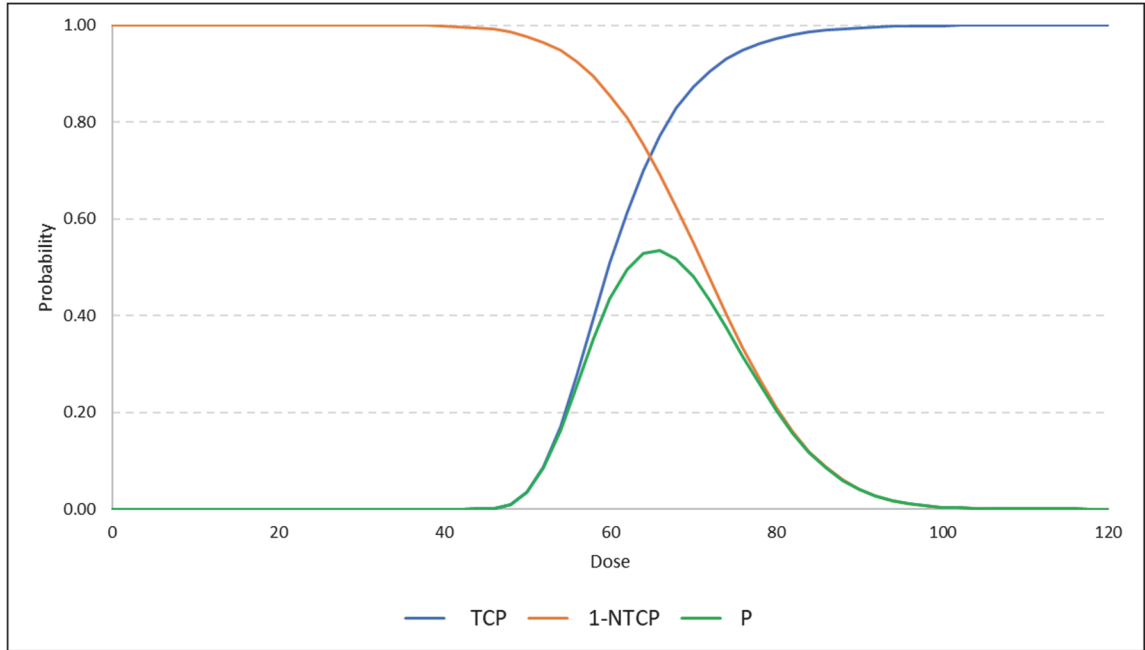
| Parameter                                                                    | Symbol   | Value   |
|------------------------------------------------------------------------------|----------|---------|
| Proportion of the organ irradiated                                           | $V$      | 0.73    |
| Uniform dose given to the entire organ that results in 50% complication risk | $D_{50}$ | 68.5 Gy |
| Empirical parameter that defines the steepness of the NTCP curve             | $m$      | 0.15    |
| Magnitude of the volume effect                                               | $n$      | 0.13    |

#### 4. RADIATION THERAPY IMPROVEMENTS IN PROSTATE CANCER TREATMENT

The following analysis combines both models detailed in the previous section, that is, the linear quadratic (LQ) tumour control probability (TCP) Poisson model, and the Lyman-Kutcher-Burman (LKB) normal tissue complication probability (NTCP) model. The goal of the analysis is to construct a curve that defines the probability of controlling the tumour in the prostate, without causing significant side effects. Since controlling the tumour and developing side effects are probabilistic independent events, the joint probability is given by the product of (4) and (5):

$$P(D) = TCP \cdot (1 - NTCP) \quad (8)$$

The intersection of the two sigmoid probability curves yields an asymmetric bell-shaped curve like the one presented in the following schematic:



For an individual patient, Equation (8) yields the probability of controlling the tumour with no significant side effects associated. However, it is a quite complex non-linear expression. In order to simplify the analysis, the resulting equation can be approximated by its second order Taylor expansion around the optimal dose,  $D^*$ :

$$P(D) \approx P(D^*) + (D - D^*) \frac{dP}{dD}(D^*) + \frac{1}{2} (D - D^*)^2 \frac{d^2P}{dD^2}(D^*) \quad (9)$$

Since the optimal value constitutes a local maximum, the second term in the previous expression vanishes.

$$P(D) \approx P(D^*) + \frac{1}{2} (D - D^*)^2 \frac{d^2P}{dD^2}(D^*) \quad (10)$$

Note that we are assuming that  $D$  is a random variable scattered around  $D^*$ . Hence,  $D^* = \mathbf{E}[D] = \mu$ . The optimal total dose for prostate cancer determined through model optimisation is  $D^* = 65.5 \text{ Gy}$ .

