MR guided adaptive radiotherapy for gynaecological cancer

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Abstract

Introduction

The gold standard treatment for locally advanced cervical cancer is concurrent chemo radiotherapy followed by image guided brachytherapy. This has led to improved survival outcomes; however, rates of long term toxicity remain high. There is evidence that the cervix and uterus can move during external beam radiotherapy, exceeding the CTV (clinical target volume) to PTV (planning target volume) margin in many patients.

Aim

The overall aim of the project is to assess causes and implications of target motion in cervix cancer to support the development of novel image guided radiotherapy.

Method

Chapters 1 to 3 are based on a retrospective cohort of patients who received external beam radiotherapy for cervical cancer, with scans at 3 time-points. The central sagittal slice is used to estimate motion at the uterine fundus. The correlation between motion and clinical outcomes is assessed. The cause of motion at the uterine fundus and cervix was also assessed qualitatively. Chapter 4 describes and quantifies intrafraction motion and is based on data from a prospective MR imaging study, with 10 patients who underwent 4 MR scans during radiotherapy. Axial sequences every two minutes for 10 minutes were contoured and the distance to agreement (DTA) calculated. Chapter 5 is an assessment of outcomes of a retrospective cohort of patients who received moderately hypofractionated palliative external beam radiotherapy for gynaecological cancer, a patient group that could be potentially the first cervix treatments on the MR-linac in our institution.

Results

A novel methodology to estimate motion of the uterine fundus was developed, and mean motion found to be greater that the CTV to PTV margin. There was no association between motion at the fundus and overall survival, progression free survival and toxicity, suggesting that fields could be shortened without detrimental effects. Interfraction motion at the uterine cervix was usually related to rectal changes or tumour shrinkage, motion at the uterine fundus is often related to bladder filling but rectal and small bowel changes as well as tumour shrinkage were also important causes. Intrafraction motion was mainly related to bladder filling at both the uterine fundus and cervix but rectal changes also led to cervix

motion. The mean max DTA was 0.5cm, however the site of maximum motion varied between fractions. Moderately hypofractionated radiotherapy was found to be an effective palliative treatment for patients with gynaecological malignancies.

Conclusions

The work presented in this thesis has provided a rationale for novel adaptive radiotherapy techniques, as the current approaches are based on bladder filling changes, which does not address the causes of motion at the cervix. Palliative treatment is a sensible initial step to develop MR guided external beam radiotherapy

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

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Preface

This thesis is focussed on the development of MR guided adaptive radiotherapy for cervical cancer. It is presented in journal format, as although they are related, the chapters represent individual pieces of work. It comprises of a literature review followed by five main pieces of work presented in journal format followed by a chapter discussing potential strategies for MR guided adaptive radiotherapy and an overall discussion and conclusion. A prospective MR imaging study was designed and completed as part of the PhD and the protocol is included as an appendix.

Introduction

A modified version of this introduction has been published as *'The Potential Value of MRI in External-Beam Radiotherapy for Cervical Cancer. Anthea Cree (AAC), ,Jac Livsey (JL) ,Lisa Barraclough (LB),Michael DubecMD, Thomas Hambrock (TH) , Marcel Van Herk (MvH), Annanya Choudhury (AC), Alan McWilliam(A McW). Clinical Oncology, Volume 30, Issue 11, 737 – 750'* [1].

Conception or design of the work: AAC MvH, AC, AMcW

Drafting of text: AAC

Editing text: AAC, AmcW, MvH, AC, JL, LB, MD, TH

Magnetic resonance imaging (MR) is suggested as the imaging modality of choice for gynaecological malignancies due to the excellent soft tissue contrast and tumour visualisation [2]. It is widely used for diagnosis and post treatment assessment and is superior to Computed tomography (CT) in this context [3,4]. The introduction of MR guided brachytherapy has increased survival and reduced toxicity in patients with cervical cancer [5].

