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Technical Note

# Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy?

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ABSTRACT

In this dosimetric comparison study it was shown that IMPT with robust planning reduces dose to surrounding organs in cervical and endometrial cancer treatment compared with IMRT. Especially for the para-aortic region, clinically relevant dose reductions were obtained for kidneys, spinal cord and bowel, justifying the use of proton therapy for this indication.



A substantial proportion of patients with cervical and endometrial cancers are treated with radiation therapy as primary or postoperative treatment, or as treatment for recurrent disease. Radiation therapy to the pelvic and/or para-aortic region is associated with risk of several acute and late toxicities, especially bowel toxicity [1–4]. Locoregional control rates are high, but recurrence in the para-aortic region is an important site of failure [2–4]. Both for elective irradiation of the para-aortic region and irradiation of para-aortic lymph node recurrences, toxicity can be substantial and dose that can be given is restricted by tolerance of surrounding organs at risk (OARs) such as kidneys, spinal cord and bowel [5].

Intensity-modulated proton therapy (IMPT) uses proton pencil beams whose intensities are individually optimized [6]. Compared with state-of-the-art intensity-modulated or volumetric-modulated arc photon therapy (IMRT or VMAT), IMPT might decrease dose to OARs. The resulting increased therapeutic window can be used, if necessary, to intensify the treatment by escalating the radiation dose or by other means.

Since IMPT is more expensive and requires sophisticated treatment facilities with limited capacity, selection of patients for whom clinical benefit will be greatest is essential. Therefore, the aim of this study was to determine which cervical and endometrial cancer patients will benefit most from state-of-the-art IMPT compared to state-of-the-art IMRT. To reach this, we determined by a dosimetric comparison study the clinical advantage of IMPT in terms of improved sparing of OARs for three pelvic and para-aortic target volumes, and evaluated for which the benefit would justify the use of IMPT. The comparisons were made for state-of-the-art IMRT and IMPT techniques including automated treatment plan generation and including robust optimization for IMPT, as IMPT is highly sensitive to errors in patient setup and proton range [7–11]. Wide and small margins were included to investigate the impact of level of image-guidance and online adaptation to account for day-to-day variations of the target shape [12].

## Material and methods

### *Patients and imaging*

Planning CT-scans from previous patients were used. Patients were scanned supine with full bladder. Apart from a standard knee support no other patient immobilization devices were used. Three treatment groups were investigated:

(1) Pelvic region: 10 patients including 5 patients treated primary for cervical cancer and 5 patients treated postoperatively for cervical or endometrial cancer. Six received a boost dose to involved lymph nodes ($n = 4$), microscopically involved resection margins ($n = 1$), or both ($n = 1$). Original target volumes were used.

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(2) Pelvic and para-aortic region: 6 patients from the first group receiving a boost dose. Original pelvic target volumes were extended to the para-aortic region.
(3) Para-aortic region alone: 5 patients with isolated para-aortic recurrence. All received a boost to macroscopic lymph nodes. Original target volumes were used.

### *Delineation and dose*

GTV was delineated if present. Primary/postoperative and nodal CTV were delineated according to international guidelines and delineation atlas [13–15]. Boost CTV consisted of GTV plus 5 mm margin. Para-aortic CTV was delineated from level L1 to the pelvic lymph node region. In patients treated for para-aortic recurrence, upper and lower CTV levels and boost CTV depended on location of involved lymph nodes.

OARs contoured were rectum, sigmoid, bowelbag, bladder, pelvic bones (including sacrum), femoral heads, kidneys, spinal cord. For bowelbag bowel loops with surrounding tissue were delineated.

Prescription dose was 48.6 Gy in 1.8 Gy fractions with a simultaneous integrated boost dose to 58.05 Gy in 2.15 Gy fractions, being equivalent to 60 Gy in fractions of 2 Gy ($\alpha/\beta = 10$).

### *Treatment planning*

Treatment plans were made using Erasmus-iCycle, a fully automated treatment planning system developed in-house that performs prioritized multi-criteria optimization [16]. It optimizes different objectives or constraints according to priorities defined in the so-called 'wish-list'. These plans are of equal or better quality than manually optimized plans [17]. In this study wish-lists were developed and optimized for each target volume and treatment technique. See Table 1 in the Supplementary materials for all wish-lists.

Erasmus-iCycle supports both IMRT and robust IMPT treatment planning [16,18,19]. The latter uses the minimax approach to include robustness against setup and range errors [10,20]. Nine scenarios were used with range robustness of ±3% and setup robustness of ±2 mm.