The standard treatment in RT01 was delivered in fraction doses of 2 Gy (Bolt 2018), with 33 sessions required to achieve a total dose of 65.5 Gy. For each individual patient, we assume that all treatment sessions are carried out with the same equipment. This implies that any variation from the optimal 2 Gy dose, is consistently delivered to the patient and thus, the same relative deviation is observed for the total dose. Moreover, we assume that this deviation of the optimal dose is present from the start and does not vary during the treatment. Both assumptions mean that we expect variation from one radiation machine to another, but no changes in the deviation over time.

To account for the average effect over all the prostate cancer patients treated, we can compute the expected value of equation (10):

$$\mathbf{E}[P(D)] = P(D^*) - \frac{1}{2}\mathbf{E}[(D - D^*)^2]|P''(D^*)| \quad (11)$$

Since we have assumed that  $D$  is a random variable scattered around  $D^*$ , by definition, the variance of the random variable  $D$  is the expected value of the squared deviation from  $D^*$ , that is,  $\sigma^2 = \text{Var}(D) = \mathbf{E}[(D - D^*)^2]$ . Considering the definition of the variance and rearranging the terms, we get:

$$\mathbf{E}[P(D)] = P(D^*) - \frac{1}{2}|P''(D^*)|\sigma^2 \quad (12)$$

Finally, if we compute the finite variation of equation (12) we get:

$$\Delta\mathbf{E}[P(D)] = -\frac{1}{2}|P''(D^*)|\Delta\sigma^2 \quad (13)$$

Equation (13) defines the changes in the probability of controlling the tumour without causing significant side effects to the patient as a function of changes in the uncertainty in the dose delivered,  $\Delta\sigma^2$ . The lower the uncertainty in the dose delivered, the lower the deviation from the optimal value; and the lower the deviation, the higher the probability of a successful outcome of the treatment. Hence, more accuracy in the dose delivered leads to greater chances of tumour control without developing undesirable side effects. When many patients are treated, this probability increase becomes very relevant. The number of patients successfully treated that otherwise would have not been cured or would have developed side effects,  $X$ , can be approximated by:

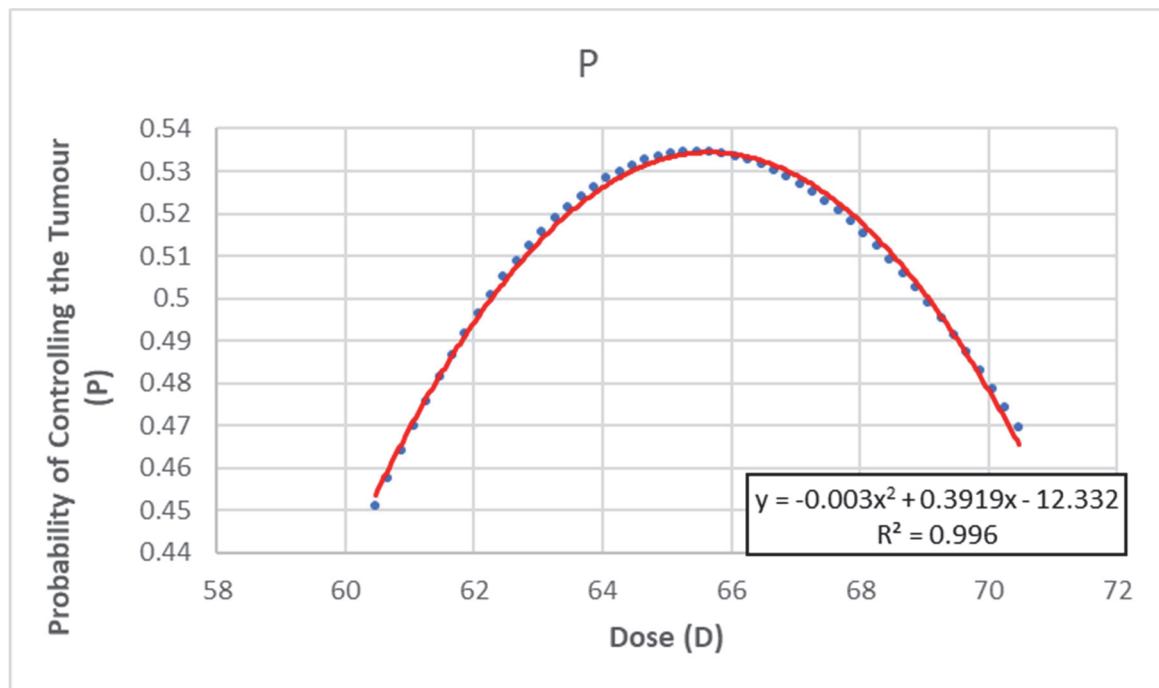
$$X = M \left( -\frac{1}{2}|P''(D^*)|\Delta\sigma^2 \right) \quad (14)$$