The potential of MR in external beam radiotherapy (EBRT) was identified as early as the 1990s, with information from MR imaging improving the definition of borders for radiotherapy planned using bony markers [6]. Initial work was focussed on MR simulation, aiming to improve delineation of radiotherapy target volumes but with the development of commercial MR linac systems, MR radiotherapy guidance with online adaption is now possible [7].

Gynaecological malignancies are an attractive target for MR guided external beam radiotherapy because of pelvic organ motion and the poor visibility of pelvic structures using cone beam CT (CBCT.) Long term toxicity following external beam radiotherapy remains a problem with grade 3 toxicity reported in up to 10% of patients treated with radical concurrent chemoradiotherapy for cervical cancer [8].

Although the initial focus of MR guided radiotherapy for gynaecological cancer was for radical treatment, there are technical problems. Due to the inclusion of an elective nodal volume for radical radiotherapy of cervical cancer, the field in at least 40% of patients is greater than the 21cm field length of the Elekta Unity MR linac [9]. Potential solutions to overcome this problem, such as a dual isocentre approach, are under investigation[10]; however, there may also be a role for MR guidance in palliative radiotherapy for gynaecological cancer, where smaller fields are used.

This introduction will start with the basic epidemiology and treatment of cervical cancer followed by MR imaging for cervical cancer and a brief introduction to MR guided external beam radiotherapy. The potential role of MR guidance in radiotherapy for cervical cancer will be then be discussed for external beam radiotherapy, SABR and palliative radiotherapy in gynaecological cancer.

Current management of cervical cancer

There were 3,224 cases of invasive cervical cancer diagnosed in the UK in 2014 with 819 associated deaths. Worldwide, 85% of cases occur in patients from low and middle income countries, with over 500,000 women diagnosed in 2012 [11]. In the UK, over 50% of cases are diagnosed in women under the age of 45. Most cases of cervical cancer are related to infection with high risk HPV sub-types (most commonly HPV 16 or 18).

This may lead to the development of cervical intra-epithelial neoplasia (CIN), which then in some cases leads to invasive cancer. There has been a national screening programme for CIN since 1988. A primary prevention strategy for cervical cancer with HPV vaccination has been introduced in the last decade. Rates of invasive cancer within the UK have remained essentially stable over the last 10 years but have declined by approximately 25% since the 1990s [12]. 5 year survival varies between 96% for stage 1 disease to 5% for stage 4 disease. [12]

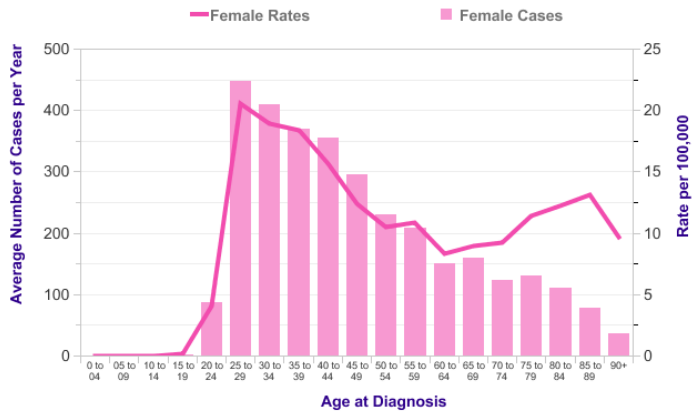

FIGURE 1 (CANCER RESEARCH UK 2017) AVERAGE NUMBER OF NEW OF CERVICAL CANCER CASES PER YEAR AND AGE-SPECIFIC INCIDENCE RATES PER 100,000 POPULATION, FEMALES, UK

Despite public health initiatives supporting HPV vaccination in lower and middle income countries, there remains a large unmet need for radiotherapy with an estimated 9 million women who would benefit from treatment from 2015-2035[13] .

Anatomy and histopathology

The cervix usually measures 2-4 cm and is situated at the top of the vagina. It is contiguous with the body of the uterus and is derived from the same embryonal unit (paramesonephric ducts). It lies posterior to the bladder and anterior to the rectum, laterally it is adjacent to the parametrium. It is the least mobile part of the uterus. The exocervix, the portion of the

cervix which lies within the vagina, is covered with squamous epithelium in common with the vaginal epithelium. There is a transformation zone within the cervical canal where the lining changes to columnar epithelium.

