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Original Research Article

Exclusion of non-Involved uterus from the target volume (EXIT-trial): An individualized treatment for locally advanced cervical cancer using modern radiotherapy and imaging techniques followed by completion surgery

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ABSTRACT

Background and purpose: Chemoradiotherapy followed by brachytherapy is the standard of care for locally advanced cervical cancer (LACC). In this study, we postulate that omitting an iconographical unaffected uterus (+12 mm distance from the tumour) from the treatment volume is safe and that no tumour will be found in the non-targeted uterus (NTU) leading to reduction of high-dose volumes of surrounding organs at risk (OARs)

Material and Methods: In this single-arm phase 2 study, two sets of target volumes were delineated: one standard-volume (whole uterus) and an EXIT-volume (exclusion of non-tumour-bearing parts of the uterus with a minimum 12 mm margin from the tumour). All patients underwent chemoradiotherapy targeting the EXIT-volume, followed by completion hysterectomy. In 15 patients, a plan comparison between two treatment plans (PTV vs PTV_EXIT) was performed. The primary endpoint was the pathological absence of tumour involvement in the non-targeted uterus (NTU). Secondary endpoints included dosimetric impact of target volume reduction on OARs, acute and chronic toxicity, overall survival (OS), locoregional recurrence-free survival (LRFS), and progression-free survival (PFS).

Results: In all 21 (FIGO stage I: 2; II: 14;III: 3; IV: 2) patients the NTU was pathologically negative. Ssignificant reductions in Dmean in bladder, sigmoid and rectum; V15Gy in sigmoid and rectum, V30Gy in bladder, sigmoid and rectum; V40Gy and V45Gy in bladder, bowel bag, sigmoid and rectum; V50Gy in rectum were achieved. Median follow-up was 54 months (range 7–79 months). Acute toxicity was mainly grade 2 and 5 % grade 3 urinary. The 3y- OS, PFS and LRFS were respectively 76,2%, 64,9% and 81 %.

Conclusion: MRI-based exclusion of the non-tumour-bearing parts of the uterus at a minimum distance of 12 mm from the tumour out of the target volume in LACC can be done without risk of residual disease in the NTU, leading to a significant reduction of the volume of surrounding OARS treated to high doses.

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1. Introduction

Cervical cancer is the fourth most common female malignancy worldwide [1]. High risk subtypes of Human Papillomavirus (HPV) cause most cervical cancers [2,3]. Concurrent chemoradiotherapy, including brachytherapy, is the standard of care treatment for locally advanced cancer. Some selected patients with stage IVB (e.g. oligometastatic disease or supraclavicular lymph nodes) benefit from definitive chemoradiotherapy [4–7]. Despite state-of-the-art treatment, one in three patients will have a recurrence [8].

Consensus contouring guidelines for External Beam Radiotherapy (EBRT) and the protocol of the IntErnational MRI-guided BRAchytherapy in CErvical cancer (EMBRACE) II all advise the inclusion of the whole uterus in the Clinical Target Volume (CTV) based on the idea that both organs are embryonically one unit with interconnected lymphatics without a clear separating fascial plane [9–11]. However, there's no unequivocal evidence supporting the dogma that the whole uterus should be included in the CTV and in the guidelines of Lim et al. 7 out of 17 experts would consider excluding the uninvolved uterine corpus [9]. This "inclusion-dogma" goes back to the pre-magnetic resonance imaging (MRI) era when one could not distinguish the tumour from the uterine corpus. MRI is the best method for assessing the primary cervical tumour over 10 mm in size and can determine tumour size and extension, parametrial invasion, pelvic sidewall invasion and lymph node metastasis with 95 % accuracy for stage IB or higher [12,13].

Although there is a slight underestimation of cervical cancer using MRI compared to the anatomopathological specimen, a safety margin of 12 mm around the tumour should allow to distinguish involved and non-involved uterus as suggested by De Boer et al.[14,15].