Where  $M$  is the total number of prostate patients treated annually (around 23,870 patients<sup>6</sup>), and  $\Delta\sigma^2$  is a negative value that represents the reduction (*i.e.* a negative increment) in uncertainty because of NPL's efforts in conjunction with the physicists in the radiotherapy community (an average reduction from 0.8% to 0.4%)<sup>7</sup>. Given the functional forms of the LQ TCP model and the LKB NTCP model, the resulting analytical equation for  $|P''|$  is quite complex. However, there is a simple way to approximate the value of the second derivative around the optimal dose,  $|P''(D^*)|$ . We can plot the values of  $P$  around that optimal dose

<sup>6</sup> This number has been approximated based on the figure reported by (Cancer Research UK 2016) and the fact that radiotherapy plays a vital role in treating around 50% of cancer cases (Cancer Research UK 2009).

<sup>7</sup> Hence  $\Delta\sigma^2 = (0.004 \cdot 65.5)^2 - (0.008 \cdot 65.5)^2 = -0.206$

(65.5 Gy). To plot the  $P$  curve, we need the parameters that the LQ TCP and the LKB NTCP models depend on. Making use of the value of the parameters reported in the previous section, the  $P$  points around the maximum value can be plotted and a quadratic curve can be fitted:



The quadratic approximation fits very appropriately ( $R^2 = 0.996$ ). The quadratic expression can be differentiated twice to obtain the value of the second derivative around the optimal dose, that is,  $|P''(D^*)| = 0.006$ . The values to be entered in equation (14) are:

| Variable                                                                                                           | Symbol           | Value  |
|--------------------------------------------------------------------------------------------------------------------|------------------|--------|
| Number of prostate cancer patients treated with radiation                                                          | $M$              | 23,870 |
| Absolute value of the second derivative of the probability of cure with complication evaluated in the optimal dose | $ P''(D^*) $     | 0,006  |
| Reduction of the uncertainty in the radiation dose delivered                                                       | $\Delta\sigma^2$ | -0.206 |

Substituting these values into equation (14) we get:

$$X = 23,870 \cdot \left[ -\frac{1}{2} \cdot 0.006 \cdot (-0.206) \right] \approx 15 \quad (15)$$

Therefore, the joint efforts of NPL's work on calibration, codes of practice and audit provision with healthcare professionals in the radiotherapy community have led to 15 additional patients with prostate cancer treated successfully each year, without any significant side effects occurring.

## 5. CONCLUSION

Our study models the positive impact that the better accuracy in radiation dose delivery underpinned by NPLs work, has on radiotherapy treatment of prostate cancer. To do so, two commonly used radiobiological models are combined to approximate the increase in the probability of controlling the tumour without causing a specific significant side effect. The study finds that the joint efforts of NPL and healthcare professionals in the radiotherapy community have led to 15 additional patients treated successfully each year at the end of the period 1995-2015.