The uterus is supported by the pelvic and urogenital diaphragm, in the centre of the pelvis by ligaments including the uterosacral and cardinal ligaments. It is covered superiorly by a layer of peritoneum called the broad ligament. The main body of the uterus is mobile and can vary with bladder and bowel filling. Its orientation is described as anteverted when the main uterus is tilted forwards and retroverted when it is tipped back. The position of the uterine fundus, the top of the uterus, is described as anteflexed when it points forwards in relation to the cervix and retroflexed with it points backwards. The parametrium is a region of connective tissue surrounding the cervix, which is bounded by the broad ligament superiorly, the pelvic side wall laterally, the posterior wall of the bladder anteriorly, the mesorectal fascia posteriorly and the pelvic floor inferiorly [14,15]

Squamous cell cancer accounts for around 80% of cervical cancer, with adenocarcinoma being the next most common histological subtype. Other rare subtypes include adenosquamous, small cell carcinoma as well as non-epithelial tumours such as sarcoma, melanoma or lymphoma. Cervical cancers often show areas of hypoxia which are associated with poorer prognosis and may lead to resistance to radiotherapy [16].

Staging

Cervical cancer is usually staged using the clinical FIGO (The International Federation of Gynecology and Obstetrics) staging. This was originally a clinical staging system, as the majority of patients are from countries where the availability of clinical imaging is potential limited (FIGO 2009). This therefore excluded lymph node status despite it being a prognostic factor.

However, a new staging system has been introduced (FIGO 2018), which has new categories; FIGO (2018) stage IIIC1 (2018), indicating the presence of pelvic lymphadenopathy stage IIIC2 indicating the presence of para aortic lymphadenopathy. FIGO stage 1B, representing tumours confined to the cervix with a depth of invasion greater than 5mm, has been further subdivided from 2 to 3 categories. FIGO (2018) 1B1 now includes tumours with a stromal depth of 5mm to 2cm in greatest diameter, FIGO (2018) 1B2 is

tumours from 2-4cm and FIGO (2018) 1B3 is tumours confined to the cervix of greater than 4cm[17].

As the majority of the published literature and work carried out in this report is based on FIGO (2009) staging, this will be considered the default and if FIGO (2018) staging is used this will be specified in the text.

Stage (FIGO 2009)	Description	Stage (FIGO 2018)	Description
I	***The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).***	*I*	***The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).***
IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.)	IA	Invasive cancer diagnosed only at microscopy with a depth of invasion less than 5mm
IA1	*Measured invasion of stroma ≤ 3mm in depth and ≤ 7mm width.*	*1A1*	*Measured invasion of stroma ≤ 3mm in depth*
IA2	*Measured invasion of stroma >3mm and > 5mm depth and ≤ 7mm width.*	*1A2*	*Measured invasion of stroma >3mm and > 5mm depth*
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA	1B	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
IB1	*Clinical lesions less than 4 cm in size*	*1B1*	*Clinical lesions greater than 5mm depth and less than 2cm*
		1B2	*Clinical lesions between 2cm and 3.9cm*
IB2	*Clinical lesions > 4 cm in size.*	*1B3*	*Clinical lesions greater than 4cm*
II	**The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina. Involvement of up to the upper 2/3 of the vagina.**	**II**	**The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina. Involvement of up to the upper 2/3 of the vagina.**
IIA	No obvious parametrial involvement.	IIA	No obvious parametrial involvement.
IIA1	*Clinically visible lesion ≤ 4cm.*	*IIA1*	*Clinically visible lesion ≤ 4cm.*
IIB1	*Clinical visible lesions > 4 cm in size.*	*IIB1*	*Clinical visible lesions > 4 cm in size.*
IIB	Obvious parametrial involvement but not onto the pelvic sidewall.	IIB	Obvious parametrial involvement but not onto the pelvic sidewall.
III	**The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the**	**III**	**The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the**

	tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes.			**tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes. Lymph nodes confined to the pelvis or para aortic region**
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.	IIIA		Involvement of the lower vagina but no extension onto pelvic sidewall.
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney.			Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney.
		IIIC	IIIC1	Involved lymph nodes confined to the true pelvis only
			IIIC2	Lymph nodes extending no further than the para-aortics
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.	**IV**		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread to adjacent pelvic organs	IVA		Spread to adjacent pelvic organs
IVB	Spread to distant organs.	IVB		Spread to distant organs.

TABLE 1 FIGO STAGING OF CERVICAL CANCER. MODIFIED FROM [17,18]

Current standard treatment

A report issued by FIGO in 2015 gives recommendations for general management of cervical cancer [18] as well as specific radiotherapy guidelines [19].

Microinvasive disease (stage IA) and small clinical tumours (stage IB1 – IIA1) can be managed surgically.

For stage IA1 simple hysterectomy, if fertility preservation is not required, or cone biopsy are recommended. For higher stage disease, radical hysterectomy or trachelectomy, the removal of the cervix, parametrium and upper third of the vagina to allow for fertility preservation, are standard. Pelvic lymphadenectomy is recommended for stages greater than IA1, but sentinel node biopsy is becoming increasingly common [18,20].

Adjuvant treatment with concurrent chemoradiotherapy is recommended for patients with positive lymph nodes or involved margins as it has been shown to improve both progression free survival and overall survival. Adjuvant chemoradiotherapy should also be considered for patients with risk factors including tumour size greater than 4cm and capillary-like space

involvement [21]. This treatment has been shown to improve progression free survival compared to surgery alone [18].

The use of neoadjuvant chemotherapy prior to chemoradiotherapy is experimental and not recommended for routine clinical practice.

The recommended treatment for patients with locally advanced disease (1B2-IVA) is concurrent chemoradiotherapy with image guided brachytherapy. The dose of external beam radiotherapy (EBRT) recommended is between 45Gy and 50.4Gy in 1.8-2Gy fractions with an EQD2 (equivalent dose at 2Gy per fraction) of 80-85Gy to point A (defined as 2cm from the midline of the cervical canal and 2cm superior to the lateral fornix.) Total treatment times should be kept within 8 weeks as delays in treatment have been associated with poorer outcomes [22,23]. There is strong evidence for the use of concurrent chemotherapy, although there is an increased risk of long term side effects. There is limited evidence surrounding the use of extended fields to cover the para aortic nodes [19].

Patients with advanced disease who are unsuitable for radical radiotherapy or surgery should receive palliative chemotherapy or radiotherapy alongside supportive care [18].

Brachytherapy (GEC–ESTRO Gynaecological brachytherapy working party group guidelines)

Brachytherapy is an important part of radical radiotherapy for cervical cancer delivering high doses of radiation to the tumour. It has been impossible to provide a similar dose distribution with an EBRT boost. Low dose rate, high dose rate and pulsed dose rate brachytherapy have all been used. Brachytherapy is usually scheduled towards the end of EBRT to take account of tumour response to treatment. The use of interstitial needles as well as intracavity treatment has been shown to be beneficial [24].

The GEC (Groupe Européen de Curiethérapie) -ESTRO (European Society for Radiotherapy & Oncology) gynaecological working part group was developed in 2000 to promote and standardise the development of image guided brachytherapy (IGBT) for cervical cancer [25]. This has led to a move away from traditional brachytherapy delivered under X ray guidance with dose reported to point A (as per ICRU (International Commission on Radiation Units

and 20easurements) 38 guidelines) to conformal 3D planned radiotherapy under 3D image guidance. Alongside the residual GTV (gross tumour volume) at the time of brachytherapy, they also defined a high risk clinical target volume (HR-CTV). This included abnormal tissue but not definite tumour, detected on clinical examination or MR imaging. The intermediate-risk (IR-CTV) includes the high-risk CTV with a 5-15mm margin [26]. Magnetic resonance (MR) has been suggested as the imaging modality of choice for image guidance due to the excellent soft tissue contrast and visualisation of the tumour [2].

