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Original Research Article

Prospective validation of craniocaudal tumour size on MR imaging compared to histoPAthology in patients with uterine cervical cancer: The MPAC study

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ABSTRACT

Purpose: To determine the accuracy of MRI in detecting craniocaudal tumour extension, compared to histopathology, of the hysterectomy specimen in patients with early-stage uterine cervical cancer. Three complementary methods were investigated.
Materials and methods: Thirty-four patients with early-stage cervical cancer had pre-operative MRI, followed by radical hysterectomy or trachelectomy. 1) craniocaudal tumour extension was measured on MRI by two radiologists and compared to microscopy by a pathologist, 2) to compensate for changes in uterine shape between pre-operative MRI and the surgical specimen, craniocaudal tumour extensions were directly compared and appreciated as being a part of a 3-dimensional tumour by a radiation oncologist and resident, and 3) tumour size on MRI was compared macroscopically after digital non-rigid registration of the uterus, uterine cavity and tumour of both modalities.
Results: The craniocaudal tumour extension measured on histopathology minus MRI gives: 1) on average +3 mm difference when measured by a radiologist compared to the microscopic extension (range −13 to +15 mm), 2) −0.2 mm (range −11 to +6.0 mm) when evaluated on MRI by a radiation oncologist compared to the macroscopic tumour; 3) after non-rigid organ registration, a margin of 10 mm around the tumour on MRI would be needed to cover 95% of the tumour in 90% of the patients.
Conclusions: Results indicate that microscopic tumour extension towards the uterine fundus is within a margin of 10 mm around the visible tumour on MRI. The major source of measurement uncertainty is post-surgical change of organ shape and form.

1. Introduction

Assessment of tumour extension in patients with uterine cervical cancer plays a crucial role in both surgical decision-making and radiotherapy treatment planning. In women with locoregionally advanced disease (FIGO stage IIB-IVA), radiation oncologists depend increasingly on MRI to determine and delineate tumour extension for external beam radiotherapy (EBRT) and brachytherapy [1–5]. With the use of MRI, adequate brachytherapy coverage became feasible and excellent local control is achieved with less toxicity [6–9].

Many radiation oncologists include the whole uterus as the clinical target volume for cervical cancer radiotherapy. The paradigm to include the whole uterus is rooted in the CAT-era; MRI and PET show that the primary tumour is usually limited to a small part of the distal uterus only [13]. If the uninvaded uterine body can be safely excluded by target tailoring to the macroscopic tumour and its microscopic extension, this will substantially reduce radiation toxicity particularly of the bladder and bowel

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[10–14]. Therefore pathological confirmation of tumour extension visualized by imaging is pivotal.

Both gynaecological surgery and radiotherapy depend on the accuracy of MRI. In previous retrospective studies, the accuracy of MRI compared to histopathology was determined using either non-rigid registration, macroscopy data, or microscopy data [15–18]. A major limitation of these studies was that microscopy compared to MRI measurements did not account for differences in uterine shape between MRI and histopathology. This implies that, in many cases, a comparison is not made of the same length in 3-dimensional (3D) space, thereby causing uncertainty regarding the actual tumour size and probably resulting in exaggerated margins. Moreover, those who did attempt to take into account a change in uterine shape between MRI and hysterectomy, did not include microscopy, which is the reference standard of choice.

Therefore, in a prospective cohort of women with early-stage uterine cervical cancer, the present study combined two methods of comparing craniocaudal tumour size measurement on pre-operative MRI with post-operative pathology data, that takes into account a change in uterine shape between MRI and hysterectomy. In addition, in the same cohort, tumour size measured on MRI was compared to microscopy.

2. Methods and materials

2.1. Study design

This prospective study compared tumour extension towards the uterine fundus (below described as 'craniocaudal extension') on pre-operative MRI with histopathology of the surgical specimen in patients with early-stage cervical cancer after a radical hysterectomy according to Wertheim-Okabayashi [19]. The study was approved by the institutional ethical board and all patients gave written informed consent before inclusion.

2.2. Patients

All cervical cancer patients had a diagnostic pre-treatment MRI. Patients were only included if they were eligible for radical hysterectomy for early-stage cervical cancer, i.e. FIGO stage IA1-IIA. Patients were excluded if there was a contra-indication for MRI. Patients were also excluded if all tumour was excised on for instance biopsy or conisation, which resulted in no tumour found in the hysterectomy specimen.