Reducing the volume of the included uterine corpus in the CTV leads to smaller treated volumes in 2 ways: directly through a reduction in CTV and indirectly by reducing the generous planning target volume (PTV) margins that take intra- and interfraction motion of the uterus into account. Influenced by bladder and/or rectal filling and tumour shrinkage, the uterus can tilt from an anteflexed to a retroflexed position [16,17]. Angle rotations of the uterus up to 91° were reported and mean displacements of the uterus of 5–40 mm in the superior-inferior direction and 0–65 mm in the anterior-posterior direction were observed [17]. This movement of the uterus and consequently the CTV remains a major problem. Concerns about these CTV movements (with the uterine fundus being the main contributor) have led to the use of generous margins (suggested margins were anisotropic and varied from 8 to 32 mm) to create the PTV [17]. Volume reduction of both CTV and PTV will substantially reduce doses to surrounding organs and thus radiation-induced toxicity.

In this single phase 2 study, we hypothesized that it is safe to omit the iconographical unaffected uterine corpus at a 12 mm distance from the tumour from the treatment volume and that it is safe to leave no tumour behind in the non-targeted parts of the uterus. This should lead to lower doses to the organs at risk (OARs) and should decrease acute toxicity.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Inclusion criteria were (1) histologically proven adenocarcinoma or squamous cell carcinoma of the uterine cervix, (2) locally advanced disease (defined at the time as FIGO 2009 stage IB or > FIGO IIB or node-positive) proven by clinical examination, 18FDG PET-CT and MRI, (3) no more than 2 distant metastases (other than *para*-aortic lymph nodes) as confirmed by CT thorax-abdomen, (4) WHO performance score 0–2, (5) adequate kidney function (serum creatinine within normal limits) for chemoradiation, if not radiotherapy would be the sole therapeutic regimen, (5) not pregnant or breastfeeding, (6) absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up, and (7)

written informed consent. Exclusion criteria were (1) unable to undergo MRI for any reason and (2) more than 2 distant metastases proven by clinical examination, 18FDG PET-CT and MRI. Patients were included from 17/03/2016 to 19/04/2018.

2.2. Power analysis

Twenty-one patients were required to achieve a confidence interval with a half-width of 11 %, considering a negative predictive value of 98 % for MRI to predict absence of tumour (Wilson Score Confidence Interval for a Binomial Proportion) [18]. Patients excluded from the study for any reason were replaced to fulfil the required amount.

2.3. Radiotherapy

2.3.1. Procedure
After imaging in treatment position (18FDG PET-CT and MRI; within a week of the RT-planning-CT) and fusion with the RT-planning-CT, target volumes and OARs were delineated as described previously [19–21].

Per patient, there were two sets of target volumes:

- PTV_EXIT (PTV_prim_EXIT + PTV_Lnn) (novel), which no longer included the non-tumour bearing parts of the uterus.

PTV_prim_EXIT was created using an anisotropic margin around the CTV_prim_exit, namely 7 mm antero-posterior (AP), 5 mm left–right (LR) and 5 mm supero-inferior (SI). CTV_prim included the primary tumour (GTV_prim) delineated using T2 weighted MRI-images, the unaffected uterus lying within 1,2 cm around the GTV_prim, the non-affected cervix and parametria and the upper third of the vagina.

PTV_lnn was created using an isotropic margin of 5 mm around CTV_lnn which consists of the union of following regions: common-, external- and internal iliac lnn, obturator and presacral region and *para*-aortic lnn if any pelvic lnn were affected.

- PTV (PTV_prim + PTV_Lnn) (state-of-the-art), which −included the whole uterus, including non-tumour bearing parts.

PTV was created using an anisotropic expansion around CTV_primary, namely 10 mm AP, 5 mm LR and 5 mm SI.

