

# Comparative Treatment Planning in Radiotherapy and Clinical Impact of Proton Relative Biological Effectiveness

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#### **Abstract**

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The development of new irradiation techniques is presently a very active field of research with increased availability of more sophisticated modalities such as intensity modulated photons (IMRT), protons and light ions. The primary aim of this work is to evaluate if the dose-distributions using IMRT and protons contribute to clinical advantages. A secondary aim is to investigate the potential clinical implication of the increased relative biological effect (RBE) for protons at the end of the Bragg peak.

The potential benefits are evaluated using physical dose measures and dose-response models for normal tissue complication probability (NTCP) and tumour control probability (TCP). Comparative treatment planning was performed using three locally advanced tumour types, left-sided node positive breast cancer, hypopharyngeal cancer, and rectal cancer. All studies showed that both IMRT and protons could improve the dose distributions compared to 3D-CRT, and significantly improve treatment results with lower NTCPs and, concerning hypopharyngeal cancer, higher TCP. Protons always resulted in smaller volumes receiving intermediate and low radiation doses.

Using protons or IMRT for left-sided node-positive breast cancer, the advantage is a significantly decreased risk for cardiac mortality (from 6.7% to 1%) and radiation induced pneumonitis (from 28.2% to less than 3%) compared to 3D-CRT. For hypopharyngeal cancer, protons and IMRT provide more selective treatment plans, higher TCP since a simultaneous boost technique is feasible, and better parotid gland sparing for several patients. For locally advanced rectal cancer, the NTCP for small bowel is potentially reduced by approximately 50% using IMRT or protons; protons have an even greater potential if the structure of the small bowel is parallel.

A variable RBE correction is developed and applied to a clinical proton treatment plan. A significant difference is obtained compared to the commonly accepted RBE correction of 1.1. This indicates that a variable RBE may be of importance in future proton treatment planning.

This thesis provides support for increased use both IMRT and proton radiotherapy, although stronger for protons. Therefore, investments in proton facilities with capacity for large clinical trials can be supported.

**Keywords:** Radiotherapy, Comparative studies, Breast cancer, hypopharyngeal cancer, rectal cancer, Proton RBE

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*To my family*



# List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals.

**I.** Johansson J, Isacsson U, Lindman H, Montelius A, Glimelius B. “Node-positive left-sided breast cancer patients after breast-conserving surgery: potential outcomes of radiotherapy modalities and techniques.” *Radiother Oncol.* 2002 Nov;**65**(2):89-98.

**II.** Johansson J, Blomquist E, Montelius A, Isacsson U, Glimelius B. “Potential outcomes of modalities and techniques in radiotherapy for patients with hypopharyngeal carcinoma.” *Radiother Oncol.* 2004 Aug;**72**(2):129-38.

**III.** Tilly N, Johansson J, Isacsson U, Medin J, Blomquist E, Grusell E and Glimelius B, “The influence of RBE variations in clinical proton beams” *Phys Med Biol.* 2005 June 21;**50**(12):2765-77.

**IV.** Johansson J, Montelius A, Glimelius B, “Treatment planning comparison of 3 dimensional-conformal radiotherapy, intensity modulated radiotherapy and proton beam radiotherapy for locally advanced rectal cancer” Manuscript.

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# Contents

|  |    |
|--|----|
| Introduction.....  | 9  |
| Irradiation modalities and techniques .....                          | 10 |
| Target volumes and risk organs.....                                  | 10 |
| 3D-CRT and intensity modulated radiotherapy .....                    | 10 |
| The potential of protons (and ions) .....                            | 13 |
| Radiobiology of protons (and ions).....                              | 15 |
| Clinical experience with IMRT and protons (and ions) .....           | 17 |
| Aims of the thesis.....  | 19 |
| Treatment Planning Comparisons.....                                  | 20 |
| Treatment planning systems.....                                      | 28 |
| Design of treatment planning comparisons .....                       | 29 |
| General considerations.....  | 29 |
| Physical dose-volume evaluation .....                                | 29 |
| Modelling treatment outcome with dose-response models.....           | 30 |
| Results and discussion .....   | 32 |
| Left-sided node positive breast cancer (Paper I) .....               | 32 |
| Hypopharyngeal carcinoma (Paper II) .....                            | 34 |
| Locally advanced rectal cancer (Paper IV) .....                      | 37 |
| Potential RBE effects in proton treatment planning (Paper III) ..... | 39 |
| Future perspectives .....  | 42 |
| Conclusions.....   | 45 |
| Acknowledgements.....  | 47 |
| References:.....   | 49 |

## Abbreviations

|        |   |
|--------|---|
| RT     | Radiation therapy                         |
| CTRT   | Chemo-radiotherapy                        |
| 3D-CRT | 3 dimensional conformal radiotherapy      |
| IMRT   | Intensity-modulated photon radiotherapy   |
| MLC    | Multi-leaf collimator                     |
| MIMiC  | Multivane intensity-modulating collimator |
| DAO    | Direct aperture optimisation              |
| IMPT   | Intensity modulated proton radiotherapy   |
| SOBP   | Spread out Bragg peak                     |
| LET    | Linear energy transfer                    |
| RBE    | Relative biological effect                |
| GTV    | Gross tumour volume                       |
| CTV    | Clinical target volume                    |
| PTV    | Planning target volume                    |
| OAR    | Organs at risk                            |
| DVH    | Dose volume histogram                     |
| CI     | Conformity index                          |
| TCP    | Tumour control probability                |
| NTCP   | Normal tissue complication probability    |
| EUD    | Equivalent uniform dose                   |
| CNS    | Central nervous system                    |
| AVM    | Arteriovenous malformation                |
| IMN    | Internal mammary nodes                    |
| CT     | Computed tomography                       |
| MRI    | Magnetic resonance imaging                |
| PET    | Positron emission tomography              |



## Introduction

The development and implementation of new irradiation techniques in radiotherapy (RT) is presently a fast growing field due to the availability of sophisticated modalities such as intensity modulated radiotherapy with photons (IMRT), protons and light ions. At the same time treatment planning, methods for fixation of the patient, compensation for patient movements and image-guided RT are developing. The dose distributions that can be obtained with protons, light ions and IMRT are generally superior to those obtained with three dimensional conformal radiotherapy (3D-CRT) techniques with photons, i.e. the techniques presently used as standard treatments at most sites world-wide. All improvements aim at delivering radiation dose more selectively and conformably adapted to the tumour volume so that high doses in volumes outside the tumour volume can be decreased, thereby sparing normal tissues. Alternatively, the improved selectivity can be used to increase the tumour dose and increase the tumour control while maintaining acceptable complication rates in the surrounding normal tissues. To take full advantage of the improved dose distributions using the new techniques, fractionation schedules and combinations with sensitising drugs must also be optimised.

Although the availability of improved treatment techniques with photons, protons and light ions increases, the important question remains whether or not the clinical outcome for the patients will be sufficiently improved. Long-term clinical experience using these more sophisticated techniques is still rare and higher treatment efficacy of sufficient extent to motivate the increased costs is still to be proven. In the absence of clinical evidence supporting new treatments, the outcome from a patient treatment could be simulated by treatment planning comparisons. The comparisons are then evaluated using physical dose measures and by applying dose-response models. The latter can estimate tumour control probability (TCP) and normal tissue complication probability (NTCP). From the results of dose-response modelling and early clinical data, it is possible to get at least an idea of the potential improvements that can be achieved. Sensitivity analyses can reveal the robustness of the estimates. An estimate of the potential number of patients eligible for treatment with IMRT, protons and light ions can also be obtained, as recently done for protons [60] and light ions [10,107,170].

# Irradiation modalities and techniques

## Target volumes and risk organs

Three-dimensional imaging is fundamental for modern radiotherapy treatment planning. Different imaging techniques, such as computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), provide a basis for definition of targets and risk organs as well as accurate dose calculations. In clinical practice a few important anatomical volumes are defined as prerequisites for treatment planning [83,84]. The primary tumour volume with the highest tumour cell density is defined as the Gross Tumour Volume (GTV). The Clinical Target Volume (CTV) is a volume, which includes the GTV, and in addition, a margin containing assumed subclinical, i.e. non-detectable disease. To account for organ movements and errors in patient set-up, a margin is applied around the CTV creating a Planning Target Volume (PTV). The dose delivered to the PTV represents the dose delivered to the CTV and ensures that the prescribed dose is delivered to the CTV [83,84]. This implies that the objective for the PTV also is the prescription dose. Normal tissues significantly affected by their radio-sensitivity, and thereby influencing the prescribed dose to the CTV, are defined as Organs at Risk (OAR).

## 3D-CRT and intensity modulated radiotherapy

A *3D-CRT* treatment plan is based on 3D imaging in the delineation of target volumes and OARs, and is delivered by combining a number of beams from different directions to irradiate the PTV. The aperture for each beam is shaped by a multileaf collimator (MLC) to be conformed with the projected contour of the PTV. The fluence of such a beam can be optimised using e.g. wedges or physical modulators (compensation filters). This optimisation is made manually by varying beam energy and beam weight or by applying beam modulators such as wedge filters. The constraints for a 3D-CRT planning are generally stated in treatment protocols or individually set for each patient by the radiation oncologist.

Modern delivery techniques, using photons, may be summarised in the term intensity modulated radiotherapy (IMRT) [2,215,216]. IMRT with associated computerised optimisation of fluence profiles is a technology that

has been developed dramatically since the end of the 1980s [18,24,29,217]. To obtain the desired dose distribution to the target and at the same time spare specific normal tissues, the fluence profiles generally have to be non-uniform. An interactive computer optimisation procedure calculates, for all the selected beam directions, the fluence profiles necessary to obtain the desired dose distribution within the patient. The optimisation algorithm uses dose or dose-volume objectives entered interactively in the calculation of the dose-distribution. Typical dose objectives are given as min/max dose (Gy) to the entire PTV or OARs, whereas dose-volume objectives are given as min/max dose (Gy) to partial volumes of a PTV or an OAR. Importance factors can be assigned to PTVs and OARs in order to improve the optimised result. Objective functions used in the optimisation process always provide results that correspond to the user-defined input in terms of the objectives. Therefore, user interaction, providing new improved objectives and importance factors, is required to obtain a clinically feasible treatment plan.

A few different types of algorithms are usually used in the optimisation of IMRT plans. In the optimisation problem, the objective function is to be minimised. A commonly used class of optimisation algorithms is gradient based. These algorithms search the local neighbourhood for a minimum value of the objective function, and could end up in a local minimum instead a global minimum. However, it has been shown that many commonly employed objective functions are convex, i.e. only have one minimum, and therefore the gradient methods are effective for optimisation [41]. Gradient based algorithms are commonly employed in commercial treatment planning systems, such as Helax TMS [70,71], Oncentra Masterplan with optimisation module from Raysearch Laboratories [81,126] and Konrad [169]. Another type of algorithm frequently used for optimisation of dose distributions is simulated annealing [217]. These algorithms are suitable also for non-convex problems. The simulated annealing optimisation was implemented in the first commercial treatment-planning optimisation program, CORVUS (NOMOS Corporation).