2.3. MRI procedure

All patients were scanned on a 3.0T MR scanner using a phased-array sensitivity encoding (SENSE) torso or cardiac coil (Ingenia, Philips, Best, the Netherlands). Sagittal, axial oblique and coronal oblique T2 weighted Turbo Spin Echo (TSE) images were obtained (TE 80 ms, TR 4298–5906 ms, TSE factor 20, matrix size 240x240, resolution $0.6 \times 0.7 \times 3.0$ mm). To avoid bowel movement artefacts, 20 mg of butylscopalaminebromide (Buscopan, Boehringer, Ingelheim, Germany) was administered intramuscularly.

Additionally, a DWI-scan with axial single-shot echo-planar imaging (EPI) sequence of the pelvic region was obtained (TE 58 ms, TR 5004 ms, matrix size 240×240, resolution $2.0 \times 2.0 \times 4.0$ mm, EPI factor 51, sensitivity encoding (SENSE) factor 3, b-values 0, 100, 500, and 1000 s/mm^2, number of averages of 1, 1, 2, 5 respectively).

For evaluation, first, a case report form with instructions was developed in conjunction with two radiologists and the first author. The MR images were independently evaluated by two radiologists with 22 and 2 years of experience, respectively, in assessing MRI of the pelvic region. To minimise bias, a dummy-run was done on an MRI of a patient not included in this study. The maximum craniocaudal tumour extension along or parallel to the uterine cavity was measured on the T2 weighted sagittal images and DWI was evaluated in case of any doubt. To facilitate optimal comparison, the radiologists were instructed to measure the craniocaudal tumour extension that would have been visible for the pathologist after exposing the uterine cavity with an anterior median incision. In this way, they aimed to make measurements in the same way as the pathologist (Fig. 1). The radiologists were blinded for each other's measurement and for the histological tumour measurements by the pathologist.

If image quality was found to be unacceptable according to the clinical standards of the radiologists, this was recorded. Reproducibility of measuring the craniocaudal extension between the two radiologists was expressed by the intraclass correlation coefficient (ICC) [20].

2.4. Histopathology

After orientation of the cervical surgical specimen, the uterine cervix and corpus were incised ventrally to expose both the endocervical channel (and uterine cavity) (Fig. 1A). Digital photos were made at straight angles. The surgical specimen was processed according to the regular protocols used at the Department of Pathology. The maximum craniocaudal extension was measured both on macroscopy (before fixation) and verified by microscopy (after fixation). All data on both the macroscopic and microscopic craniocaudal extensions were reviewed by a gynaecopathologist blinded for the MRI-data.

2.5. Comparison between MRI and (histo)pathology

Three complementary methods were used to minimise uncertainties in measurements due to differences in uterine shape between MRI and histopathology:

1) MRI vs. histopathology

The average craniocaudal tumour extension on MRI independently measured by two radiologists was compared with both the macro- and microscopic tumour extension as measured by the pathologist. The agreement of measured craniocaudal tumour extension between MRI and macroscopic pathology was visualised in a Bland-Altman plot. Furthermore, descriptive statistics and Pearson's correlations were calculated.

2) 3D-comparison

This method is similar to conventional radiation oncology practice: Typically, when defining a target for radiotherapy the physician's goal is to delineate the 3D shape of the target volume, while interpreting data from 2D images. Analogous to this, after interpretation of the 2D images knowing they are a part of a 3D shape, we measured craniocaudal tumour extension of the delineated tumour on MRI-target in the dissection plane of the surgical specimen to minimise 3D inaccuracies. These measurements were made by a resident in radiation oncology(PB) and a radiation oncologist(LS). The same statistical analyses were applied as described in 1) above (Fig. 1).