CTV_primary included the primary tumour delineated using T2 weighted MRI images (GTV_prim), whole uterus, non-affected parts of the cervix and parametria, upper vaginal 1/3 to ½ (minimal vaginal margin of 2 cm to the GTV_prim).

PTV_lnn was created as described in PTV_EXIT.

2.3.2. Dose prescription
A treatment plan was made using the GRATIS treatment planning platform (Sherouse Systems Inc., Chapel Hill, NC, USA) for the first 4 patients and the Raysearch planning system (Raysearch Laboratories, Stockholm, Sweden) thereafter, using identical prescription and constraints as in our previously published work [20,21]. In short, a minimal dose (D98) of 45 Gy in 25 fractions is prescribed to the PTV and PTV_EXIT, 62 Gy to the PTV_GTV_prim and 60 Gy to any affected lymph node.

In 15 patients, 2 plans were created to compare the impact of a reduced target volume (PTV vs PTV_EXIT) on the dosimetry of OARS. We performed a plan comparison in all consecutive patients planned using Raysearch, except for 2 patients who needed multiple treatment plans due to patient (positioning) and machine problems.

2.3.4. Treatment
The patients were treated with the "PTV_EXIT" treatment plan. All treatments were performed on an Elekta (Crawley, UK) Synergy linac with gantry mounted Cone Beam CT option. Daily Couch setup

correction was performed after pre-treatment CBCT imaging consisting of M20 Field of View (i.e. 27,7 cm in SI direction), with bowtie filter, 120KV, 40 mA and 40 ms per frame, and 0,5 rpm gantry rotation speed. If necessary, adaptive treatment planning (following the same instructions as above, 18FDG PET-CT excluded) or plan-of-the-day was allowed.

2.4. Chemotherapy

Radiotherapy was combined with weekly cisplatin 40 mg/m^2 if kidney function was normal (defined as a serum creatinine level lower than 0,96 mg/dL). In case of inadequate kidney function or other contra-indications, 5-FU or no chemotherapy was also allowed.

2.5. Surgery

A radical hysterectomy was performed 6–8 weeks after completion of CRT. Surgery consisted of type II Wertheim hysterectomy. Pelvic lymphadenectomy was performed whenever there were suspicious lymph nodes present on the pre-treatment 18FDG PET-CT. Both open and robotic-assisted surgery were performed.

2.6. Pathology

The hysterectomy specimens were oriented, measured and weighed. The parametrial tissues, the soft tissue margins of the cervical canal and the vaginal cuff margin were inked blue and green, signifying the left and right side, respectively. Parametria were removed and entirely submitted for histological examination. Next, a probe was inserted into the endocervical canal and the uterine cavity. The uterus and cervix were bisected into posterior and anterior halves, to allow sufficient tissue fixation. These halves were pinned on plastic to avoid curling of the tissue. The specimen was inspected and described. Any macroscopically visible tumour was measured and, if larger than 10 mm, a tissue sample of about 5 × 3 × 3 mm was snap-frozen to allow future molecular studies. The bisected specimen was fixed in formalin for 24 h. After fixation, the vaginal cuff and the cervix were transversally amputated and were serially sectioned. These perpendicular clockwise approach allowed the assessment of the relationship of the tumour to the margin. Twelve, 3, 6 and 9o'clock corresponded with the anterior, left, posterior and right side of the cervix, respectively. Transverse sections of the endocervical canal and isthmus were submitted for histological examination as well. The uterine corpus, fallopian tubes and ovaries were macroscopically examined for abnormalities, and representative tissue samples were submitted for histological examination. If initial hematoxylin and eosin (HE) stained tissue sections did not reveal any tumour, multiple deeper sections were performed to rule out tiny foci of tumour cells with high certainty. Additional immunohistochemistry for p40 and Cytokeratin 5 were performed to illustrate any residual isolated tumour cells when HE slides were deemed unclear. Any residual tumour, its localization and its relation to the surgical resection margins were described in the report.