## 6. REFERENCES

- American Association of Physicists in Medicine. 2012. *The use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM*. Task Group Report, American Association of Physicists in Medicine.
- BEIS. 2017. *UK Measurement Strategy. The Value of Measurement: Supporting information for the UK Measurement Strategy*. Department for Business, Energy & Industrial Strategy.
- Bolt, Matthew Andrew. 2018. *Evidence based assessment of the clinical impact of dose variations arising in the clinical radiotherapy dosimetry chain*. London: University of Surrey.
- Cancer Research UK. 2009. *Achieving a world-class radiotherapy service across the UK*. Cancer Research UK.
- . 2016. *Cancer Statistics for the UK*. Accessed July 02, 2019. <https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk#heading-Zero>.
- Clark, Catharine H., Edwin GA. Aird, Steve Bolton, Elizabeth A. Miles, Andrew Nisbet, Julia AD. Snaith, Thomas AS. Russell, Karen Venables, and David I. Thwaites. 2015. "Radiotherapy dosimetry audit: three decades of improving standards and accuracy in UK clinical practice and trials." *The British journal of radiology* 88 (1055).
- Dale, Roger G., and Bleddyn Jones. 2007. *Radiobiological modelling in radiation oncology*. London: British Institute of Radiology.
- Dearnaley, David P, Gordana Jovic, Isabel Syndikus, Vincent Khoo, Richard A Cowan, John D Graham, Edwin G Aird, David Bottomley, Robert A Huddart, and Chakiath C Jose. 2014. "Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial." *The lancet oncology* (Elsevier) 15 (4): 464-473.
- Joiner, Michael C., and Albert Van der Kogel. 2016. *Basic Clinical Radiobiology*. CRC press.
- Kutcher, Gerald J., and C. Burman. 1989. "Calculation of complication probability factors for non-uniform normal tissue irradiation: The effective volume method." *International Journal of Radiation Oncology Biology Physics* (Elsevier) 16 (6): 1623-1630.
- Lillicrap, S. C., B. Owen, J.R. Williams, and J. C. Williams. 1990. "Code of practice for high-energy photon therapy dosimetry based on the NPL absorbed dose calibration service." *Physics in Medicine and Biology* 35 (10): 1355-1360.

- Lyman, John T. 1985. "Complication probability as assessed from dose-volume histograms." *Radiation Research* (Academic Press, Inc.) 104 (2S): S13-S19.
- Munro, T. R., and C. W. Gilbert. 1961. "The relation between tumour lethal doses and the radiosensitivity of tumour cells." *The British journal of radiology* (The British Institute of Radiology) 34 (400): 246-251.
- Palmer, A., B. Mzenda, J. Kearton, and R. Wills. 2011. "Analysis of regional radiotherapy dosimetry audit data and recommendations for future audits." *The British journal of radiology* (The British Institute of Radiology) 84 (1004): 733-742.
- Sachs, R. K., L. R. Hlatky, and P. Hahnfeldt. 2001. "Simple ODE models of tumor growth and anti-angiogenic or radiation treatment." *Mathematical and Computer Modelling* (Elsevier) 33 (12-13): 1297-1305.
- Smittenaar, C. R., K. A. Petersen, K. Stewart, and N. Moitt. 2016. "Cancer incidence and mortality projections in the UK until 2035." *British journal of cancer* (Nature Publishing Group) 115 (9): 1147.
- The Society of Radiographers. 2019. *Patient information*. Accessed July 02, 2019. <https://www.sor.org/public-and-patient/patient-information>.
- Thomas, Russell AS., Matthew A. Bolt, Graham Bass, Rebecca Nutbrown, Tao Chen, Andrew Nisbet, and Catharine H. Clark. 2017. "Radiotherapy reference dose audit in the United Kingdom by the National Physical Laboratory: 20 years of consistency and improvements." *Physics and Imaging in Radiation Oncology* (Elsevier) 3: 21-27.
- Van Leeuwen, C. M., A. L. Oei, J. Crezee, A. Bel, N. A.P. Franken, L. J. Stalpers, and H. P. AKok. 2018. "The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies." *Radiation Oncology* (BioMed Central) 13 (1): 96.