Two main IMRT delivery techniques can be recognised, viz. cone beam IMRT and tomotherapy. Cone beam IMRT uses standard C-arm linear accelerators equipped with MLCs. One technique, called *step and shoot*, builds up the fluence profiles from multiple static fields from each beam direction. *Sliding window* is a technique where dynamic movements of the MLC are used to obtain the fluence profiles from each direction. Theoretically, it offers higher resolution in obtained fluence profiles and a faster realisation, although the calculations of the movements of the MLC are more complex.

Tomotherapy can be described as slice or fan beam IMRT. With serial tomotherapy, one slice of the tumour is treated at a time with a series of gantry angles up to a full rotation after which the patient is moved to treat the next slice. Serial tomotherapy was the first commercially available system for IMRT, using the multivane intensity-modulating collimator (MIMiC) as

an add-on to a conventional accelerator. MIMiC was used together with the CORVUS treatment planning system for integrated optimisation (NOMOS Corporation). MIMiC provides a fan beam divided into two thin slices, which can be fluence modulated during the treatment. Inspired by the spiral CT technology, Mackie [138] introduced spiral tomotherapy with a rotating linac using a similar collimator as the MIMiC. The main difference between serial and spiral tomotherapy is that in spiral tomotherapy the patient is moved continuously by the couch while being irradiated with the rotating linac, which gives a spiral irradiation pattern.

The non-uniform fluence profiles from each beam direction calculated with the optimisation techniques are delivered by using different settings for the MLCs. Thus, the fluence profiles must be converted into machine parameters (segmentation). There are numerous algorithms published to perform this conversion, e.g. [36,199,201]. However, an important objective in treatment planning is adequate dose coverage to the target volumes, which in most cases means homogenous dose within the target volume. In the segmentation process, the dose distributions may be degraded. To overcome this degradation, also the MLC settings can be directly involved in the optimisation process e.g. [81,190]. This is called direct aperture optimisation (DAO), and this approach is now becoming available in treatment planning systems. As an example both these methods were used to optimise a breast cancer case with exactly the same beam configuration and objectives. The dose volume histograms (DVHs) are shown for the respective technique in Figure 1. In this specific case, a significant difference with respect to homogeneity between the dose distributions was obtained in favour of the DAO technique. Using fluence optimisation with segmentation, acceptable plans may still be obtained although the DAO method appears to be more robust.

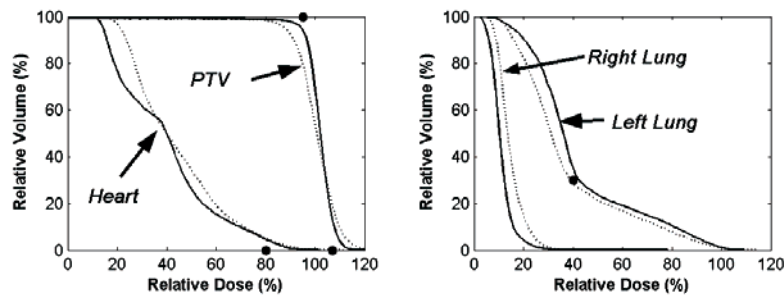


Figure 1. DVHs for a) PTV and heart and b) left and right lung using either direct aperture optimisation (solid lines) or segmentation of optimised fluence profiles (dotted lines). The • are the objectives set for the optimisation algorithm.

## The potential of protons (and ions<sup>1</sup>)

In 1946, Robert Wilson suggested that protons could be used for medical purposes [226]. In 1954, the first proton beam (340 MeV) was used to irradiate the pituitary gland at the Lawrence Berkeley Laboratory, California, USA. Between 1954 and 1992, 2054 patients were treated, the first 30 with protons and the remaining ones with helium ions [118]. This centre was followed in the 1950s and 60s by other centres: the Gustav Werner Institute (GWI), Uppsala, Sweden, the Harvard Cyclotron Laboratory, Boston Massachusetts USA, Dubna and Institute of Theoretical and Experimental Physics (ITEP), Moscow, Russia. The proton beam from the synchrocyclotron at the GWI was developed both for neurosurgery [111,115] and for large-field proton treatments [44,63,108,203]. The first medically dedicated proton beam facility was built at Loma Linda University in California, USA in 1990 [195]. As of July 2005, there are 23 active proton centres and 3 centres using C ions [192]. In total  $\approx 43000$  patients have been treated with protons and  $\approx 4500$  patients with light or heavy ions Figure 2. Currently a number of facilities are planned, 15 with protons only, 4 combining protons and ions, and one with C-Ar ions.

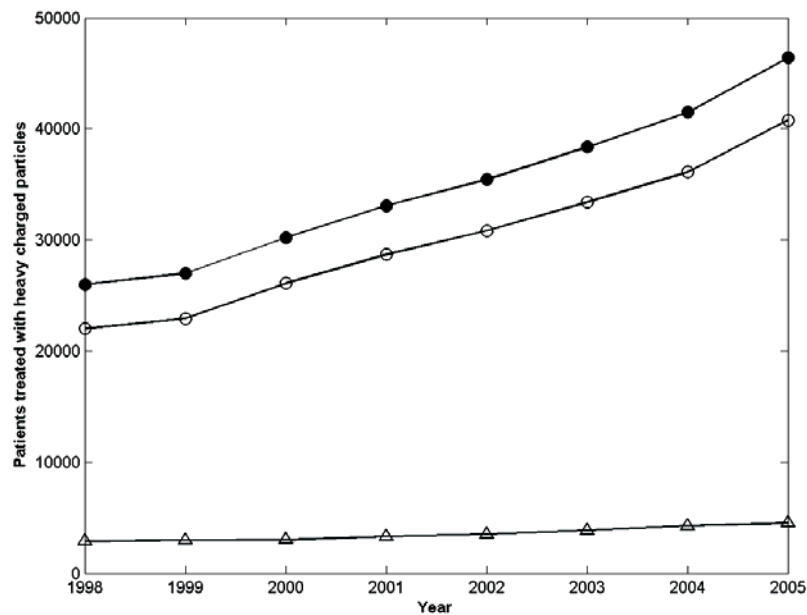


Figure 2. The total number of patients treated with heavy charged particles. (Total number treated ●, protons ○, other heavy charged particles △).

<sup>1</sup> In this thesis, particles with atomic number  $Z = 2-6$  will be considered as light ions and  $Z \geq 7$  as heavy ions.

The positively charged hydrogen ions or protons deposit energy in matter by Coulomb interactions with electrons and nuclei, by bremsstrahlung energy loss, and by nuclear reactions. These interactions lead to a slowing down of the primary protons. The dominant effect of energy loss is Coulomb interaction with the atomic electrons. As the protons penetrate into the material the absorbed dose increases gradually and near the end of the range the dose increases rapidly (shaded light grey curve in figure 3). This peak in the dose distribution was discovered by Bragg [22] and bears his name. The absorbed dose is proportional to the energy deposition per unit path length, i. e. the stopping power. The stopping power increases as the proton energy decreases until very little energy remains. The dose distribution has a sharp fall-off near the maximum range, as all protons have approximately the same range due to the small fluctuations in energy loss over the path (range straggling). As the protons are much heavier (approximately 1835 times) than the electrons, the multiple scattering by the atomic electrons will lead only to small lateral deviations along the path. Proton beams will therefore have relatively sharp penumbras. The penumbra will increase with depth and at 15-20 cm in tissue, it will be comparable to those of high-energy photon beams.

The mono-energetic proton beam extracted from the accelerator is a narrow pencil beam with a sharp Bragg-peak. This beam cannot provide a uniform dose to a target of any significant size. Therefore, different methods to spread out the Bragg peak both laterally and in depth are implemented. The simplest method to spread out the beam laterally to a useful size is to use high atomic number scattering foils, the so called passive scattering method [65,108,142]. A proton beam passing through a single scattering foil shows a Gaussian fluence profile [65,142]. Therefore, to achieve larger field sizes, techniques using double scattering foils are used [17,26].

An alternative method to passive scattering is the use of active scanning of the narrow proton pencil beam by means of magnetic deflection. The use of scanning to achieve large uniform treatment fields was first implemented by the Uppsala group, where scanning magnets produced diamond patterns of variable size to cover the treatment field [109]. The narrow proton beam can also be scanned in a raster pattern or in concentric rings to produce uniform fields of variable size [96,172]. Dynamic scanning minimises energy losses and the maximum useful range is preserved.

The sharp Bragg-peak of the proton beam must be modulated in range in order to give a homogeneous dose to an extended volume. In a passively spread out beam this is done by using a rotating stepped absorber [103], a ridge filter [97] or a spiral ridge filter [99,100,104]. The range is shifted in discrete steps and an almost flat extended spread out Bragg-peak (SOBP) can be obtained. In Figure 3, the Bragg peak of a 173 MeV proton beam has been modulated in 10 steps to create a uniform dose over the last 54 mm of the depth dose curve. This technique for passive modulation can only pro-

duce a uniform range modulation (constant SOBP) throughout the entire portal, and the extent of the SOBP is determined by the maximum size of the target.

In Figure 3, a mono-energetic and range modulated proton depth dose distributions are compared to a 6 MV photon beam. Photons interact with matter in rare single events and the photon depth dose curve is characterised by an exponential decrease with depth. The figure shows that photons give much higher dose both on the entrance and exit sides of the target (represented by the SOBP) as indicated with dark shaded areas. The proton energies required to reach any target location in the human body would be in the range of approximately 70-250 MeV corresponding to a range in depth of approximately 4-35 cm. The range for a passively scattered therapy beam is adapted to the distal end of the target volume by applying a range compensator or bolus. This filter is machined such that the maximum range is conformed to the shape of the distal surface of the target.

With actively scanned pencil beams it is possible to deliver the beam even more selectively than with passively scattered beams. With a scanned pencil beam, the modification of the Bragg-peak is accomplished by varying the absorber thickness or energy of the incident beam over the beam portal. The use of scanned beams to vary the range modulation allows the high dose region of the SOBP to be conformed to both the distal and proximal target extension [27,33,127]. This 3D computer controlled pencil beam scanning is, in analogy with photon IMRT, called intensity modulated proton therapy or IMPT. Depending on the time structure of the proton beam from the accelerator, IMPT can be delivered in different ways [127]. The dose from the pencil beam can be deposited as a sequence of static applications (discrete spot scanning) [95,167] or as a continuous scanning of the pencil beam, on a raster pattern, throughout equal-range layers (raster scanning) [82,132].

## Radiobiology of protons (and ions)

The biological effects of a proton beam are close to those of photons. This implies that most of the knowledge from photon therapy can be applied also to protons, with respect to treatment protocols. However, protons have a slightly higher relative biological effectiveness (RBE) compared to photons and electrons and in general, a clinical RBE of 1.1 (with  $^{60}\text{Co}$  used as reference) is applied over the entire SOBP [8,68]. As the proton energy decreases at the end of the range, the linear energy transfer (LET) increases, and thus also the RBE. Gerweck and Kozin [59] reviewed RBE data from several studies and found RBE values between 1.1 and 1.6 with a tendency that RBE increases with depth of the beam. Early researchers also made similar observations [45,110]. Figure 4 shows the results of a RBE corrected depth dose curve, where also the calculated RBE is shown as a function of proton range.