2.7. Endpoints

Primary endpoint was the absence of tumour in the non-targeted uterus (NTU).

Secondary endpoints were dosimetric comparison between both plans, acute and chronic toxicity as defined by CTCAE v3.0, overall survival (OS), progression free survival (PFS) and Local Regional Free survival (LRFS).

For each plan, the volume, V_{15Gy}, V_{30Gy}, V_{40Gy}, V_{45Gy}, D_{max} and D_{mean} for bladder, sigmoid, rectum and bowel bag were compared. This was supplemented by V_{43Gy} for bowel bag, V_{50Gy} for sigmoid and rectum and Volume and D_{98} for the different PTVs. The volume, D_{98}, D_{mean} and D_{02} of the NTU (created by extracting CTV_prim_EXIT from the

CTV_prim) was calculated.

OS was defined as the time of diagnosis to the time to death from any cause. PFS was defined as the time to the first evidence of disease recurrence or death from any cause.

Acute toxicity consisted of toxicity during treatment or within the first 3 months after treatment and were evaluated weekly during therapy, 10 days and 1 and 3 months after completing CRT. Chronic radiation toxicity (toxicity occurring > 3 months after completing CRT or acute toxicity lasting longer than 3 months) were assessed at every follow-up visit.

2.8. Statistical analysis

Descriptive analyses were performed for demographic, clinicopathologic, and treatment data. Survival curves for time-to-event endpoints and cumulative survival rates were estimated using the Kaplan-Meier method. Data cutoff for analysis was November 1, 2022. Data analysis was conducted from November 5th, 2022 to November 22nd, 2022.

Patient-specific Dose Volume Histogram differences between the PTV and the PTV_EXIT plan were tested pairwise for significance using a paired two sample T-test.

Data analysis and visualization was performed using SPSS version 28 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics and primary endpoint

A total of 21 patients were prospectively followed from 2016 to 2022. Population characteristics are summarized in Table 1., TNM stage at diagnosis in Table 2..

3.2. Secondary endpoints

Reduction of the target volume resulted in significant reductions in D_{mean} in bladder, sigmoid and rectum; V_{15Gy} in sigmoid and rectum, V_{30Gy} in bladder, sigmoid and rectum; V_{40Gy} and V_{45Gy} in bladder, bowel bag, sigmoid and rectum; V_{50Gy} in rectum. The dose (D98) in the NTU ranged from 21 Gy to 43 Gy. All plan comparison results are summarized in Table 3.

OAR: organ at risk; Dmean: mean dose; Dmax: maximal dose: D02/D98: dose 2/98 % of the volume; V15-50: volume receiving 15 up to 50 Gy in percentage (%) or absolute volumes (cc); NTU: non-targeted uterus.

Acute gastrointestinal toxicity was mainly grade 2 or lower (diarrhea

Table 1
Patient characteristics.

Number of patients, n	21 (100 %)
Age at diagnosis, mean (range)	51 (28–79)
Follow-up, mean (range)	54 months (7–79)
Surgery	16 (76 %)
Robot	5 (24 %)
Open	
Histology	5 (24 %)
Adenocarcinoma[a]	16 (76 %)
Squamous cell carcinoma	
FIGO STAGE 2009	2 (10 %)
I	15 (71 %)
II	3 (14 %)
III	1 (5 %)
IV	
PET-positive lnn, % (n)	12 (57 %)
Average diameter (range), cm	4,8 (1,5–9)
Complete response to treatment, % (n)Iconographic	3 (14 %)
(MRI)	7 (33 %)
Pathological	

[a] of which 1 adenosquamous carcinoma.