3) Non-rigid registration of the uterus

Macroscopic photographs of the uterus with the exposed uterine cavity were matched to the corresponding pre-operatively acquired T2-weighted sagittal MRI slice by digital non-rigid registration of the organs by a PhD student (physics)according to the description of a recently published paper [17]. In this way the uterus, uterine cavity and tumour were delineated both on photographs and MRI. Next, delineated parts of the photograph were simultaneously registered to the sagittal MRI slice using a three-step multi-image registration strategy. These three steps in non-rigid registration were

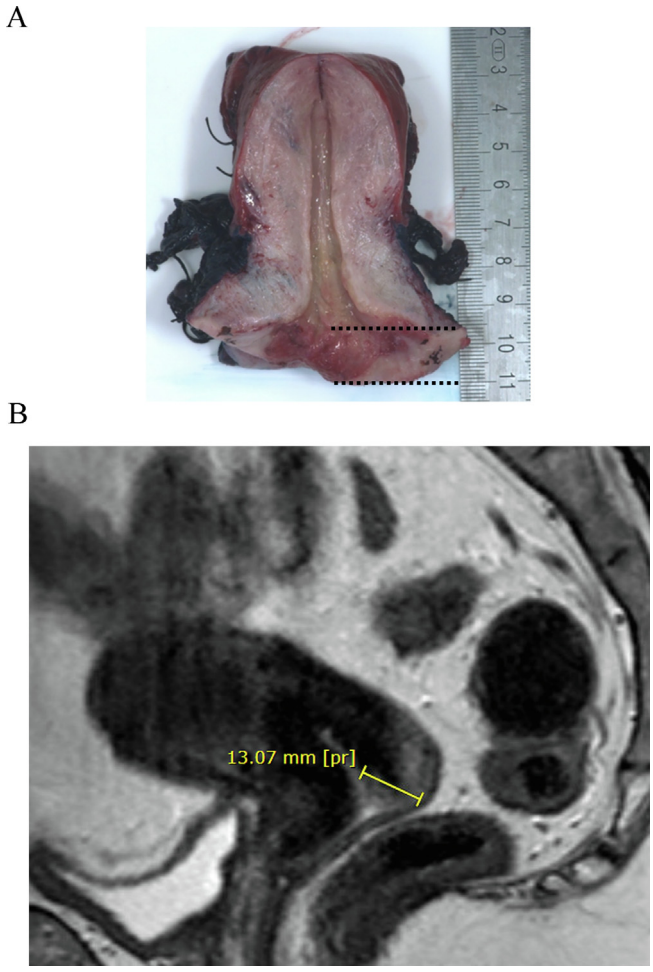

Fig. 1. 54-Year-old patient with FIGO stage IB squamous cell carcinoma of the cervix which was measured as 14 mm on the macroscopic pathology photograph (A), and 13 mm on MRI (B) when measurement took place in the same 3D direction. This example shows why, in this study, appreciating tumour as a 3D structure is one of the crucial conditions for correct comparison.

developed to minimise registration errors by respecting internal structures and boundaries of the uterus and the uterine cavity. Results of the registration were evaluated with the Dice Similarity Coefficient (DSC) and the surface distance error (SDE). Further details can be found in the referred paper [17].

3. Results

3.1. Patients

Between May 2013 and October 2016, 36 women with early-stage uterine cervical cancer were included who had pre-operative MRI and radical hysterectomy according to Wertheim-Okabayashi. Two patients had no tumour in the surgical specimen after hysterectomy due to conisation or large loop excision of the transformation zone and were excluded from the study (Fig. A1). For the remaining 34 patients, baseline characteristics at the time of inclusion are presented in Table 1.

3.2. Evaluation of MR images

All MR-examinations were found to be of 'acceptable' quality by both radiologists. They found a mean craniocaudal tumour size of 18 mm (range 0–42, SD 11 mm) and 17 mm (range 0–41, SD 11 mm), respectively. For each patient, when the average of both radiologists was calculated, a tumour size of 18 mm (0–42, SD 11 mm) was found. The ICC showed a value of 0.93 (95% confidence interval [CI] 0.85–0.96) which is classified as an 'almost perfect' agreement between the two radiologists.

During 3D-comparison by the radiation oncologist in conjunction with the resident, mean tumour extension was 21 mm (range 0–47, SD 11 mm). The ICC between the average measurements per patient of the two radiologists and measurements during 3D-comparison was 0.93 (95% CI 0.76–0.97) and is classified as 'almost perfect'.

Table 1
Baseline characteristics of the patients.

(n = 34)	
Median age (range) on MRI: in years	45 (24–67)
FIGO stage	
IA2	1
IB1	29
IB2	4
Histopathological subtype	
SCC	20
AC	9
ASC	2
Other	3
Lymphovascular space invasion	
SCC	9
AC	2
ASC	1
Mucinous carcinoma	1
Treatment before MRI	
LLETZ	8
Conisation	6
Median period (range) between MRI and hysterectomy: in days	30 (3–94)
Predominant tumour location in relation to the internal ostium	
Central	19
Ventral	2
Dorsal	6
Left lateral	2
Right lateral	5
Type of lesion	
Exophytic	21
Endophytic	13

FIGO = International Federation of Gynaecology and Obstetrics; SCC = squamous cell carcinoma; AC = adenocarcinoma; ASC = adenosquamous carcinoma; LLETZ = large loop excision of the transformation zone.

