Intensity Modulated Proton therapy (IMPT) is a highly promising approach for radiation treatment of cancer patients due to its increased potential to reduce side effects and improve quality of life compared to contemporary radiation therapy techniques, such as IMRT. However, IMPT is associated with high costs and hence limited availability. Ideally, patient selection for IMPT should be based on the highest expected complication reduction compared to IMRT. For a given patient, it is possible to predict the risk of side effects for proton and photon therapy by applying Normal Tissue Complication Probabilities (NTCP) models to optimized dose distributions. Only patients with clinically relevant reductions in NTCP exceeding minimum pre-defined thresholds will then qualify for proton therapy. While this approach should guarantee effective use of proton therapy, there are several concerns that will be discussed in this presentation:

1. The generation of a radiotherapy treatment plan is a complex procedure and its quality is highly dependent on the planner skills. To enable unbiased comparisons between IMPT and IMRT for each patient, automation of the treatment planning process is imperative.

2. IMPT is highly susceptible to inaccuracies in patient setup, anatomic changes, and to uncertainties in the calculation of the proton range. IMRT, uncertainties in dose delivery are accounted for in the CTV-to-PTV margin. In IMPT, however, the PTV concept is not applicable. Alternatively, robust treatment planning can be used to take into account patient setup and range uncertainties. However, it is currently unknown which robustness settings need to be used to achieve an adequate NTCP reduction and hence on the selection of patients qualifying for proton therapy.

3. Image-guidance technology improves the accuracy of radiation therapy delivery, however its impact and current state-of-the-art may vary for proton and photon radiotherapy due to the physical differences between protons and photons and for historical reasons. The applied image-guidance technology will have an impact on the magnitude of NTCP reduction and hence on the selection of patients qualifying for proton therapy.

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**Future selection practice for proton therapy: selection of patients based on treatment planning comparison and NTCP-modelling**

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The last decade, many new radiation delivery techniques have been clinically introduced without being subjected to randomized controlled trials. Many of these new techniques have been introduced in order to reduce the dose to the healthy tissues and subsequently to prevent radiation-induced side effects. Due to its superior beam properties, radiotherapy with protons compared to photons enables similar dose administration to the target volume with substantially lower dose to the normal tissue. In the Netherlands, we applied a 4-step model-based approach to select patients for proton therapy and to validate the benefit of protons compared to photons with regard to reducing the risk on radiation-induced side effects.

Step 1, consists of the development and validation of multivariable Normal Tissue Complication Probability (NTCP) models. NTCP models describe the relationship between radiation dose distribution parameters and the probability of a given side effect (NTCP-value). One of the output parameters of this step are the most relevant Dose Volume Histogram (DVH) parameters that can be used to optimize radiation treatment.

Step 2 includes in silico planning comparative studies. In this phase protons are compared with photons with regard to their ability to reduce the most relevant DVH-parameters resulting from step 1 (ΔDose).

Step 3: Integration step 1 and 2. By integrating the results of the individual in silico planning comparison into the validated NTCP-models, the differences in dose can be translated into a difference in NTCP-value in each individual patient.