Table 2

Summarizes the anatomopathological examination of the hysterectomy specimen and uterine corpus invasion on mri before and after crt. in all patients, the uterine corpus and ntu examined in the hysterectomy specimen were free of carcinoma. seven patients (33 %) had a pathologic complete response (ypT0N0).

	cTNM	UCI @diagn (MRI)	UCIAfter CRT (MRI)	CR	Histology	Grade	PnI	LVI	UCI (path)	Parametria	LN	Resection margin	ypTNM
1	cT3b cN1	+	+	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0N0
2	cT3a cN0	–	–	No	SCC	2	No	No	–	–	–	R0	ypT2a1 N0
3	cT2b cN1	–	–	No	SCC	3	No	No	–	–	–	R0	ypT1b N0
4	cT2b cN0	–	–	No	SCC	3	No	Yes	–	–	–	R0	ypT1b1 N0
5	cT2b cN1	–	–	No, ITC	SCC	3	No	Yes	–	–	–	R0	ypT1a1 N0
6	cT2b cN1	–	–	No	SCC	3	No	Yes	–	+ right	1 +	R1	ypT2b N1
7	cT2b cN1	–	–	No	AC	2	No	No	–	–	–	R0	ypT1b1 N0
8	cT2b cN0	–	–	Yes	AC	n/a	n/a	n/a	–	–	–	R0	ypT0N0
9	cT2b cN0	–	–	No	SCC	3	No	No	–	–	–	R0	ypT1b1 N0
10	cT2b cN1	+	–	No	SCC	2	No	Yes	–	–	1 +	R0	ypT1b N1
11	cT2b cN0	+	–	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0
12	cT3b cN1	+	–	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0N0
13	cT2b cN0	–	–	No	AC	2	Yes	No	–	–	–	R0	ypT1b1
14	cT1b2cN0	–	–	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0N0
15	cT2b cN0	+	–	No	ASC	3	No	Yes	–	+ left	–	R0	ypT2b
16	cT2b cN1	–	–	No	SCC	2	No	Yes	–	–	–	R0	ypT2a2 N0
17	cT2b cN1	+	–	No	SCC	2	No	No	–	–	–	R0	ypT1B1 N0
18	cT1b cN0	–	–	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0
19	cT2b cN1	–	–	No	AC	2	No	No	–	–	–	R0	ypT2a1N0
20	cT1b2 cN1	–	–	No	AC	2	No	No	–	–	1 +	R0	ypT2a1 N1
21	cT2b cN1	–	–	Yes	SCC	n/a	n/a	n/a	–	–	–	R0	ypT0N0

Fourteen patients (66 %) had residual cervical tumour cells at the primary tumour site or in the lymph nodes. All but one (95,2%) had a complete resection. In the one patient with incomplete resection, the circumferential cervical resection margin was focally positive at the lateral right between 8 and 9o'clock. Three of the patients with clinically staged suspicious lymph nodes (n = 12, 57 %) had residual carcinoma in the lymphadenectomy specimen.

List of abbreviations: SCC = squamous cell carcinoma; AC = adenocarcinoma; ASC = adenosquamous carcinoma; CR = complete pathological response; ITC: isolated tumour cells, LVI = lymphovascular invasion; LN: lymph Node; path: pathology; PnI = perineural invasion; pTNM version 8; R0 = complete resection; R1 = microscopic residual tumour; UCI: Uterine Corpus Invasion

and/or neausea). One patient (5 %) was hospitalized shortly after radiochemotherapy for grade 3 nausea and constipation. Acute urinary toxicity was mainly grade 2 or lower. One patient (5 %) had a grade 3 urinary infection. No grade 4 or 5 gastrointestinal and urinary toxicity was observed. One patient (5 %) had hydroureteronephrosis based on fibrosis post-radiotherapy/post-surgery, treated with nephrostomy. An overview of toxicity can be found in Table 4.

Postoperative transfusion need, intra-abdominal infections, and urinary retention occurred in 2 patients (9 %) each. No thrombo-embolic events, bowel (sub)obstructions, fistulas nor postoperative mortality were observed.