3.3. Histopathology

Of the 34 included patients, six were treated elsewhere for trachelectomy or a second opinion and could not be processed at the department of Pathology (Fig. A1). Of the remaining 28 patients, in 26 of them macroscopic photographs were available for assessment of the craniocaudal extension. Additionally, one macroscopic photograph could be retrieved from a patient that was treated elsewhere, which could be used for the 3D-comparison method. In 20 patients, the microscopic craniocaudal extension could be measured accurately. In 14 cases the craniocaudal microscopic extension was estimated but could not be reconstructed with full certainty; therefore, these patients were excluded from analysis.

On macroscopy (n = 26) and microscopy (n = 20), craniocaudal tumour extension was on average 21 mm (range 0–50, SD 14 mm) and 17 mm (range 3–42, SD 8 mm), respectively. In a paired comparison of 18 cases, the median macroscopic craniocaudal extension was 4 mm smaller (range −7 to 22, SD 7 mm, test for normality borderline negative) compared to the microscopy measurement (median 14 vs. 18 mm). Three outliers showed an underestimation of macroscopic photographs of 15–22 mm; however, in these cases, MRI showed a smaller underestimation of −3.5 to

15 mm. In four cases the microscopic tumour extension was in fact 1–7 mm smaller than estimated on macroscopy. In 2 of 20 cases in which the microscopy was evaluated, no photograph was taken and therefore no comparison could be made.

On 3D-comparison by the radiation oncologist and the resident radiation oncology, craniocaudal tumour extension was found to be on average 20 mm (range 0–44, SD 11 mm). It should be noted that, with this method, 3D-reproducibility between macroscopic photographs and MRI was found to be crucial; therefore, in some cases only a part of the tumour was measured that could be well recognised on both modalities (Fig. 1).

3.4. Comparison between MRI and histopathology

1) MRI vs. histopathology

The craniocaudal tumour extension measured by radiologists on MRI was on average 3 mm smaller (range −25 to 20 mm, SD 10.0 mm) compared to all 26 macroscopic measurements by the pathologist (18 vs. 21 mm, respectively, $p = 0.135$) and both measurements showed a good correlation ($r = 0.72$, $p < 0.001$) (Fig. 2).

The difference in craniocaudal extension between all 20 microscopy cases and MRI was 3 mm (range −12 to 15, SD 7.6 mm), this difference was not significant (14 vs. 17 mm, respectively, $p = 0.098$) and both measurements showed a good correlation ($r = 0.73$, $p < 0.001$). Craniocaudal extension on MRI compared to microscopy showed a smaller 95% CI than compared to macroscopic photographs (−12 to 18 mm vs. −17 to 23 mm, respectively) (Figs. 2 and 3).

From a radiation oncologist point of view, there were four outliers where tumour extension would be underestimated on MRI by ≥10 mm and would, therefore, potentially not be recognised as tumour in radiotherapy target volumes. One patient had a conisation before MRI and hysterectomy: no tumour was recognised on MRI or on the macroscopic photographs, but microscopy revealed a tumour with a craniocaudal extension of 15 mm (Fig. A2). In the other three patients, the craniocaudal plane of the tumour was altered between MRI and histopathology; therefore, these underestimations were probably caused by measuring tumour in different directions (Fig. 4,A3,A4).