The calculation was made by averaging the LET at each depth for all the individual Bragg peaks contributing to the dose. An effect of the RBE correction is that the effective range of the beam increases by a few millimetres, which may be important in certain applications. The RBE corrected dose was calculated using the linear-quadratic cell survival model with tissue specific parameters for cell survival as a function of LET (**Paper III**). Uncertainties in the in vitro and the clinical in vivo data are still large, but until these are resolved, a clinical RBE of 1.1 is used [68].

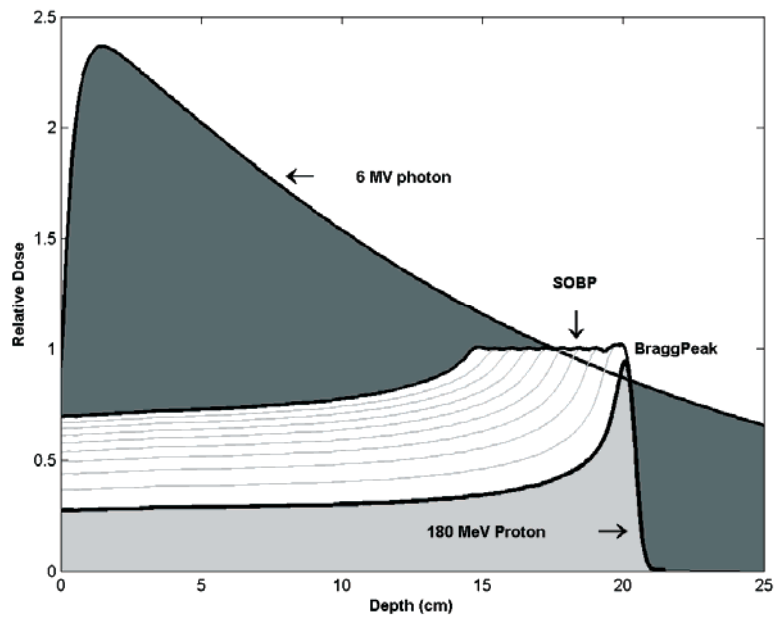


Figure 3. Central-axis depth dose curves for one mono-energetic 173 MeV proton beam (light grey), one spread out Bragg peak based on the mono-energetic 173 MeV proton beam and 6 MV photon beam (dark grey).

Compared to protons, light ions have an even higher LET and RBE in the Bragg peak region while the RBE is still fairly low in the entrance region [28]. The heavy ions have not only higher RBE in the Bragg peak but also, in the entrance region of the beam which can introduce too much normal tissue damage [28]. Well oxygenated tumours are less radio-resistant than hypoxic tumours and an argument for light ions compared to protons is that the treatment of tumours containing many hypoxic cells would be improved [25].



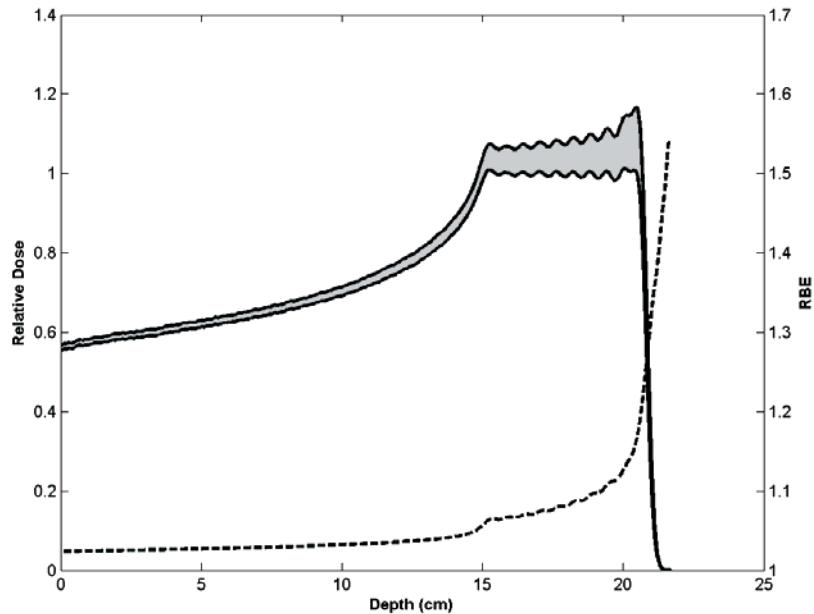


Figure 4. Central-axis depth dose curves for one spread out Bragg peak built from the mono-energetic 173 MeV proton beam and one corrected for RBE (lower solid line not corrected for RBE, upper solid line corrected for RBE), grey indicate excessive dose). The RBE correction for the corresponding 173 MeV proton beam is also shown (dashed lines).

## Clinical experience with IMRT and protons (and ions)

The clinical outcome of IMRT has so far mainly been reported from early clinical trials, and no definite trials directly revealing superiority over 3D-CRT have been published. The studies have typically concerned the feasibility of the techniques, investigating toxicity and presenting only preliminary, however promising, results of efficacy. The most common tumour sites so far treated with IMRT have been various tumours in the head and neck region [7,20,40,43,76,112,154,165,228], and prostate cancer [40,90,228]. Also lung cancer [14,73,188], gynaecologic malignancies [14,73,188] and miscellaneous cancer sites [79,141,186] have been treated with IMRT. The experience using IMRT has been summarised in many recent reviews e.g. [12].

For protons and ions, several studies have been published providing results concerning local control, survival and toxicity. The situation for protons is otherwise similar to that of IMRT, i.e. there are no randomised trials, with only one exception, for prostate cancer [233]. Skull-base chordomas and chondrosarcomas have been treated with doses between 60-79 CGy with protons [80,157,176,220] and carbon ions [187]. Local control is generally

higher for chondrosarcomas (90-100%) compared to chordomas (76-87.5%) [80,157,176,187,220]. For meningiomas, high tumour control and an overall survival between 90-100% have been reported [66,67,156,219]. In the treatment of arteriovenous malformations in the brain, the relations between dose and volume are very important, and protons may provide particular benefits for the larger malformations not possible to optimally treat with any other method [119,191,202,223]. Protons have also been extensively used in the treatment of intraocular melanomas, particularly when large and centrally located, due to the favourable dose distribution of the proton beam [42,120,155]. There are also several other tumour types investigated using both protons and carbon ions, e.g. lung cancer [16,31,105,149,152] and prostate cancer [88,194,233]. An overview of studies using charged particles, particularly protons was recently published in a special issue of *Acta Oncologica* (Vol 44, No 8, 2005).

## Aims of the thesis

The overall aim of this thesis is to investigate the potential clinical advantages of various techniques and modalities in radiotherapy. A primary aim is to investigate the potential advantages of protons and IMRT compared to conventional 3D-CRT. The comparisons are based on calculated physical dose distributions for the respective technique. Whenever possible, dose-response models have been used to predict the outcome of patient treatments. Three tumour locations have been selected in the comparisons, left-sided node positive breast cancer, hypopharyngeal carcinoma, and rectal cancer. In all locations, locally advanced tumours were selected. A secondary aim has been to investigate the potential clinical relevance of the slightly increased relative biological effectiveness at the end of the proton range.

## Treatment Planning Comparisons

Most of the early clinical trials investigating the use of IMRT, protons, and other ions show encouraging results both regarding efficacy and toxicity. Large investments in new facilities, and knowledge of these new techniques should be based upon proven superiority of one technique compared to others. In the long term perspective large prospective and controlled clinical trials are needed for evidence based assessment of the various techniques and modalities. As the availability of IMRT, proton and ion beam therapy increases, it will be easier to initiate the necessary clinical studies comparing the different techniques. To initiate such clinical studies, an indication of the potential magnitude of benefit from a certain technique is valuable when designing the study. To correctly design a clinical trial, the difference in the expected outcome of the different techniques must be approximated in either absolute or relative terms. However, the number of facilities (IMRT, protons or ions) available for treating large series of patients required to claim the superiority of one technique over another is still limited. It could be discussed why conclusive evidence from trials is still lacking; despite over 40000 patients have been treated with charged particles. This is not unique for charged particles, but is also seen for many other sophisticated new treatment modalities [139]. The investments in new technology today are sometimes more based on encouraging results from preliminary evidence than solid evidence from trials. However, concerning radiation therapy, model treatment planning studies contribute to the knowledge about potential gains. In treatment planning studies, patient treatments are compared using calculated dose distributions for the various techniques.

Treatment planning comparisons have also been used to compare different techniques and modalities in attempts to predict differences in treatment outcome for a patient. The studies have been comparing dose volume statistics for tumours/targets and OARs. Most treatment planning comparisons are made using calculated dose distributions for various techniques and the results generally show superiority for protons and light ions compared to IMRT. Some of the treatment planning studies have also included attempts to predict the outcome by using dose-response models that give an estimate of TCP and NTCP. In this thesis, both comparisons of dose-distributions and dose-response models have been used to compare protons with IMRT and protons and IMRT with 3D-CRT. Table 1 shows a list of published treatment planning comparisons, where protons have been included as one part of the

comparison. There is a large variety in how the studies were performed. The early studies compared 3D-CRT (or a conventionally given standard treatment) and protons, neither IMRT nor IMPT were then available. Several of the newer comparisons have included both IMRT and IMPT, but only comparably few studies have estimated the possible clinical outcome using dose-response models. The number of patients included in the studies also varies significantly, actually, most of them only included one patient.