At the end of the follow-up period, five patients died due to cancer progression (23,8%) and 16 patients were still alive (76,2%). Four in-field local relapses (2 at the vaginal vault; 1 parametrical relapse and 1 at the iliac nodes) occurred. Three-year OS, LRFS and PFS were 76,2%, 81 % and 64,9% respectively.

4. Discussion

This is the first study to prove histopathologically that it is safe to exclude the MRI-assessed non-involved uterus from the Clinical Target Volume (CTV) in the treatment planning of locally advanced cervical cancer patients: no carcinoma was found in the uterus of the hysterectomy specimen. Earlier studies validated MRI-based tumour volume delineations with histopathology in cervical cancer, with respect of a margin of 12 mm around the GTV delineation on T2-weighted MRI [14,15,22]. There is a slight underestimation of cervical cancer size using MRI compared to the anatomopathological specimen. In the MPAC study, there was an average difference of + 3 mm between the measurement on MRI and the histopathological specimen [15]. It remains uncertain how much of this underestimation is due to changes in the shape of the surgical specimen after hysterectomy and processing. De Boer et al. investigated retrospectively the craniocaudal extension of the tumour on both the preoperative MRI and the hysterectomy specimen in 21 patients. They found a median underestimation of 4 mm (range −6 mm to 22 mm), leading to the proposal of using a margin of 12 mm distance to the tumour when delineating the target volume, including the non-tumour-bearing uterus to cover at least 91 % of the tumours [14]. Another surgical cohort showed a maximal underestimation of 15 mm when comparing MRI to histopathology [23]. The used margin is also safe concerning microscopical extension of the tumour. In a multicenter study, surgical resection specimens of 318 cases of stage Ib-IIa squamous cell carcinoma of the cervix were evaluated for microscopic extension toward the uterus body (METU) [24]. In this cohort, METU was uncommon (12,3%), and an expansion from GTV to CTV of 5 mm would cover 99 % of all METU cases. Sanuki et al. investigated microinvasion extension in 31 cervical tumour cancer specimens by comparing primary tumour size with the size on MRI [25]. They found that the median maximal longitudinal tumour length by microscopy was 5 mm larger than by MRI [25]. Therefore, the authors suggested a 1 cm margin from GTV to CTV.

We demonstrated that excluding the NTU out of the treatment volume leads to significant reduction of dose in the surrounding OARs: D_{mean} in bladder, sigmoid and rectum; V_{15Gy} in sigmoid and rectum, V_{30Gy} in bladder, sigmoid and rectum; V_{40Gy} and V_{45Gy} in bladder, bowel bag, sigmoid and rectum; V_{50Gy} in rectum. Amongst others, a notable reduction in volume is seen in the bowel bag, where the mean volume (range) receiving 45 Gy decreases from 115 (19 cc-246 cc) to 81 cc (10

Table 3
Plan comparison.