The benefits in the use of IGBT have been described in the retroEMBRACE study with 5-year local control rates of 91% and overall survival of 74%. Actuarial rates of grade 3-5 toxicities at 5 years were 5% bladder toxicity, 7% gastrointestinal toxicity and 5% vaginal toxicity [5]. This work forms the basis of the ICRU 89 'Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix' guidelines [27].

Radical external beam radiotherapy development

Initially radiotherapy for cervical cancer was delivered using two beam directions, an anterior/posterior (A/P) parallel opposed pair. The technique was then refined to a four field brick with lateral fields added, allowing some shielding of organs at risk. The use of this technique defined by bony landmarks was shown to be at risk of a geographical miss [28]. The development of CT planned 3D conformal radiotherapy has allowed better coverage of the tumour and sparing of the organs at risks (OARs). The areas defined for treatment are the GTV, clinical target volume representing areas at risk of microscopic spread (CTV) and planning target volume to cover uncertainties in radiotherapy planning and delivery (PTV.) Two groups have developed consensus guidelines for the definition the primary CTV and there are also nodal CTV guidelines [15,29,30]. These vary slightly but the primary CTV encompasses the entire GTV, the whole cervix, uterus and parametrium. There is variation as to whether the ovaries are included in all cases as well at the extent of vaginal coverage required.

The nodal CTV aims to cover the internal, external and common iliac as well as the obturator nodes including any visible nodes and then is delineated using the internal, external and common iliac vessels with a modified 7mm margin [31,32]. The recommended PTV guidelines are 15-20 mm around the primary CTV and 7-10mm around the nodal CTV.

The use of IMRT (intensity modulated radiotherapy) and VMAT (Volumetric Arc Therapy) have become more common in patients with cervical cancer. Benefits in overall survival and reduction in late toxicity have been seen in single institutional series compared with historical cohorts [33,34]. Two meta-analyses have also shown comparable survival, reduced doses to organs at risk, reduction in acute toxicity but there is weaker evidence of reduction in late toxicity [35,36]. The non-randomised phase II INTERTECC-2 trial showed some benefit in reduction of haematological toxicity especially with FDG-PET guided bone marrow delineation [37]. A small randomised study comparing IMRT with 3D conformal therapy with 22 patients in each arm reported reduced toxicity in the IMRT arm with comparable survival – although the study was underpowered to assess this [38]. Although there are no firm consensus regarding dose constraints for organs at risk, there is evidence that lower doses correlated with a reduction in toxicity [36].

The conformality and steep dose gradients achieved using IMRT has led to concerns regarding the risk of a geographical miss due to organ motion [34]. The concept of image guided radiotherapy has been developed to reduce inaccuracies in treatment delivery due to set up error as well as internal organ motion. Volumes for image guided radiotherapy have been defined in the ICRU-62 and ICRU 83 reports with a breakdown of the PTV into an internal margin (IM) to account for internal organ motion and the set up margin (SM) to account for uncertainties in planning and delivery of radiotherapy. The internal target volume (ITV) is a combination of the CTV and the IM (see figure 2.) To calculate accurate margins, both systematic and random errors for a population of patients must be considered [39]. The implementation of VMAT or IMRT should be closely monitored as over generous margins can lead to increased toxicity, while too small margins may lead to recurrences [40]. The use of image guided and adaptive techniques for cervical cancer will be discussed in the next section.