2) 3D-comparison

Paired comparison of craniocaudal tumour extension on MRI and macroscopic photographs (both performed in consensus by radiation oncologist and a resident radiation oncology) could be performed in 27 patients. There was a minor difference (mean −0.2 mm; range −11 to 6.0, SD 3.4 mm) between craniocaudal tumour extension on photographs minus MRI (19.9 vs. 20.1 mm, respectively, Pearson's correlation 0.95, $p < 0.001$) (Fig. 5). The 95% CI of the difference ranged from −7 to 7 mm. Intraclass correlation coefficient of tumour extension on macroscopy between the pathologist and radiation oncologist was 0.91 (95% CI 0.79–0.96)

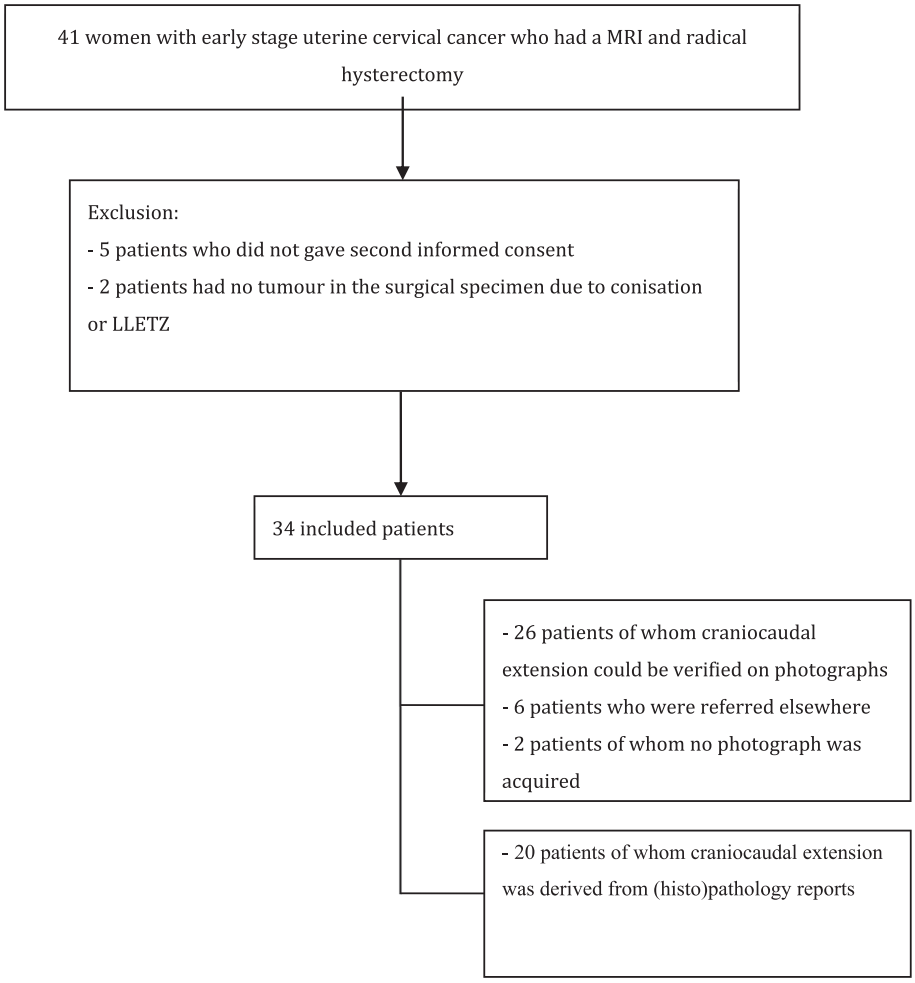

Fig. 2. Bland-Altman (A) and waterfall plot (B) for craniocaudal extension measured on MRI vs. macroscopic photographs evaluated by the pathologist.