Table 1. Comparative treatment planning studies (Reproduced from [60], with permission)

| Reference                | Year | Tumour type                    | Number of patients planned | Photons |      | Protons |         | Comments   |
|--------------------------|------|--------------------------------|----------------------------|---------|------|---------|---------|--|
|                          |      |                                |                            | 3D-CRT  | IMXT | Passive | Scanned |  |
| Suit et al [205]         | 1988 | Cervical cancer                | 1                          | X       |      | X       |         | Better dose distributions with improved local control, less toxicity   |
| Brown et al [30]         | 1989 | Nasopharynx                    | 2                          | X       |      | X       |         | Better dose distributions with improved local control, less toxicity   |
| Urie + Gotein [211]      | 1989 | Chordoma/<br>chondrosarcoma    | 12                         | X       |      | X       | X       | Variably (intensity) modulated protons reduce dose to normal tissues (integral dose by 3 – 12%-units) compared to fixed (SOBP) protons, however, the largest difference was between protons and photons (2 patients) |
| Austin-Seymour et al [9] | 1990 | Skull base                     | 1                          | X       |      | X       |         | Less dose to OARs, e.g. the optic nerve  |
| Austin-Seymour et al [9] | 1990 | Prostate                       | 1                          | X       |      | X       |         | Less dose to OARs  |
| Tatsuzaki et al [209]    | 1991 | Rectum                         | 1                          | X       |      | X       |         | Reduced dose to small bowel using protons  |
| Archambeau et al [5]     | 1992 | Thalamic pediatric astrocytoma | 1                          | X       |      | X       |         | Improved dose distribution, lower normal brain dose, higher tumour dose possible   |

|                              |      |                                   |    |   |   |  |
|------------------------------|------|-----------------------------------|----|---|---|--|
| Gademann & Wannenmacher [55] | 1992 | Pediatric retroperitoneal tumours | 1  | X | X | Better dose localization, less second cancers  |
| Levin [117]                  | 1992 | Para-aortic nodes, cervix cancer  | 1  | X | X | Higher doses could be reached using protons, improved tumour control by 10 – 20%                       |
| Miralbell et al [144]        | 1992 | Maxillary sinus                   | 1  | X | X | Less dose to OARs using a proton boost   |
| Slater et al [196]           | 1992 | Tonsil                            | 2  | X | X | Superior dose distributions, higher tumour doses, less doses to OARs (chiefly mandible parotid glands) |
| Smit [197]                   | 1992 | Cervical cancer                   | 1  | X | X | Higher doses (by 20%) could be reached using protons, 40% increase in tumour control                   |
| Tatsuzaki et al [208]        | 1992 | Glioblastoma                      | 1  | X | X | Less dose to non-target brain using protons  |
| Wambersie et al [212]        | 1992 | Pediatric brain tumours           | 3  | X | X | Less dose to non-target brain using protons  |
| Miralbell & Urie [148]       | 1993 | Large AVM                         | 1  | X | X | Less dose to non-target brain, brain stem and optic chiasm using protons                               |
| Lee et al [114]              | 1994 | Prostate                          | 12 | X | X | Distinctly reduced rectal NTCP using protons in one-third of the cases, minimal gain in the remaining  |
| Isacsson et al [87]          | 1996 | Rectum                            | 6  | X | X | At 5% NTCP any organ, TCP is increased by 14%-units with protons                                       |

|                       |      |                                       |    |   |   |   |   |  |
|-----------------------|------|---------------------------------------|----|---|---|---|---|--|
| Isacsson et al [85]   | 1997 | Ewing/paraspinal                      | 1  | X |   | X |   | At 1% NTCP in spinal cord, TCP is increased by 5%-units  |
| Miralbell et al [145] | 1997 | Medulloblastoma-supratentorial target | 1  | X | X |   | X | Better sparing normal tissues with protons and IMXT compared to conventional with less IQ-reduction  |
| Miralbell et al [147] | 1997 | Medulloblastoma-spina techa target    | 1  | X | X |   | X | Decreased dose to all critical organs using protons  |
| Sandison et al [179]  | 1997 | Chest wall                            | 1  | X |   | X |   | Less lung dose using protons   |
| Isacsson et al [86]   | 1998 | Oesophagus                            | 5  | X |   | X |   | At 5% NTCP in any organ TCP is increased by 20%-units (from 2 to 25%) with protons                   |
| Verhey et al [222]    | 1998 | CNS                                   | 5  | X |   | X |   | Less dose to normal brain  |
| Fuss et al [53]       | 1999 | Optic nerve, gliomas                  | 7  | X |   | X |   | CI 2.9 photons, 2.3 protons, larger differences in larger tumours                                    |
| Glimelius et al [61]  | 1999 | Sacral chordoma                       | 1  | X |   | X |   | Lower doses to rectum and urinary bladder using one proton beam compared to 3D-CRT photons           |
| Lee et al [113]       | 1999 | Lung                                  | 13 | X |   | X |   | More patients could be treated to higher tumour doses using protons compared to any photon technique |
| Lomax [127]           | 1999 | Nasopharynx                           | 1  |   |   | X | X | Intensity modulation show advantages when few beams are used   |



|                         |      |                              |     |   |   |   |   |   |
|-------------------------|------|------------------------------|-----|---|---|---|---|---|
| Lomax et al [129]       | 1999 | Various                      | 9   | X | X |   | X | Reduced medium to low dose for protons compared to IMXT   |
| Fuss et al [54]         | 2000 | Pediatric optic nerve glioma | 7   | X |   |   | X | Reduced NTCPs, likely clinically significant for cognitive impairment   |
| Lin et al [122]         | 2000 | CNS, pediatric fossa         | 9   | X |   |   | X | Protons result in increased normal tissue sparing, e.g. the cochlea (25% of dose compared to 75% of prescribed dose)              |
| Miralbell et al [143]   | 2000 | Orbital and paraorbital      | 4   |   |   | X | X | Similar PTV coverage, lower integral doses to OARs (x1.5-1.9), predicted NTCPs (severe late tox) similarly low                    |
| Oelfke + Bortfeld [158] | 2000 | -                            |     |   |   | X | X | IMPT advantages to SOBP protons and IMXT in a theoretical study, integral dose 30% lower using IMPT vs SOBP, a factor 2-3 vs IMXT |
| Paulino et al [166]     | 2000 | Medulloblastoma              | 5   | X |   |   | X | Lower doses to all risk organs  |
| Smith et al [198]       | 2000 | Multiple sites               | 10+ | X | X | X | X | Improved clinical outcomes at all sites, reduced NTCPs/higher TCPs  |
| Zurlo et al [234]       | 2000 | Pancreas/biliary             | 4   | X | X |   | X | Protons allowed delivery of planned dose in all patients, not or barely possible with photons                                     |
| Baumert et al [11]      | 2001 | CNS                          | 7   | X |   |   | X | For complex PTV shapes and when PTV close to critical organs, protons yield better dose distributions than photons for SRT        |

|                                    |             |  |           |          |          |          |   |   |
|------------------------------------|-------------|--|-----------|----------|----------|----------|---|---|
| Cella et al [34]                   | 2001        | Prostate                                 | 1         | X        | X        | X        | X | Both IMXT and IMPT gave better dose distributions than non-IM plans and less NTCP in rectum, all proton plans improved PTV homogeneity and reduced medium-low dose in normal tissues compared to the photon plans |
| Cozzi et al [37]                   | 2001        | Head and neck                            | 5         | X        | X        |          | X | Protons give improved dose homogeneity, higher EUD, better preserved organ function and quality of life   |
| <b>Johansson et al<br/>Paper I</b> | <b>2002</b> | <b>Breast</b>                            | <b>11</b> | <b>X</b> | <b>X</b> | <b>X</b> |   | <b>Lowest NTCP values for protons for the heart (0.5 vs 2.1%) and lung (0.6 vs 14.7%) compared with the best other plan</b>   |
| Miralbell et al [146]              | 2002        | Pedicatric rhabdo-<br>myosarcoma         | 1         | X        | X        | X        | X | Reduced risk of sec. malignancy by $\geq 2$   |
| Miralbell et al [146]              | 2002        | Medulloblastoma                          | 1         | X        | X        | X        |   | Reduced risk of sec. malignancy by a factor of 8 - 15   |
| Bolsi et al [15]                   | 2003        | Small intracranial,<br>different tumours | 12        | X        | X        | X        | X | Improved CI, reduced OAR dose at all sites, less sec. cancer induction  |
| Lomax et al [130]                  | 2003        | Breast                                   | 1         | X        | X        | X        |   | Protons spare lungs and heart better than IMXT/standard treatment   |
| Lomax et al [131]                  | 2003        | Paranasal sinus                          | 1         |          | X        |          | X | Critical structures could be spared best by protons at all dose levels  |
| Suit et al [204]                   | 2003        | Rectum                                   | 1         |          | X        | X        |   | Improved dose distribution, less toxicity   |

|                                     |             |                      |           |          |          |   |          |   |
|-------------------------------------|-------------|----------------------|-----------|----------|----------|---|----------|---|
| <b>Johansson et al<br/>Paper II</b> | <b>2004</b> | <b>Hypopharynx</b>   | <b>5</b>  | <b>X</b> | <b>X</b> |   | <b>X</b> | <b>Protons give lower non-target doses compared to 3D-CRT/IMXT. NTCP parotid glands 40 – 43% protons, 51 – 65% IMXT, 93+% 3D-CRT</b>                            |
| Mock et al [150]                    | 2004        | Paranasal sinus      | 5         | X        | X        | X |          | Similar CI but reduced doses to OAR (by 60%) and integral doses using protons   |
| St Clair et al [200]                | 2004        | Medulloblastoma      | 1         | X        | X        | X |          | Substantial normal tissue sparing, e.g. to the cochleas and the heart   |
| Weber et al [221]                   | 2004        | Paraspinal sarc      | 5         |          | X        |   | X        | Similar conformity, reduced integral dose to OARs, dose escalation to 93 CGE possible with protons  |
| Yoch + Tarbell<br>[231]             | 2004        | Pediatric, CNS       | 2         | X        | X        | X |          | Better dose homogeneity and conformity  |
| Krengli et al [106]                 | 2005        | Retinoblastoma       | 3         | X        |          | X |          | Protons can achieve significant lens sparing and reduced risk of second malignancies  |
| Mu et al [153]                      | 2005        | Medulloblastoma      | 5         | X        | X        |   | X        | Risk second cancer conv RT 18%, IMXT 28%, IMPT 4%   |
| <b>Johansson et al<br/>Paper IV</b> | <b>2006</b> | <b>Rectal Cancer</b> | <b>16</b> | <b>X</b> | <b>X</b> |   | <b>X</b> | <b>50% reduction of NTCP using IMXT or protons. If the small bowel is a serial organ, 50% reduction using IMXT and 90% using protons if it is more parallel</b> |

## Treatment planning systems

The main treatment planning system (TPS) used in this thesis is the Helax-TMS™ (Treatment Management System, NUCLETRON, Uppsala, Sweden). The system provides algorithms for photons, electrons and protons, making it suitable for treatment planning comparisons. The dose calculation algorithms in the TPS have been described in detail elsewhere [4,177,178]. For the proton calculations in **Paper I, II, and III**, the 180 MeV clinical beam at the T Svedberg laboratory has been used. Monte Carlo calculated proton beams with higher energies (200 and 230 MeV) were also introduced into the TPS [101] since the range of the 180 MeV proton beam was not sufficient for the most deep-seated targets (**Paper IV**).

A gradient based optimisation algorithm for IMRT is available in the TPS with various modifications in different versions of TMS [70,71]. These algorithms were used in **Papers I and II**. The optimised fluence profiles from Helax-TMS IMRT are segmented into MLC settings a predefined number of times during the optimisation and this may influence the dose distribution negatively. In **Paper IV** Oncentra Masterplan 3.0 (NUCLETRON) with an IMRT algorithm from Raysearch Laboratories was used [81,126]. This algorithm uses a direct aperture optimisation (DAO).

In Helax TMS two different proton algorithms are available, a depth penetration algorithm and a pencil beam kernel algorithm [177,178]. The differences between the algorithms are in the accuracy and the calculation time. The depth penetration algorithm is fast and therefore suitable for interactive treatment planning, where beam direction and proton range are optimised manually. The dose prediction accuracy of depth penetration algorithms is limited, particularly in the vicinity of heterogeneities [74,168,182,184]. For the passively scattered proton beams, a range modulator with suitable SOBP is applied to cover the entire target with homogenous dose for each beam direction. The planning of the scanned beam means, firstly, a calculation of range compensation filters, defining the maximum range of the proton beam, and, secondly, a calculation of the modulation range which varies over the beam portal allowing the SOBP to be conformed to both the distal and proximal target extension.