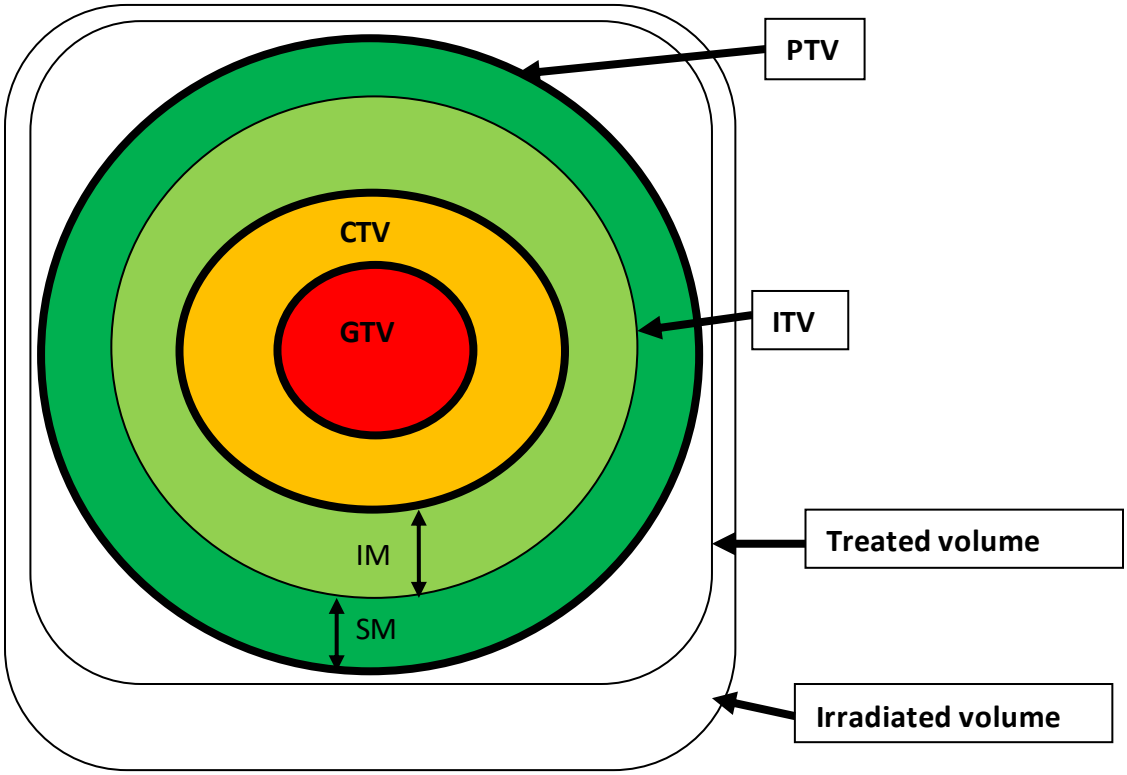

FIGURE 2 SCHEMATIC OF VOLUMES DESCRIBED IN ICRU-62 AND ICRU-83 REPORT

Good local control rates can be obtained with chemoradiotherapy and IGBT with actuarial local control rates of 98%/91%/75% for IB, IIB and IIIB stages reported. Acute toxicity, although common and unpleasant, is usually manageable. However, there is significant associated long term toxicity. All premenopausal women will become infertile and post-menopausal after completion of EBRT whatever technique is used, and hormone replacement therapy should be given. Oocyte or embryo preservation can be considered for use in a surrogate pregnancy.

There is also a risk of long term bowel, bladder, bone and vaginal toxicity. Rates of long term grade 3 toxicity, requiring intervention or hospitalisation, vary significantly between studies ranging from 0 to 11%. It is likely that physician reported outcomes underestimate toxicity, with 50% of patients reporting long term side effects that impact their quality of life [41]. A detailed study using patients included in the EMBRACE cohort showed late, persistent, substantial treatment related effects (LAPERS) with 6.8% of patients experiencing diarrhoea, 4.6% difficulty controlling bowels, 11.1% increased urinary frequency and 5.2% urinary leakage [42].

Second malignancies are also a concern for patients who have received treatment for cervical cancer, with standardised incidence rates of cancer even within the first 10 years following treatment. Common risk factors for cervical cancer such as HPV infection and smoking are likely to account for a proportion of this increase [43,44]. It is difficult to

quantify the impact of radiotherapy with no increased risk seen in patients who were randomised to receive post-operative radiotherapy for rectal or endometrial cancer compare to those treated with surgery alone[45].