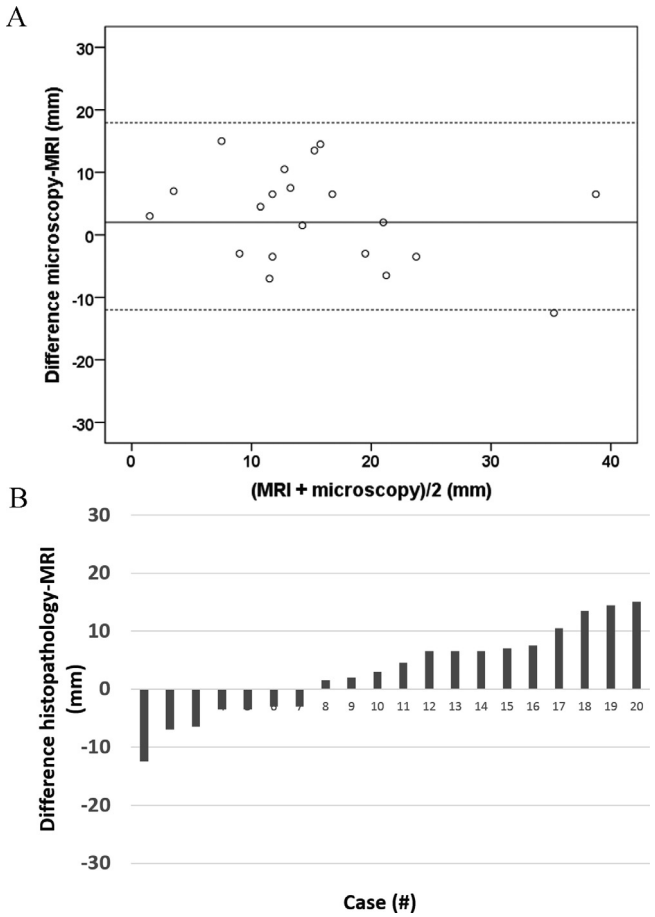

Fig. 3. Bland-Altman (A) and waterfall plot (B) for craniocaudal extension measured on MRI vs. histopathology (microscopy).

and is classified as 'almost perfect' (see also Supplementary Table A1).

3) Non-rigid registration of the uterus

In 10 patients, the minimal requirements were met for an adequate non-rigid registration [17]. We found a median DSC and SDE of 0.99 and 1.75 mm (whole uterus) and 0.82 and 5.24 mm (uterine cavity), respectively. An average SDE of 0.74 mm (range 0.36–0.89 mm) around tumour was found. A margin was applied to the tumour on MRI to cover the non-rigid registered tumour on microscopy. For 95% coverage of the tumour in at least 90% of the patients, a margin of 10 mm was needed.

4. Discussion

Craniocaudal tumour extension in early-stage cervical cancer measured on MRI gives a small underestimation of (on average) 3 mm of the length measured on the microscopy specimen, but may be as high as 10 mm, which we therefore recommend as a minimal clinical safety margin for radiotherapy target delineation.

In three patients, underestimation of tumour extension exceeded 10 mm; which was probably due to the change in uterine shape between MRI and post-hysterectomy (Fig. 4,A3,A4). In a fourth patient, conisation probably caused the difference in tumour size (Fig. A2), since tumour measurement on MRI after conisation might be less reliable [21]. Another cause of measurement inaccuracy is shrinkage of the tumour during fixation (generally 10% in any direction), whereas on MRI the size remains unaffected [22]. If we also compensate for 10% tumour shrinkage,