The calculated range compensation filter often needs manual adjustments. For the final dose calculation the more accurate pencil kernel algorithm is used [177,178]. Several other similar pencil beam kernels algorithms have been published [74,168,182,184,207]. For target volumes with complicated shapes the planning becomes an iterative process where the plans must be evaluated with slightly modified range compensation filters. Full 3D IMPT is not available in Helax-TMS, and therefore it has not been used in any of the comparisons in this thesis.

## Design of treatment planning comparisons

### General considerations

In this thesis, the treatment planning studies have had the following design:

1. In all studies, protons and IMRT were compared to conventional planning (3D-CRT) used in the clinic today. The objectives were the same concerning dose homogeneity, i.e. as homogenous dose as possible to the targets.
2. Targets/tumours for several patients were planned to simulate the anatomical variability between patients with the same disease. Five or more patients were used in the investigations.
3. The evaluations included physical dose-volume information for the tumour and relevant risk volumes.
4. Dose response models were used to investigate the potential clinical outcome of the treatment. For all studies NTCP and, for one study, TCP was calculated. Since input parameters of these models suffer from uncertainties, different approaches for sensitivity analyses were made both for the TCP and for the NTCP calculations.

### Physical dose-volume evaluation

In all treatment planning studies, the dose volume histograms for the planning target volume (PTV) were used to describe the dose given to the tumour. ICRU 62 [84] recommends that dose distributions are normalised to a reference point within the PTV to ensure a precise dose delivery. This is not always suitable for treatment planning comparisons, particularly if the dose distributions are inhomogeneous, which is the case for the IMRT plans. Therefore, the mean dose to the PTV was used as normalisation in the comparisons.

One way of evaluating the dose coverage in target volumes or dose burdens to OARs is to calculate volumes receiving more dose than a specified dose level. Such volumes can be extracted from DVHs. These volumes are typically denoted as  $V_{\text{dose}}$  and the volumes and dose levels can be given either in absolute or in relative terms. Other measures that can be calculated from DVHs are e.g. mean and integral doses, and efficiency factors that sometimes can be useful for comparisons. Significant maximum and minimum doses should, however, be explored directly in the dose distributions since information on position and extent of each maximum or minimum will be lost in a DVH. Several conformity indices have also been suggested [84,102,214] as a measure of how well a dose distribution is shaped around the PTV.

## Modelling treatment outcome with dose-response models

Several models for calculating tumour control have been proposed (e.g. [23,123,137,218]). The basic model used in **Paper I, II, III** and **IV** used to determine the tumour and normal tissue response was the linear Poisson model or the equivalent linear quadratic Poisson model [123]. This model was selected since input parameter data have recently become available for many risk organs. The probability for controlling a tumour or induce a certain injury to an organ is given by

$$P(D) = e^{-e^{\gamma - (nd / D_{50})(e\gamma - \ln \ln 2)}} \quad (1)$$

The tumour control probability for a heterogeneous tumour can then be calculated from:

$$TCP = \prod_i^N P_i(D)^{\Delta v_i} \quad (2)$$

The normal tissue complication probability according to the relative seriality model [94] is defined as

$$NTCP = \left[ 1 - \prod_i^N [1 - P_i(D)^s]^{\Delta v_i} \right]^{\frac{1}{s}} \quad (3)$$

where  $D_{50}$  is defined as the dose for which the response is 50%, and  $\gamma$  is defined as the maximum normalised value of the dose response gradient and  $s$  is a relative seriality parameter describing the structure of the organs (serial or parallel). The parameters  $D_{50}$ ,  $\gamma$  and  $s$  are determined for a fixed fraction size, usually 2 Gy per fraction. The dose input to these models then requires fraction sizes equivalent to 2 Gy. Therefore, every dose step in a DVH must be recalculated to represent a 2 Gy equivalent dose. The main approach was to use every single dose step as input to the models. The consequence of this is that TCP values were calculated as a worst case value, since the lowest TCP value determines the level of tumour control (**Paper II**). The uncertainties in the model parameters may be large, and therefore sensitivity analyses of TCP and NTCP calculations were made in selected cases to investigate to what extent the parameter uncertainties will influence the predicted outcome for different treatment techniques.

In the rectal cancer **Paper (IV)** the main OAR is the small bowel. No updated parameter data for the small bowel have been published recently. Gagliardi et al [57] derived a set of parameter data for  $D_{50}$ ,  $\gamma$ , and  $s$  for cardiac

mortality based on clinical data. In that study clinical data for a given risk was available, but the input DVHs were not. The approach used then was to simulate a number of model patients with the treatment technique used and derive new DVHs to be used for modelling. The parameter values for  $D_{50}$ ,  $\gamma$ , and  $s$  values could then be derived using the average DVH of the model patients and the risk for cardiac mortality as input to the dose response model. Other methods use DVHs from individual patient treatments and each patient is followed to obtain specific set of parameters for a selected endpoint [56].

Here a simple model is described to obtain approximate values for  $D_{50}$ ,  $\gamma$ , and  $s$  for the linear quadratic Poisson dose response model from a set of model patients using their average DVH. The idea is to derive  $D_{50}$  from relevant data of  $\gamma$ ,  $s$ , and  $\alpha/\beta$ . Common values of  $\gamma$  are usually between 1 and 4, and  $s$  is defined by the structure of the organ and must be between 0 (parallel) and 1 (serial).  $\alpha/\beta$  is either usually low (3 Gy) for late responding tissue while for acute responding tissues it is high (10 Gy). Within these limits, a parameter space can be derived for  $D_{50}$  with corresponding values for  $\gamma$ , and  $s$  for specific clinical endpoints with an associated NTCP value. This method was applied in **Paper IV** to derive  $D_{50}$  as a function of  $\gamma$  and  $s$  for the acute endpoint (diarrhoea) and for the late endpoint (obstruction, ileus), see Figure 5. In these two cases,  $D_{50}$  is nearly constant independent of the value of  $\gamma$ . Evaluating NTCP for various treatment techniques should then be made for the entire parameter space.

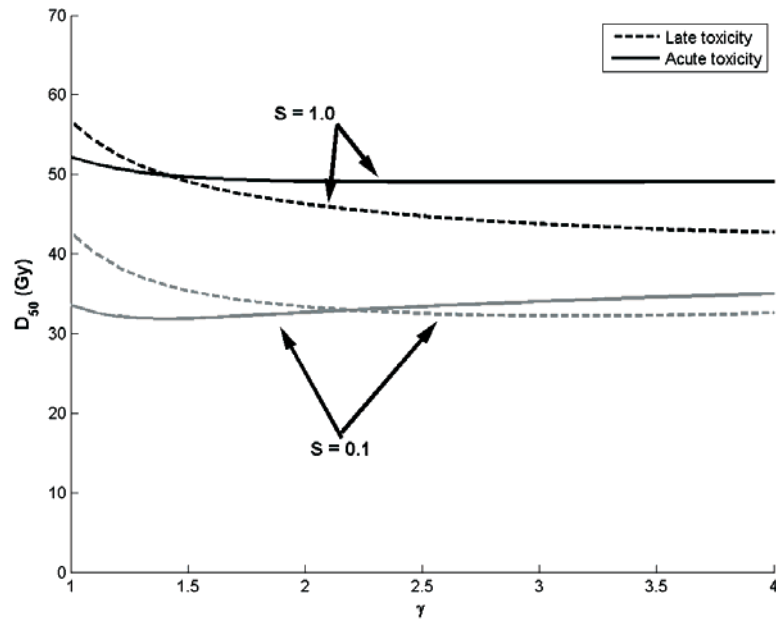


Figure 5. Parameter space for late and acute toxicity for rectal cancer.  $D_{50}$  plotted as a function of  $\gamma$  and  $s$ .

## Results and discussion

### Left-sided node positive breast cancer (Paper I)

Loco-regional radiotherapy after mastectomy or breast-conserving cancer surgery decreases loco-regional recurrence rates with a factor three or more [1], and result in a small but definite increase in survival. After radiotherapy, the risk for lung toxicity is about 10% [125], and it correlates well with a dose level of 20 Gy to 30% of the volume. The dose to the heart and the lungs varies depending on how many of the internal mammary nodes (IMN) are included in the target volume, i.e. how far distally along the chain the target extends [181]. Early studies showed a markedly increased risk of severe cardiac mortality, up to 7% after 10 years [57], whereas later studies have shown less risk [160,161]. Loco-regional RT of breast cancer where also the IMN are included in the target volume is complex with difficulties to spare volumes of lung and heart and requires advanced techniques to achieve satisfactory dose distributions [91,124]. Several authors have suggested tangential plan optimisation with the objective to obtain a more homogenous dose distribution [35,75,98,171]. One report deals with clinical implementation of IMRT for breast cancer [38]. Sandison suggested a proton arc technique aiming at minimising dose to lung tissue [179]. Three planning comparisons between protons and photons for breast cancer have been performed. One study, reported by Fogliata et al [47], did not include the lymph nodes, whereas the two other studies did (including the IMNs) (**Paper I** and [130]). They concluded that it is possible to achieve the same target homogeneity or spare the surrounding tissues to about the same extent with either of the techniques, but that only protons could result in both a homogeneous dose within PTV and low doses to surrounding tissues.

In **Paper I**, eleven consecutive left-sided stage II (UICC stage T1–2 N1–2 M0) breast cancer patients were included in the comparison. The target volume included the breast parenchyma, and the lymph nodes in the supraclavicular fossa, the axilla and the parasternal region (IMN). The treatment planning was performed with four different techniques, one tangential (3D-CRT) and one patched technique with photons and electrons (3D-CRT), IMRT and protons. All plans in **Paper I** including IMRT were made with Helax-TMS. The dose given to the tumour volumes was assumed to be appropriate for controlling the disease and the same TCP can thus be expected for all the techniques. The difference between the plans is mainly due to a reduction of dose to the left lung and the heart. The results, in terms of NTCP (Table 2),



clearly show an advantage using protons as compared to the other techniques.

During the past few years, IMRT has been tuned to yield even better treatment plans than was possible to achieve in **Paper I**. Therefore, all IMRT plans have been replanned in Oncentra Masterplan 3.0 (OM3.0) using DAO (Figure 6). The main objectives for the lung and heart were taken from the IMRT algorithm comparison by Fogliata [48] which had a similar target definition, including also IMN, but a stronger homogeneity constraint was set for the PTV. In order to push the more powerful OM3.0 optimiser to its limits, other objectives than those used with the old TMS optimiser, had to be used. The results from the OM3.0 optimisation are similar to the results reported by Fogliata [48].

In the new IMRT optimisation, a more homogeneous dose distribution is achieved, and less dose is given to both the lung and heart. The calculated risk for cardiac mortality decreased to nearly 1% and the risk for radiation induced pneumonitis decreased from 28.2% to 2.5% by using OM3.0 compared to the old TMS optimisation (Table 2).