MR imaging for cervical cancer

MR imaging was first used for human imaging in the 1970s, became widely available in the 1990s and is now an essential part of imaging for patients with cervical cancer[17].
Images are produced by detecting signal changes in patient tissues in response to radiofrequency excitation of the protons within the body within a strong magnetic field. Different tissues have different properties including proton density as well as different relaxation times (how long the excitation takes to return to normal after a radiofrequency pulse).
Varying the pulse sequences allows for different image weighting with differing tissue contrast and appearance. The standard image weightings are; T1, with fluid appearing dark, fat bright and other tissues intermediate and T2 with fluid appearing bright and fat and water saturated tissues intermediate.
Unlike CT, MR slices can be acquired in any plane. The standard technique is for a 2D data set to be obtained and reconstructed. There are often gaps between slices and there is a limit on how thin the slices can be. The resampled images are often therefore of limited use and images in different planes are required. The signal to noise ratio increases with higher strength of the magnet, with 1.5T being in common clinical use. Higher strength magnets are at risk of geometric distortion, however 3D acquisition techniques have been developed to obtain data in 3 planes simultaneously which solves some of these problems. The disadvantage is that the scanning times are long and motion can lead to degradation of images.
The major benefits of MR include the excellent soft tissue contrast which allows accurate localisation of the tumour and OARs as well as functional imaging assessment with sequences such as diffusion weighted imaging (DWI). This is commonly produced using a Pulsed Gradient Spin Echo technique and is an assessment of diffusion of water in tissue. This effect can be quantified as an apparent diffusion coefficient (ADC) map, with areas of restricted diffusion, for example in areas of high cellularity appearing dark [46–48]. Other functional imaging techniques include dynamic contrast enhanced MR (DCE MR) which

assesses tissue perfusion [10,25]. Perfusion is increased in areas with abnormal vasculature such as tumours and hypoxia using blood oxygenation level dependant (BOLD) imaging [49,50]. MR spectroscopy is a method of assessing the quantity of different metabolites in the tissues but has not yet been shown to be useful in imaging for cervical cancer [51]
A major limitation of MR is the length of time required to obtain images with a correlation between the size of the scan, image resolution and signal to noise ratio [47]. The availability of MR is also limited in many institutions. It is not suitable for all patients, for example those with certain pacemakers or metallic fragments, due to the strong magnetic field. It can be difficult to tolerate as together with long treatment times, it can also be noisy and cause claustrophobia. Artefacts and distortions can occur due to patient motion as well as due to distortions of the magnetic field caused by the equipment or the patient. These problems are particularly relevant for the use of MR in radiotherapy planning [52].

Diagnostic imaging

MR scanning was initially used in the staging of cervical cancer in the 1980s [53]. Many studies have shown MR to be superior to CT in assessing tumour size, parametrial involvement as well as rectum and bladder invasion [3,4]. The sensitivity of lymph node detection was reported to be 54% with a specificity of 93% with lymph node involvement assessed by size criteria [54]. This is a limitation of other imaging methods but FDG-PET (fluorodeoxyglucose – positron emission tomography) has a higher accuracy for nodal disease outside the pelvis [53]. SPIO (super-paramagnetic iron oxide) MR may help with identification of small pathological nodes but is not in routine use in patients with cervical cancer [55,56]. The use of MR is particularly important in the selection of patients with early stage disease who may be suitable for surgical treatment [57].
The European Society of Urogenital Radiology published guidelines for staging cervical cancer with MR. The recommended that T2 weighted imaging in at least 2 planes should be obtained alongside an axial T1 weighted imaging covering the abdomen to assess for nodal involvement (although T2 imaging can also be used for this purpose). The use of contrast as well as diffusion weighted imaging was considered helpful but not mandatory. There was no consensus about the use of bowel preparation or anti peristaltic agents. [57,58]
MR imaging is used to assess tumour response, with reasonable sensitivity (around 70%) and specificity (up to 80%) and set criteria have been developed that may help to improve

this [59]. DWI may also be used [51]. There is also an interest in radiomics approaches, using quantitative image processing, to improve diagnostic and response assessment [60–62].