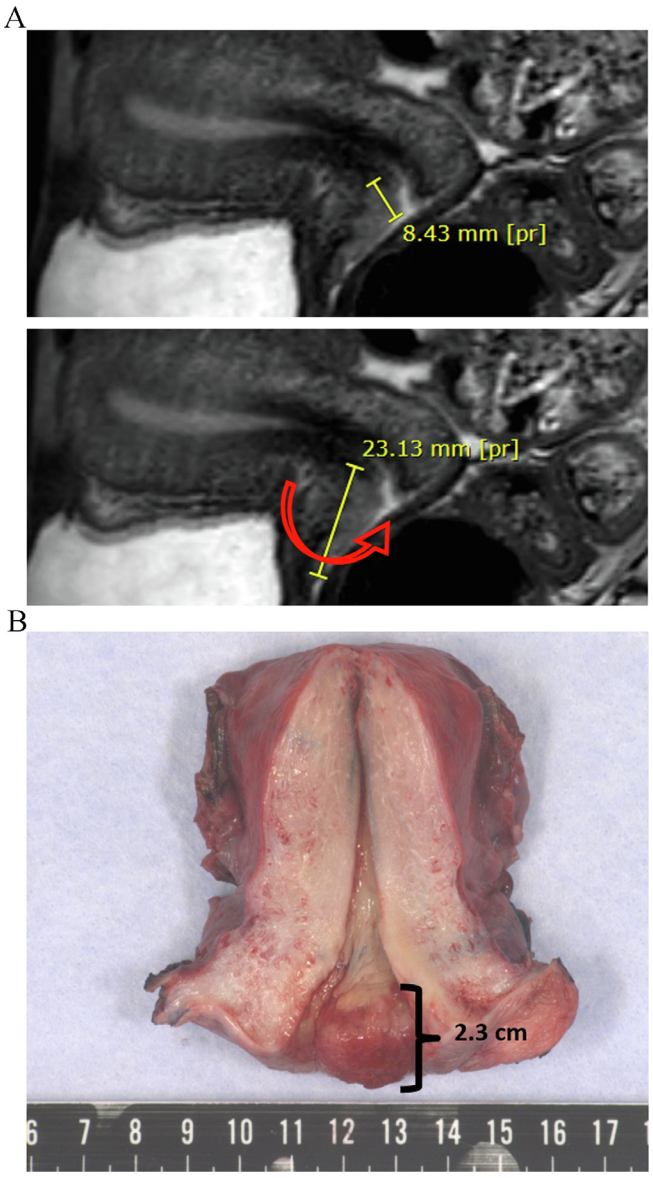

Fig. 4. 38-year-old women with a FIGO stage IB1 adenocarcinoma of the cervix. Measurement of the craniocaudal tumour extension on the sagittal MRI slice shows a tumour of 8.4 mm (A; upper image), however on histopathology the measurement is 23 mm (B). The cervix in this patient felt weak and free to be bent and, therefore, would accommodate to the flat shape of the table (red arrow); therefore, the right distance according to A (lower image) was probably 23.1 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the required safety margins need to be correspondingly 10% wider, i.e. an extra 3 mm in case of a 30 mm tumour.

Only a few studies have compared cervical cancer tumour size measured on MRI with histopathology. For example, Sanuki et al. (2013) compared cervical tumour length in hysterectomy specimens with 1.5T MRI in 31 patients and found that MRI underestimates tumour length along the uterine cavity by 5 mm (19 on MRI vs. 24 mm on microscopy); their data suggests that a 10-mm margin around tumour delineated on MRI would be sufficient to include microscopic extension in 95% of the patients [18]. However cases where tumour was hard to recognise due to resemblance to surrounding tissue were excluded. Remarkably, Sanuki *et al.* did not report problems in 3D shape alternations between MRI and histopathology. Bourgioti et al. (2014) confirmed these results in 21 patients with tumours of 1–4 cm in maximum diameter, who

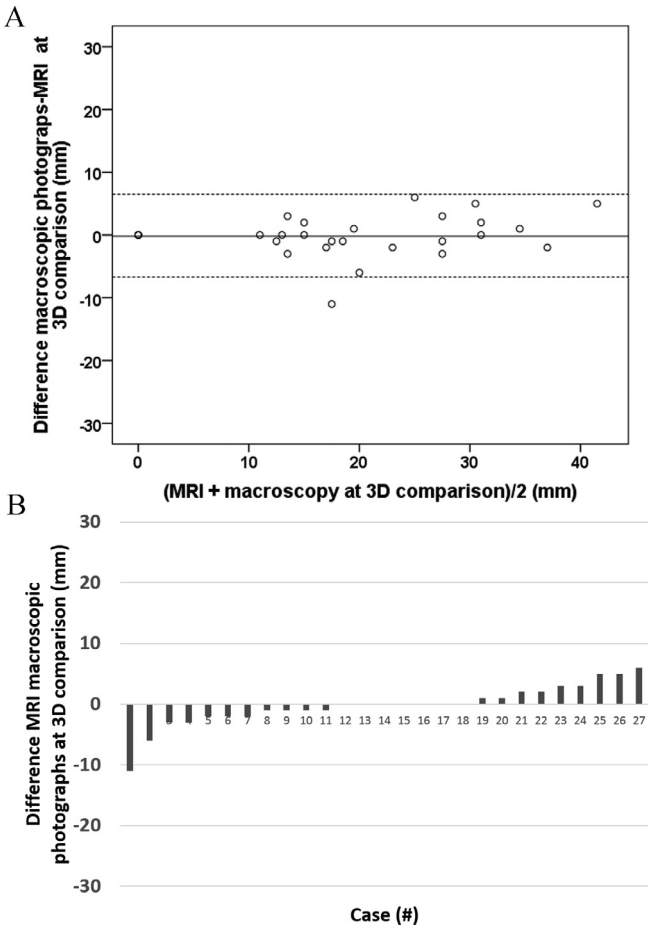

Fig. 5. Bland-Altman (A) and waterfall plot (B) for craniocaudal extension measured at '3D comparison' vs. macroscopic photographs.

had MRI before trachelectomy whereby no more than 10-mm underestimation of tumour size was found compared to microscopy [23]. Also de Boer *et al.* found in a retrospective series of 21 patients an underestimation 10 mm by MRI compared to microscopy and report similar spatial uncertainties due to difference of uterine between both modalities [15].