For IMPT different beam angles, including oblique beams, have been tested. The beam setup that provided the most optimal combination of target coverage and sparing of organs at risk was chosen. The beam angles differed per target volume; pelvic region 2 beams at 90 and 270 degrees, pelvic and para-aortic region 4 beams at 0, 90, 180, and 270 degrees, para-aortic region alone 2 beams at 0 and 180 degrees. Available proton energies ranged from 70 to 230 MeV with pencil beam widths ranging from 7 to 3 mm sigma, respectively. The implemented proton dose calculation algorithm was developed at the Massachusetts General Hospital - Harvard Medical School where it is implemented in the in-house developed treatment planning system 'ASTROID' [21]. We used a dose grid resolution of $3 \times 3 \times 3\ mm^3$ (CT slice spacing was 3 mm). Proton spots were selected and optimized using the 'pencil beam resampling' method [18], which consists of iteratively performing: (1) random sampling of candidate spots from a very fine grid, (2) prioritized multi-criteria optimization and (3) exclusion of low-contribution spots. In this study, the resampling method used a sample size of 5000 randomly selected candidate spots per iteration. Plan optimization was terminated when none of the optimized dose parameters improved more than 3% in subsequent resampling iterations.

For photon therapy, IMRT plans with 20 equi-angular beams to be delivered with dynamic multi-leaf collimator (dMLC) were generated for all target volumes. This was previously demonstrated to be superior to 12-beam IMRT and dual arc VMAT [22].

To investigate the impact of the level of image-guidance and online adaptation (plan of the day), treatment plans were made using both a wide and small margin for internal organ motion and setup errors. Wide margin, requiring in-room soft-tissue image-guidance, was 15 mm for primary/postoperative region and 7 mm for lymph node region. Small margin, requiring daily adaption of the treatment plan e.g. using a plan library [12], was 5 mm and 2 mm, respectively. For IMPT 2 mm of the margin around CTV was included as setup robustness, the remaining part was used to expand CTV to an internal target volume. See Table 1 for an overview of the margins used in this study. In the end, the availability of volumetric in-room imaging and strategies to correct for internal organ motion and variations in patient setup, determines the margin and robustness settings that are actually needed to treat the target accurately. For the remainder of this paper, we denote for robust optimized IMPT the internal target volume as PTV.

### *Evaluation of treatment plans*

At least 99% of PTV should receive more than 95% of the prescribed dose, and volume receiving more than 107% of prescribed dose should be less than 1% for IMRT and nominal IMPT plans. The nominal IMPT plan refers to the treatment plan that is based on the planning CT scan that was not shifted to simulate a setup error or was not scaled to simulate an undershoot or overshoot of the proton pencil beams. For worst-case scenario of IMPT plans, volume receiving >107% should be <5%.

Descriptive analysis of differences in dose to OARs was done for different parameters (mean and maximum dose, V15 Gy, V45 Gy). For these parameters mean, minimum and maximum values and differences between both techniques were calculated. For IMPT, dose to OARs was evaluated for the nominal scenario.

## Results

### *PTV coverage*

All IMRT and IMPT treatment plans had V95% >99%, except for one IMRT plan, where V95% was 97.1%. V107% was always below 1%. For IMPT, worst-case V95% was always above 98.5% for primary target volumes and above 99.0% for boost target volume. Worst-case V107% was always below 3.7% for primary target volumes (excluding boost target volume) and below 0.5% for boost target volumes.

### *Organs at risk; wide margin*

In Fig. 1 typical dose distributions for pelvic and para-aortic target volumes are shown, with steep dose fall-off and excellent sparing of bowelbag and kidneys with IMPT. Table 2 lists parameters for OARs for all three target volumes. IMPT reduced dose in all OARs compared with IMRT. This benefit was higher in the lower dose region than in the higher dose region, where in most cases only small differences were found.

For treatment of pelvic region, volume of bowelbag receiving 15 Gy was 383 cc with IMPT and 535 cc with IMRT. V45 Gy for bowelbag was similar for IMPT and IMRT. Dose in pelvic bones was on average 29% lower with IMPT, dose in femoral heads 6% lower.

For treatment of both pelvic and para-aortic region, V15 Gy for bowelbag was 684 cc for IMPT and 1915 cc for IMRT (reduction 64%). Also V45 Gy for bowelbag was lower for IMPT than for IMRT: 234 cc vs 355 cc (reduction 34%). V15 Gy for both kidneys was reduced: 1.1 Gy vs 7.8 Gy (left kidney) and 2.4 Gy vs 11.8 Gy (right

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