Target/OAR	Whole Uterus, mean (range)	EXIT, mean (range)	significance
PTV_prim (_EXIT)			
Volume (cc)	**365 (171–599)**	**246 (124–416)**	**<0,001**
D98 (Gy)	45,31 (45,00–45,71)	46,43 (44,75–53,26)	0,074
PTV_Lnn (_EXIT)			
Volume (cc)	878 (624–1123)	878 (624–1123)	
D98 (Gy)	45,10 (45,00–45,77)	45,20 (44,16 – 45,98)	0,337
PTV_All(_EXIT)			
Volume (cc)	**1188 (876–1481)**	**1088 (809–1373)**	**<0,001**
D98 (Gy)	45,16 (45,00–45,52)	45,26 (44,09–45,91)	0,412
NTU			
Volume (cc)	46 (3–228)	46 (3–228)	
D98 (Gy)	**46,04 (45,12–47,46)**	**30,94 (21,37–42,56)**	**<0,001**
Dmean (Gy)	**48,26 (46,48–51,75)**	**41,22 (31,74–47,22)**	**<0,001**
D02 (Gy)	52,89 (48,68–58,91)	51,19 (46,68–60,03)	0,074
Bladder			
Volume (cc)	180 (34–568)	180 (34–568)	
Dmax (Gy)	63,01 (58,93–65,64)	62,62 (59,10–64,52)	0,125
Dmean (Gy)	**40,58 (29,79–49,85)**	**36,41 (26,93–47,70)**	**<0,001**
V15 (%)	98,89 (85,97–100)	96,82 (77,07–100)	0,200
V30 (%)	**81,00 (50,50–100)**	**65,83 (35,75–94,15)**	**<0,001**
V40 (%)	**57,68 (23,86–92,69)**	**41,75 (18,25–75,41)**	**0,001**
V45 (%)	**40,66 (12,01–69,86)**	**29,72 (9,38–63,66)**	**0,002**
Bowel bag			
Volume (cc)	2228 (1352–4099)	2228 (1352–4099)	
Dmax (Gy)	61,77 (48,49–66,44)	61,47 (48,89–66,31)	0,102
Dmean (Gy)	19,85 (10,38–26,13)	19,41 (9,88–27,04)	0,329
V15 (cc)	1339 (792–2155)	1345 (773–2508)	0,889
V30 (cc)	471 (237–697)	457 (173–827)	0,626
V40 (cc)	**239 (81–390)**	**187 (45–328)**	**0,008**
V43 (cc)	**172 (42–335)**	**123 (24–223)**	**0,006**
V45 (cc)	**115 (19–246)**	**81 (10–157)**	**0,018**
Sigmoid			
Volume (cc)	182 (78–339)	182 (78–339)	
Dmax (Gy)	61,91 (49,94–66,44)	61,83 (53,02–66,06)	0,810
Dmean (Gy)	**30,28 (20,38–41,85)**	**28,52 (16,49–36,23)**	**0,008**
V15 (%)	**73,66 (46,78–92,73)**	**69,22 (29,64–88,49)**	**0,039**
V30 (%)	**53,02 (21,61–87,04)**	**49,58 (21,96–72,77)**	**0,023**
V40 (%)	**44,20 (20,52–76,21)**	**37,56 (19,46–55,82)**	**0,011**
V45 (%)	**32,45 (17,88–65,75)**	**25,99 (15,32–39,04)**	**0,044**
V50 (%)	8,47 (00,00–22,85)	9,33 (1,04–28,62)	0,246
Rectum			
Volume (cc)	26 (14–45)	26 (14–45)	
Dmax (Gy)	**63,28 (59,19–65,84)**	**62,76 (56,82–65,77)**	**0,033**

Table 3 (*continued*)

Target/OAR	Whole Uterus, mean (range)	EXIT, mean (range)	significance
Dmean (Gy)	**40,04 (29,25–50,37)**	**35,57 (22,17–48,95)**	**<0,001**
V15 (%)	**86,76 (59,79–100)**	**79,65 (47,49–99,89)**	**0,005**
V30 (%)	**76,24 (50,52–97,85)**	**65,78 (33,83–89,73)**	**0,002**
V40 (%)	**65,18 (36,13–83,79)**	**51,18 (24,68–84,99)**	**<0,001**
V45 (%)	**53,19 (26,64–79,94)**	**42,44 (12,72–75,90)**	**<0,001**
V50 (%)	**7,26 (1,37–14,91)**	**6,34 (0,81–13,94)**	**0,047**

Table 4
Acute and chronic toxicity.

CTCAE v3 grade	Gastrointestinal		Urinary	
	Acute	Chronic	Acute	Chronic
0	1 (5 %)	11 (52 %)	8 (38 %)	13 (62 %)
1	2 (9 %)	4 (19 %)	5 (24 %)	4 (19 %)
2	18 (86 %)	6 (29 %)	7 (33 %)	3 (14 %)
3	0 (0 %)	0 (0 %)	1 (5 %)	1 (5 %)
4	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
5	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)

cc-157 cc) and the mean volume receiving 43 Gy decreased with approximately 50 cc. This decrease in dosages is the result of both a reduction in CTV (leaving out the NTU itself) and PTV_prim_EXIT margin: a reduction of the PTV margin by 2 mm in the anteroposterior direction was incorporated into the protocol since the excluded NTU also encompasses the most mobile part of the uterus.