A limitation of the present study is that only early stage cervical cancer histopathology data is available for comparison with MRI. Therefore the margin of 10 mm should only be applied in the direction of the uterine fundus and not towards the parametrium and vaginal vault. Another limitation, and that of previous studies, is that comparison of tumour size measured by the radiologist and by the pathologist strongly depends on the spatial orientation of the tumour; this may result in spurious differences. For example, in the case shown in Fig. 4, the craniocaudal tumour extension was 8 mm on MRI but, due to anterior flexion of the radial cervical extension after hysterectomy, the craniocaudal tumour extension became 23 mm on pathological macroscopy. By evaluating Fig. 4, underestimation of tumour size by the radiologist seems unlikely causing such large difference. In general, post-surgical organ deformation is most misleading for microscopic measurements in which the spatial orientation of the pathological section is usually lost. It seems remarkable that other authors did not encounter/report this problem. However, this was recognised in studies on prostate cancer [24–26], head and neck cancer [27] and lung cancer [28], in which imaging and pathology were compared.

We aimed to minimise these measurement uncertainties due to alterations of the shape of the cervix and uterus by directly comparing MRI and macroscopic specimen measurements, interpreting both modalities as being part of a 3D-shape, and found (on average) almost no difference between measuring tumour size on the macroscopic specimen and MRI (mean difference −0.2 mm, range −11 to 6 mm, SD 3.4 mm) (Fig. 5). The 3D-comparison method did not include microscopic data since it was not possible to repeat microscopy slicing in a different 3D-direction; this is a limitation of this method. On macroscopy, our pathologists found a median underestimation of tumour extension of 4 mm when compared to microscopy. Xie et al. (2015) compared macroscopy with microscopy in 318 hysterectomy specimens of women with cervical squamous cell carcinoma (SCC) and found that with a 5-mm margin around GTV, 99% of all microscopic invasion towards the uterine body would be covered [29].

In the third method, we followed the methodology for non-rigid registration as described by van de Schoot et al. and found similar results [17]. Here, we found it difficult to perfectly align a 2D sagittal MR-slice with a photograph of a 3D-object where depth is not visible. This limitation was reported earlier [17], particularly also because the exact plane in which the incision is made to expose the uterus is unknown. This limitation can be tackled by embedding the whole fresh hysterectomy specimen and systematically slicing the embedded organ into sections, thereby enabling direct 3D-comparison with MRI in multiple sections [17,25]. Moreover, embedding followed by systematic slicing of the uterus into whole-mount sections would eliminate most of the limitations in all three described methods.

With brachytherapy delineation and trachelectomy decision-making, physicians rely heavily on what they see on T2-weighted MRI when physical examination under anaesthesia does not provide the answer [2,3,30,31]. Our results, and those of other recent studies, indicate that a 10-mm margin would be sufficient to cover invisible microscopic extent for primary cervical tumour delineation on MRI [12]. Also in brachytherapy, a minimal margin from high risk to intermediate risk CTV of 10 mm in cranial direction is recommended. Our data support the MRI guided brachytherapy recommendations to not load the tandem fully up to the uterine fundus [2,3]. Ideally, EBRT and brachytherapy dose of target volumes and organs at risk have to be summed, for instance by deformable registration as shown by van Heerden et al. [32]. Furthermore, it has been suggested that microscopic tumour extension is smaller in SCC and in tumours without LVSI [29,30]. However, these preliminary observations deserve further confirmation. If data from 3D-pathology sections could be compared to multiple MRI-slices of cervical tumours, the difference between MRI and pathology caused by a change in uterine shape by surgery might be reduced.

5. Conclusions

In these patients with early-stage cervical cancer, MRI gives (on average) a 3-mm underestimation of the pathological extension towards the uterine fundus. However, in 10% of these patients, the underestimation may be as high as 10 mm; nevertheless, in these latter cases the tumour was limited within the uterine cervix. In these outlying patients, measurement uncertainty is mostly caused by changes in the shape of the uterus between the *in situ* situation as captured on MRI and the pathological specimen.

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Conflicts of interest

Dr. Bel reports grants and non-financial support from Elekta AB, Stockholm, Sweden, during the conduct of the study; Prof. Stoker reports grants from Robarts Clinical Trials, outside the submitted work. All other authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.06.004.

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