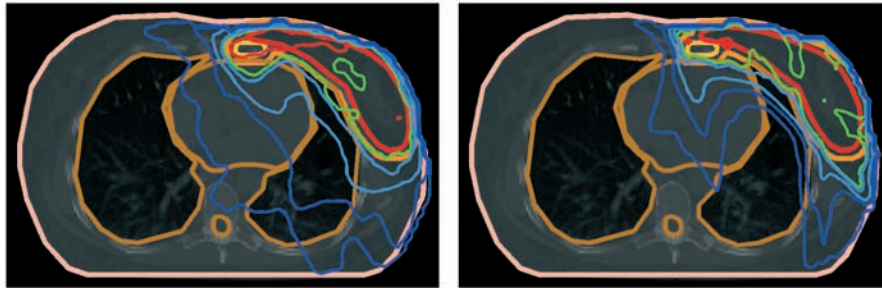


Figure 6. Two IMRT treatment plans optimised with TMS 5.0 (left) and OM3.0 (right). Note that dose to the left lung is much lower using the OM3.0 optimised plan.

Breast cancer is a large group of patients and the size of the subgroup that would require these complex treatments in order to have very low risks of late toxicity can still be considerable. Comparing the different techniques, protons appear superior with very low NTCP values for both the heart and lungs. However, the differences in NTCP are small when comparing with a new and more powerful IMRT optimiser. Some patients may still benefit sufficiently from protons compared to IMRT. This fraction can not be estimated with any certainty. Other factors may also be of relevance with protons, such as a higher skin dose or a lower integral dose with less risk of late radiation-induced secondary malignancies.

Table 2. NTCP values for heart and lung for the 4 techniques used in **Paper I** and a new improved IMRT technique. Abbreviations: PTV = planning target volume; IMRT = intensity-modulated radiotherapy,  $V_{105}$ ,  $V_{95}$ ,  $V_{90}$ , = partial volume (%) receiving more than 105, 95, 90 dose.  $D_{average}$  = average dose in volume, NTCP = normal tissue complication probability.

|       |                    | Protons    | IMRT <sub>TMS</sub> | Patched     | Tangential  | IMRT <sub>OM3.0</sub> |
|-------|--------------------|------------|---------------------|-------------|-------------|-----------------------|
| PTV   | $V_{90}$ (%)       | 97.5 ± 1.7 | 93.3 ± 1.6          | 92.7 ± 1.7  | 98.5 ± 0.9  | 98.7 ± 0.8            |
|       | $V_{95}$ (%)       | 94.0 ± 2.7 | 85.9 ± 2.5          | 84.4 ± 2.7  | 93.2 ± 3.2  | 92.2 ± 4.1            |
|       | $V_{105}$ (%)      | 8.6 ± 8.3  | 22.5 ± 3.5          | 24.7 ± 5.7  | 11.1 ± 4.7  | 10.5 ± 4.6            |
| Heart | NTCP               | 0.5 ± 0.5  | 2.2 ± 1.7           | 2.1 ± 1.1   | 6.7 ± 2.7   | 1.3 ± 0.4             |
|       | $V_{35Gy}$ (%)     | 1.4 ± 1.0  | 11.0 ± 7.6          | 10.5 ± 4.6  | 19.3 ± 6.6  | 9.0 ± 2.3             |
|       | $V_{45Gy}$ (%)     | 0.8 ± 0.8  | 2.2 ± 2.2           | 2.3 ± 2.0   | 13.1 ± 6.1  | 0.2 ± 0.1             |
| Lung  | NTCP               | 0.6 ± 0.8  | 28.2 ± 9.7          | 14.7 ± 10.2 | 28.3 ± 15.9 | 2.5 ± 0.6             |
|       | $V_{20Gy}$ (%)     | 20.7 ± 9.1 | 65.6 ± 9.2          | 45.5 ± 9.0  | 49.1 ± 8.9  | 22.9 ± 0.7            |
|       | $V_{25Gy}$ (%)     | 17.4 ± 7.9 | 55.9 ± 9.4          | 40.0 ± 8.9  | 47.3 ± 9.7  | 18.6 ± 0.7            |
|       | $D_{average}$ (Gy) | 9.8 ± 3.8  | 27.5 ± 2.8          | 21.7 ± 4.0  | 24.5 ± 4.5  | 17.2 ± 0.7            |

## Hypopharyngeal carcinoma (Paper II)

For patients with locally advanced head and neck (H&N) cancers stage T3-4N0, treated with a standard schedule of 70 Gy given in 35 fractions, a local control of about 40-50% is obtained after 2 years [52,78,159]. A local recurrence at the primary site is a common reason for failure [92] and much effort is spent to increase local control. Several studies have shown an increase in local control and disease specific survival by using accelerated or hyperfractionated treatment schedules. There is, however, little difference in overall survival between the different schedules [232]. The randomised trials have used 3D-CRT planning to investigate the effects of the altered regimens. The use of moderately accelerated or hyperfractionated schedules have not introduced more late toxicity [52,78,159], whereas more aggressive regimens have resulted in unacceptable late toxicity [89]. The risk for acute toxicity, particularly confluent mucositis, is generally higher in accelerated treatments as compared to conventional treatments, which limits the use of these treatments [52,78,159,193].

H&N tumours often have complex shape and several organs are at risk, which means that tumours in the H&N region are sites of interest for IMRT. With modern treatment techniques, it is meaningful to be more precise in the target definitions. For example, one department reported a significant decrease in target volumes after a few years use of IMRT [189]. A wide variation between departments has also been reported for a tonsil cancer case [77]. However, new recommendations for delineation of tumour and nodal

regions of the H&N are under development [64,116]. The target volumes in **Paper II** were delineated as if the treatments were designed for 3D-CRT. They were not updated for more conformal techniques [64,116], but still representative of advanced hypopharyngeal cancer target volumes. The PTV was divided into three volumes, where PTV1 was the primary tumour and PTV2 and 3 were the right and left side lymph node volumes, respectively.

In the H&N region, the prescribed total dose is higher for the primary tumour than for the lymph-node targets. With 3D-CRT techniques, the extra dose to the primary tumour is given as a boost. For conformal techniques such as IMRT or protons, another strategy has been proposed, the simultaneously integrated boost (SIB). This means that the primary target (PTV1) is given a relatively high dose per fraction, while the targets with subclinical involvement (PTV2-3) receive a lower, but sufficient dose per fraction. Several fractionation schedules have been suggested [32,39,112,151,230]. To control subclinical disease in the lymph nodes, the prescription dose should be about 50 Gy in 2 Gy fractions, but slightly lower fraction doses can be used with maintained beneficial effects [227]. A dose of 1.8 Gy per fraction has been suggested [151,229]. This altered fractionation schedule results in a dose escalation which appears to be clinically feasible [32,112]. and suitable for both IMRT and protons. However, acute and late effects of such a fractionation must be investigated further.

Several treatment planning studies comparing dose distributions for various H&N tumour sites have been performed for different techniques. One study included only protons [127], whereas protons have been compared with 3D-CRT and IMRT in the others [37,129,131,150]. These studies generally show that proton beams result in improved dose distributions, particularly regarding volumes receiving low and inter-mediate doses. In **Paper II**, calculations of NTCP and TCP have also been performed.

In **Paper II**, treatment plans were prepared for five patients using 3D-CRT (standard fractionation 2 Gy per fraction with 35 fractions), IMRT, and protons (2.39 Gy per fraction with 30 fractions). The resulting dose distributions were used to quantify the potential gains according to dose-response models. **Paper II** shows that there is no significant difference in target coverage between IMRT and protons for the PTVs. The main difference is seen in the dose to the non-target tissues, where protons give lower doses.

By increasing the fraction dose from 2 Gy given in 35 fractions to 2.39 Gy given in 30 fractions, it is possible to increase TCP from 38% to 55%. A further increase in dose to the primary tumour would theoretically give an even larger gain in TCP. In the comparison between IMRT and protons, the fractionation schedule was the same and TCP values of about 55% were found for both techniques. In Figure 7, the reliability of these values was tested in a sensitivity analysis. The ratio between the average TCP for the 3D-CRT plans on the one hand and the IMRT and proton plans on the other

hand was nearly independent of  $D_{50}$ , while the ratio increased slightly with increasing  $\gamma$ .

NTCP values were calculated for the parotid glands using parameter values from Schilstra [183]. The NTCP values for the parotid glands favour the proton and IMRT plans compared to the conventional plans. However, there is a large individual spread in the NTCP for the parotid glands and it is difficult to find a general superiority for either protons or IMRT based upon this treatment planning study. NTCP values varied between 3-91% for the proton plans and between 22-99% for the IMRT plans, whereas they were well above 90% for all the conventional plans. The NTCP values for the parotid glands will depend on clinical decisions regarding target delineation and the type of technique used. In this study, the parotid glands were spared so that the CTV was delineated side by side with the parotids. When adding the PTV margin, it partly covered the parotid glands, which means that part of the parotid gland received full dose.

IMRT and protons provided sufficient doses, according to the prescription, to the target volumes, whereas the 3D-CRT plan did not, using a slightly lower dose prescription. IMRT and protons also improved the sparing of the OARs compared to 3D-CRT. The results from this, and other studies, indicate that IMRT and protons offer more flexibility in the treatment planning than 3D-CRT. The sparing of OARs with IMRT and protons provides, at the same time, a possibility for dose escalation to the target volume. This could result in increased local tumour control and survival compared to standard 3D-CRT techniques. The 3D-CRT technique could also spare non-target tissue, but only because of insufficient lymph node target coverage. Both IMRT and protons give approximately the same coverage of the target volume, although there is a difference in the low doses to non-target volumes, favouring protons.

In a comparison between different IMRT optimisers, TMS gave higher doses to normal tissues compared to two other systems. Thus, it could be argued that IMRT could probably do slightly better than was achieved in **Paper II** [46]. However, protons could also achieve even lower doses to non-target tissues, e.g. using IMPT.

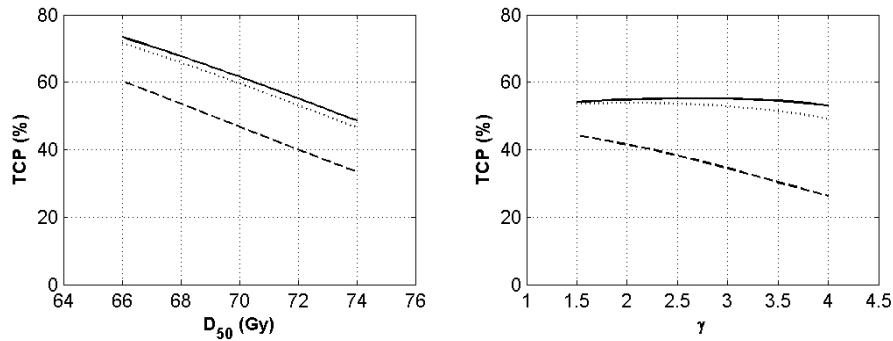


Figure 7. Average TCP for various values of the parameters  $D_{50}$  and  $\gamma$  for the primary tumour, the proton plan (solid line), the IMRT plan (dotted line), and the 3D-CRT plan (dashed line).  $\gamma$  varied between 1.5–4 with  $D_{50} = 72$  Gy and  $D_{50}$  between 66–74 Gy with  $\gamma = 2$ .