Our study was not set up to show a reduction in acute toxicity, but we anticipate that this reduction in volume of irradiated organs will result in reduced toxicity, as demonstrated previously by both Roeske et al. and Jensen et al. regarding the volume irradiated to > 45 Gy and > 43 Gy, respectively, and its association with bowel toxicity [26,27]. We did not differentiate in the volume of NTU (ranging from 3 cc to 228 cc, median 46 cc) when performing the plan comparison and included also patients with very small NTU volumes. The 2 patients left out the plan comparison had a NTU of 71 cc and 108 cc respectively. De Boer et al. compared the radiotherapy plans of 11 patients with a > 4 cm tumour-free part of the proximal uterus on diagnostic MRI, namely conventional target volumes and MRI-based target tailoring (non-invaded proximal part of the uterus was excluded). They showed a significant reduction in V15Gy, V30Gy, V45Gy and Dmean for bladder and small bowel and estimated a NTCP reduction of 10 % for half of their patients with a bowel bag initially treated to 45 Gy in volumes > 200 cc [28]. Kozak et al. reported on 53 patients with stage IB to IVB cervical carcinoma who underwent definitive chemoradiotherapy, including brachytherapy [29]. As per institutional standards, the whole uterus was not included. To better delineate the target, gold seed implementation was used to visualize the extent of the tumour to the uterus and vagina. When < 90 % of the uterus was included in the PTV, a significantly lower bowel V40Gy (10,3% versus 14,9%) was achieved [29].

In our cohort, no chronic grade 3 or higher gastrointestinal toxicity was observed and only 5 % chronic grade 3 urinary toxicity. Surgical morbidity was low. This is in line with what can be expected after chemoradiation + brachytherapy [8,30–32]. With a 3-year OS, LRFS and PFS of respectively 76,2%, 81 % and 64,9%, our survival data are also in line with reported data, although direct comparison is certainly not feasible [33–38].

Strengths of the current study are the prospectively followed cohort and the fact that hysterectomy allowed for histopathological confirmation of the primary endpoint. The sample size is small but sufficient

based on the power analysis beforehand. The use of minimal invasive surgery could be considered as a weakness; however, we believe that this could not affect the primary endpoint and stopped after the publication of the LACC-trial [39]. In the current preoperative chemoradiation schedule, the delivered dose was not as high as the standard full dose of EBRT + IGABT. Nonetheless, this approach facilitated the surgery required to meet the primary endpoint.

5. Conclusions

Our findings indicate that excluding the non-tumour-bearing parts of the uterus based on MRI, with a minimum distance of 12 mm from the tumour, from the target volume in locally advanced cervical cancer, can be accomplished without risking residual disease in the uterus. This reduction in treatment volume results in a significant decrease in the dose delivered to the surrounding organs at risk, particularly reducing the volumes treated to 40 Gy and higher.

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CRediT authorship contribution statement

Axel Van Damme: Validation, Formal analysis, Investigation, Writing – original draft, Project administration. **Philippe Tummers:** Methodology. **Pieter De Visschere:** Methodology, Investigation. **Jo Van Dorpe:** Investigation. **Koen Van de Vijver:** Methodology, Validation, Investigation. **Tom Vercauteren:** Software, Investigation. **Werner De Gersem:** Software, Investigation. **Hannelore Denys:** Conceptualization, Investigation. **Eline Naert:** Validation, Investigation. **Amin Makar:** Validation, Investigation. **Wilfried De Neve:** Conceptualization, Investigation. **Katrien Vandecasteele:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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