## Locally advanced rectal cancer (Paper IV)

In the treatment of advanced rectal cancer, T3-T4, N0/+, less severe acute toxicity in the small bowel has been reported for pre-operative (27%) compared to post-operative radiotherapy (40%) with doses up to 50.4 Gy in combination with 5FU [180]. In phase II trials exploring other drugs in addition to 5FU, grade 3-4 toxicity has been reported in between 8-40% of the patients [6,174]. Radiotherapy alone gives a very low risk for severe toxicity, and this is also true for cytotoxic drugs alone in the doses possible to give with radiotherapy, whereas it appears as if chemoradiotherapy (CTRT) gives higher risks. Therefore, since CTRT is more efficient than radiotherapy alone [19,21,58], it is of importance to further minimise the irradiated volume of the small bowel to minimise both acute and late effects and, at the same time, allow further attempts to intensify the chemotherapy. The small bowel is the critical OAR in rectal cancer irradiation. Several authors have suggested that it is the highest doses in the small bowel that needs to be decreased [51,175]. This would imply a serial structure of the small bowel according to the dose-response models.

A few comparative treatment planning studies have been made for rectal cancer [87,209]. One of them investigated passively scattered proton beams with a conventional radiotherapy treatment [87]. In that study, including patients with in-extirpable rectal cancers, the aim was to maximise the TCP, using the objective to obtain 5% NTCP in any risk-organ. The results indicated a 14% gain in TCP.

In **Paper IV** treatment plans were made for 16 patients with T3-T4, N+ rectal cancer were done. In the study, the main objective was to decrease the dose given to the small bowel, since acute toxicity in the small bowel is of

immediate concern using CRT, but also the bladder and femoral heads were spared in the optimisation process. The  $V_{95}$  of small bowel decreased by 60-70% using protons or IMRT compared to 3D-CRT. In the dose-response modelling, NTCP values were evaluated using the derived values of  $D_{50}$  with the associated values of  $\gamma$  and  $s$ . It is not obvious if the structural behaviour of the small bowel is serial ( $s=1$ ) or more parallel ( $s = 0.1$ ). Therefore, both these alternatives were evaluated. If the small bowel is serial, NTCP for acute toxicity show that it could potentially be decreased by 50% using protons and slightly less using IMRT (Fig. 8a). If the small bowel is more parallel the late toxicity would also be roughly 50% lower for IMRT but significantly lower (about 90%) for protons (Fig. 8b).

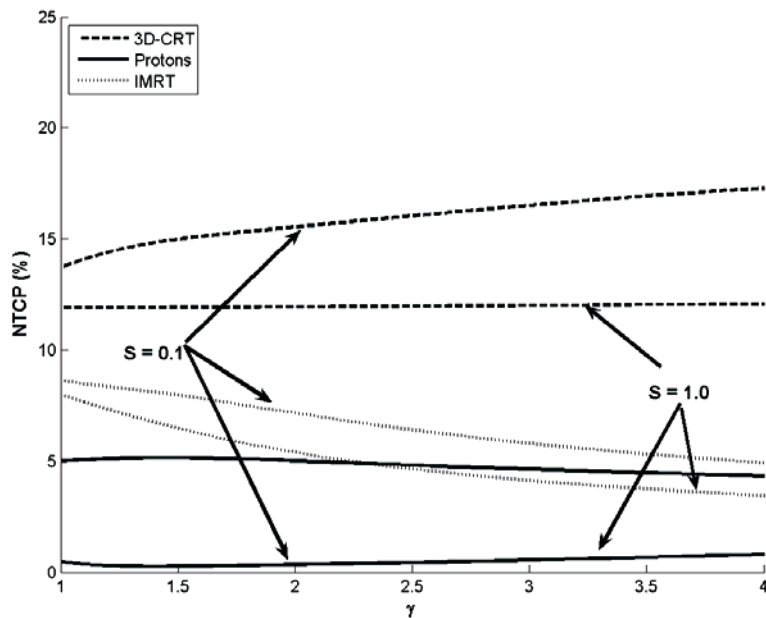


Figure 8a. NTCP as a function of  $\gamma$  and  $s$  for acute toxicity (diarrhoea) for protons, IMRT and 3D-CRT.

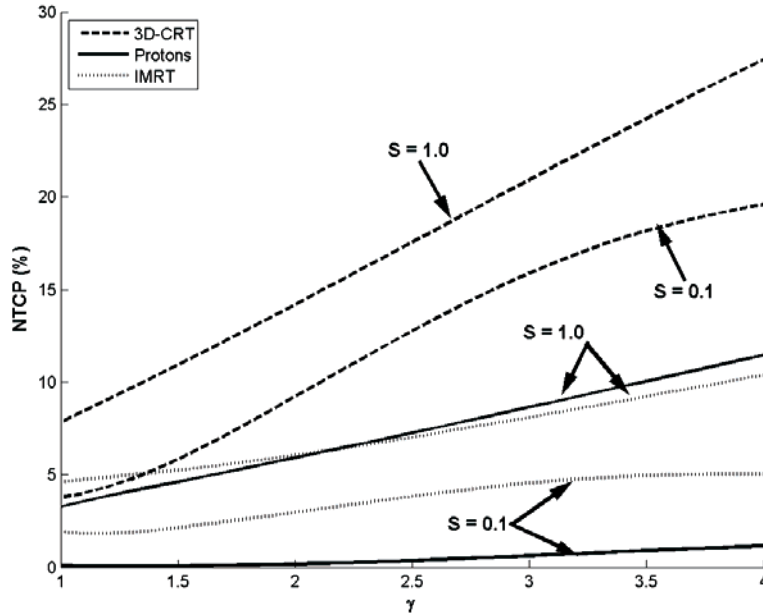


Figure 8 b. NTCP as a function  $\gamma$  and  $s$  for late toxicity (obstruction, ileus) for protons, IMRT and 3D-CRT.

## Potential RBE effects in proton treatment planning (Paper III)

In the clinical setting, most centres take RBE into account by applying a constant RBE value of 1.1 over the entire SOBP. Paganetti [162] reported RBE values both for in vitro and in vivo systems and concluded that an RBE value of 1.1 can be used clinically. However, there is experimental evidence from in vitro studies, that RBE is not a constant value over depth. In a multi-centre comparison [69], RBE values for intestinal crypt regeneration in mice were investigated. In the middle of the SOBP, the RBE value ranged between 1.08 and 1.18 and it was always 5-10% greater at the end of the SOBP compared to the middle part.

Depending on the irradiation technique used, the distribution of LET can vary considerably [224,225]. In a scanned 3D proton beam, the LET distribution would be nearly homogenous, while for distal edge tracking techniques, the border of the target volume would have higher LET values compared to the centre of the target [224,225]. A variable RBE correction based on the LET distribution for each beam should be applied.

In **Paper III** implications of RBE effects have been considered for a case of hypopharyngeal carcinoma. A treatment plan was made with three proton beams directed such that the distal penumbra was positioned just in front of the spinal cord. Passively scattered beams were used and these were modulated in range to obtain a fixed extent of the SOBP. Three target volumes are outlined, the primary target (CTV1), and two lymph node targets (CTV2 and 3) (Figure 9 a). Three beams were applied with the beam angles  $0^\circ$ ,  $45^\circ$  and  $315^\circ$  (Figure 9 b). These plan results in multiple Bragg peaks with a high LET close to the spinal cord, i.e. with the potential risk of an increased biological effect close to the spinal cord (Figure 9 b). In the study, the physical dose without RBE correction was compared to the dose calculated with either a constant (RBE  $\sim 1.1$ ) or a variable RBE correction. The variable RBE correction was made using the Linear Quadratic model [50] for cell survival with the modification that  $\alpha$  and  $\beta$  depends on LET.

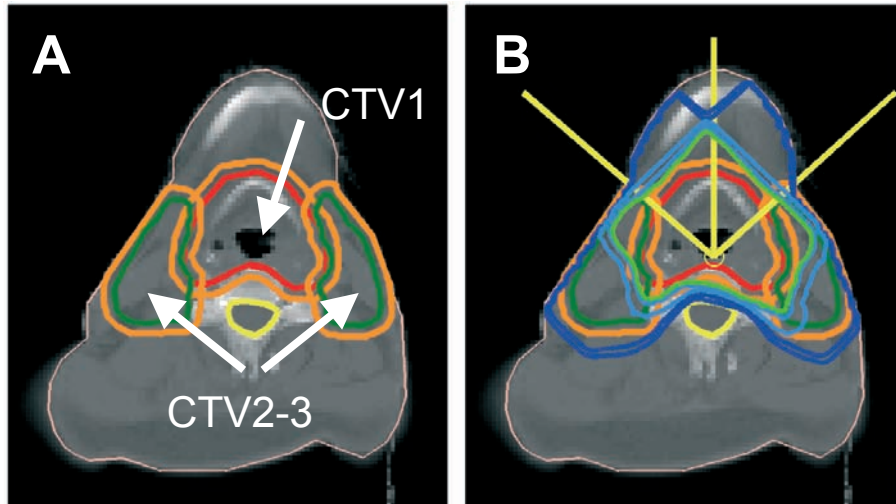


Figure 9. a) Hypopharynx cancer defining CTV1 and CTV2-3, and spinal cord. b) The three beam directions, and the physical dose distribution.

In figure 10, the DVHs for the CTV1, CTV2-3 and the spinal cord are presented. Normally the DVHs would be presented for PTV, but the RBE calculations are based upon tissue specific parameters, the CTV would better represent the tissues of interest. It can be debated whether or not the margin belongs to the target or to the normal tissue. For the spinal cord, it can be seen that the effective dose is increased by a factor 1.5, but still well below any critical dose levels. This indicates that the safety margin to the spinal cord has been sufficient.

The DVH for the CTV shows that the effective dose is increased by on an average a factor of  $\sim 1.2$  for the variable RBE correction. The plans using physical dose, dose with constant RBE, and dose with variable RBE, give



approximate TCP values of 48%, 70%, and 84%, respectively. This indicates that RBE variations cannot be neglected and that the effect of the treatment may be more efficient than what an uncorrected dose distribution indicates. NTCP values for the normal tissues are large and depend on the large volume of normal tissue within the margin between CTV and PTV, which contain high LET contributions from the distal parts of the beams.

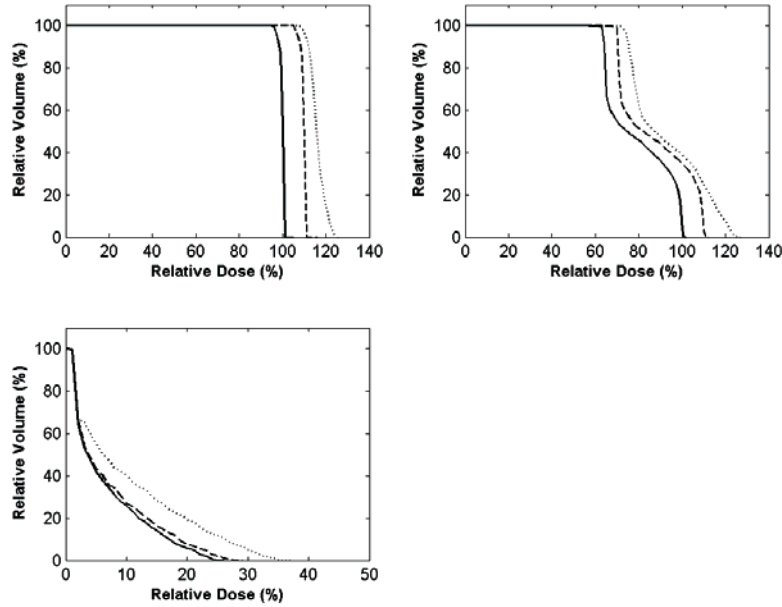


Figure 10. Cumulative DVHs for a) CTV1, b) CTV2,3, c) spinal cord without RBE correction (solid line), with a fixed RBE of 1.1 (dashed line) and with the variable RBE correction (dotted line)

Despite the large uncertainties in  $\alpha$  and  $\beta$  values, this investigation has shown that by applying a variable RBE correction instead of a constant RBE, there will be qualitative differences in the dose distribution. The variable RBE correction gives a higher effective dose than the constant RBE value of 1.1. This illustrates that this effect is not negligible, Paganetti et al [163] suggested that an RBE correction should be applied in patient treatment planning. When creating a highly selective and conformal dose distribution it can be desirable to employ the distal part of the proton beam close to organs at risk. One strategy is, however, to avoid heavily weighted Bragg peaks close to OARs because of the increased RBE at the end of the proton range [128,163], and the uncertainties in calculating the range when the beam passes through inhomogeneous tissues.

## Future perspectives

It has been estimated that radiotherapy contributes to cure of at least 20% of newly diagnosed cancer patients [13,139]. In Sweden, the total number of patients that receive radiotherapy have also increased in recent years, from 32% in 1992 to 47% in 2001 [173]. With the advances in other treatment modalities, particularly in medical oncology with new cytotoxic and biological drugs, it has also been estimated that the relative importance of radiation therapy may actually increase [72,139]. Better possibilities to eradicate spread tumour cells with drugs will actually increase the demand for more effective local treatments with less adverse effects. More conformed radiation therapy is a promising modality that may fulfil many of these demands. Further developments in radiation oncology is to be expected in many areas, as e.g. discussed in the Swedish Cancer Society Radiation Therapy Investigation [139].

The attempts to rank and quantify the gains that can be reached with new developments in radiation oncology, studied in this thesis, should be looked upon in these perspectives.

To achieve an increase in anti-tumour efficacy, contributions from several different radiation technologies are required. At present, much research and technology development is devoted to refinement and implementation of techniques such as IMRT, protons and light ion therapy, improving the physical distribution of the dose. In addition, light ions may have biological advantages [25,210]. Of great potential relevance is also better imaging techniques, not only anatomical (CT, MRI) but also functional (MRI, PET) that will improve the staging of the tumour and the delineation of the target volumes [49]. With more accurate target delineation than generally has been the case in the past, conformed radiotherapy will be even better appreciated.

With the introduction of IMRT, it can be expected that photon radiotherapy will certainly be improved. Although the basic principles of IMRT were defined already in the 1980s [18,24,29,217], the introduction into clinical routine has been rather slow but it is definitely increasing. A survey in the USA showed that 32% of the radiation oncologists uses IMRT [140], and most of them had begun to use IMRT after year 2000. In the group, who did not yet have IMRT, most of them were planning to introduce it within very few years. Economical aspects have likely contributed to its popularity in e.g. the USA [12,164].

IMRT has the potential to improve the outcome of radiotherapy to properly selected patient groups, although the benefits have been debated [93,185,216]. In the absence of results from prospective, preferably randomised trials, there is only a limited knowledge of what groups of patients that will benefit the most. Several comparative model treatment planning studies, including the three presented in this thesis, give some indications of the magnitude of the gains that can motivate investments in more advanced equipment and know-how.

Are the gains so marked that IMRT, solely based upon the indirect evidence we presently have, immediately should be a new standard? If this is the case, at what tumour sites? Concerning the three sites explored in this thesis, it is not apparent that the gains are sufficient considering the potential disadvantages of IMRT, e.g. the increased induction of secondary cancers [146,153]. If the calculated magnitude of the gain in TCP and the reduction in NTCP of salivary glands in the hypopharynx cancer case and of small bowel toxicity in the rectal cancer case, are true, a randomised study including a couple of hundred patients will be sufficient. In breast cancer, many more patients will be necessary, and it could be questioned if such a study is realistic. The very long delay before a study would give any results also precludes a randomised study in breast cancer patients, even if only those at high risk to get late adverse effects from the conventional radiotherapy are included.

An increase of costs for investment follows with each step of improvement of the dose distribution, or from 3D-CRT to IMRT, to protons, IMPT, and light ions, etc. There are considerable investment costs for proton therapy and probably even more so for light ion therapy.

The greatest difference between IMRT and protons is significantly lower doses to surrounding normal structures by protons, which can be used either to decrease toxicity, or to give higher doses to the tumour target with improved tumour control. The three examples studied here together with the many other model studies performed up to now (see Table 1) tell that protons for many tumour sites will be sufficiently better to motivate investments in such facilities. These are also the conclusions reached by a Swedish Proton Therapy Investigation [3], although the main conclusion from the investigation was that the gains appear sufficient to invest in a facility for clinical research. The facility should be designed and dimensioned so that clinical trials could be run within a reasonable time. Other groups [10,107,170] have also reached similar conclusions concerning investments in particle therapy. The number of planned new facilities for proton (and light ion) therapy is an expression of this increased knowledge, although other aspects are likely also prevailing.

Development and implementation of IMPT will further improve the technology, with a possibly even greater efficacy compared to the “conventional” protons [127]. Therefore, the technology of scanned beams should be

further developed. However, the magnitude of the gain going from regular proton beam therapy to IMPT is unknown, although a few model studies have been performed with even lower doses to the surrounding tissues [15,34,127,146,158,198].

Is then proton therapy too expensive? Based on the results from the clinical studies performed, and the treatment planning comparisons, it has been estimated that for, e.g. breast cancer, medulloblastoma, prostate cancer and head and neck cancer, the additional costs are reasonable if the patients are selected properly [134-136]. Lundkvist et al based their calculations on the potential number of patients that could be eligible for proton therapy in Sweden [60]. Goitein and Jermann [62] calculated the costs for protons compared with IMRT and found a relative cost of 1.3-2.4 depending on how the investment costs in the facility are handled. The increased costs relate not only to the accelerators but also to the beam lines, gantries and buildings, and personnel. Lievens discussed the cost of protons [121], and concluded that the cost of proton therapy is in the order of what society can accept for a new treatment (either RT, new drugs or surgical techniques), and therefore acceptable.

Further improvement using light ion therapy could result in even more selectively conformed dose distributions, making use of an even sharper lateral penumbra and a higher RBE within the SOBP [25,213]. The tail from light ion fragments may however make the depth dose distribution less advantageous. It has been estimated that the cost per fraction for light ion therapy will be 3 times higher compared to protons [210]. Although it is claimed that using hypo-fractionation, the cost per patient can be decreased significantly [25,206]. However, before utilising such fractionation schedules, first they must be carefully evaluated in clinical trials.

The improved dose distributions from IMRT, protons, particularly IMPT, and light ions create conditions conducive for therapies with combinations of cytotoxic and targeted drugs. Radiotherapy in these combinations will dramatically increase the risk for normal tissue toxicity. Therefore, the importance of conformal radiation will likely increase once we get more knowledge of the efficacy of newer radiation-drug combinations.

## Conclusions

From treatment planning studies such as the ones performed in this thesis, it is possible to identify not only the technique that provides the best outcome but also to quantify the improvement.

Techniques using protons and IMRT have major advantages compared to 3D-CRT plans in delivering the dose more conformally. The studies show that IMRT and protons are more flexible compared to 3D-CRT and the two methods obtain equally good results in shaping the dose to the target volume. Since protons spare volumes of normal tissue better than IMRT, because of steeper dose gradients close to the target volume, protons also offer a potential for dose escalations, which may improve local tumour control. The greatest possibility of dose-escalation with protons was, among the tumours investigated here, shown for patients with hypopharyngeal cancer (**Paper II**).

Both protons and IMRT can for left-sided node-positive breast cancer (**Paper I**) decrease the risk for cardiac mortality from 6.7% with a tangential 3D-CRT technique to 0.5% and 1.3%, respectively. The risk for radiation induced pneumonitis can also be reduced significantly, to 0.6% and 2.5% for protons and IMRT, respectively, compared to 14.7% for the best 3D-CRT technique. These new, more complicated and expensive techniques may be of relevance for certain patients at greater risk for late complications.

For hypopharyngeal carcinoma, protons and IMRT provide more selective treatment plans than the 3D-CRT plan (**Paper II**). A simultaneous boost technique, with protons and IMRT, allows potential dose-escalation, with an increase in TCP of 17%. The NTCP values for the parotid glands were also reduced significantly using either of the new techniques. IMRT can be of value for many patients with head and neck cancers such as hypopharyngeal cancer, and once proton beams are generally more available, these sites should be clinically explored.

In locally advanced rectal cancer (**Paper IV**), both acute and late toxicity from the small bowel, the main OAR can be reduced by approximately 50%, using either protons or IMRT, if the small bowel is considered serial. Protons are even more favourable if the small bowel is parallel while the reduction with IMRT remains at approximately the same level. Also other tissues around the rectum and adjacent nodes can be spared with the new techniques. Both of them may allow further intensification of CTRT combinations, having the potential to improve treatment results.

With a variable RBE correction of proton treatment plans, including LET dependence and tissue specific parameters, significant differences were found in the corrected dose distributions compared to the uncorrected distribution (**Paper III**). The relevance of these differences must be further investigated, particularly since the RBE correction depends on tissue specific parameters. The possibility to directly account for RBE should at least be included in the treatment planning systems. Intensity modulated protons should include RBE in the optimisation process to take advantage of the variable RBE in the proton beam, unless future studies show that these variable corrections are clinically insignificant at most or all major tumour sites.

In this thesis, three treatment planning studies have shown a large potential for both protons and IMRT compared to the treatment presently used at most radiation departments, 3D-CRT. The estimates of potential improvements in clinical outcome, either in terms of decreased NTCP or increased TCP, are more favourable for protons compared to IMRT. In the absence of results from large clinical trials, decisions about investments in new technology will rely on treatment planning studies. These should be accompanied by studies analysing cost-benefits. The results of this thesis show that increased use of both IMRT and protons can be supported, although the potential for protons is stronger. Thus, together with a health economical study performed in parallel [133], investments in proton facilities with a capacity and willingness to treat many patients in clinical trials can be supported.

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