MR based EBRT radiotherapy for Cervical Cancer

In current clinical practice, most patients will have an MR staging scan prior to EBRT and reference to this scan will be made when delineating the CTV and OARS on the planning CT scan. The EMBRACE 2 protocol mandates the use of both a pre-treatment MR and FDG-PET to aid delineation. It is also possible to fuse MR with CT using registration of bony landmarks to provide better soft tissue contrast for treatment planning [63].

The current gold standard in brachytherapy is MR only planning. This is has been achieved as the whole-body contour is not required for treatment planning and dose calculations do not require electron density information (due to the limited impact of tissue inhomogeneity on dose delivery) [2]. In view of resource limitations, alternative strategies such CT imaging only or a combination of MR and CT have been used for sequential fractions but may not offer the same benefits [64] .

The use of MR in external beam radiotherapy has been limited as there are significant technological barriers to overcome. MR has been initially used for treatment planning when co-registered with CT. However, there are now two commercially available MR linacs available, allowing for online MR based treatment verification [65].

MR based delineation

MR/CT co registration

In current clinical practice, MR scans are usually co-registered with CT planning scan [10]. Co-registration introduces additional uncertainties that should be considered in the setup margin. MR only planning strategies are currently under development including synthetic CT [66].

MR simulation

Initially, there were several practical problems that limited the use of MR for simulation. These included the lack of a flat top couch, lack of MR compatible immobilisation equipment and the limited bore size of the scanner. These have now been overcome for most situations [67].

Other issues to be overcome with the use of MR only simulation include the lack of electron density information but algorithms producing pseudo CT scans have been developed [68]. MR scans can also be affected by geometric distortions, although these are likely to be small, [69] as well as being subject to motion artefacts [65].

Consensus MR simulation protocols have been developed, with 1.5T scanners recommended as the ideal magnet strength. The recommended sequences for cervical cancer simulation are multi slice 2D T2 weighted TSE (turbo spin echo) in the axial and sagittal planes with slice thickness between 1-4mm and in plane resolution of <1mm. There should be no gaps between slices and both the target volume and OARs should be contoured on MR. There was no consensus about whether the field of view should include the nodal volume. Co registration with a planning CT is still advised [70]. All MR based GTV contours are smaller than CT based contours, with T2 weighed imaging being the most useful, while it is suggested that addition of DWI may ensure all functionally active disease is included [71].

Contouring studies

Most inter-observer studies using MR have been performed for brachytherapy target volume delineation. Hellebust et al reported on the intra observer variations between the MR brachytherapy contours for 6 patients created by 10 experienced oncologists. The mean relative SD was up to 10% for the GTV with similar variation noted for the OARs [72]. The biggest uncertainties surrounded the contouring of the IR-CTV [73].

Eminowitz et al reported the intra observer differences between more than 20 contours of two CT based clinical cases as part of the INTERLACE trail RTQA. These were compared to a consensus outline by the trial management group and simultaneous truth and performance level estimation (STAPLE). There was significant intra-observer differences with up to a two-fold difference in volume between the smallest and largest contours [74]. Large intra observer difference in CTVs were also seen in a previous study [75]. Lim et al found

moderate correlation for GTV, parametrial, uterine and nodal volumes but poor correlation for the vagina and cervix for 3 difficult cases contoured on MR [76].

There has been one study that compared CT with MR contouring for external beam radiotherapy, in the majority of cases delineation on MR slightly improved correlation and reduce the volume of the GTV but the combined CTV volume was only slightly smaller [77]. Therefore, whilst the dose delivered to the CTV remains uniform, the benefits of MR simulation compared to CT/MR fusion or CT based contouring with access to MR may be small. Clear guidelines, the development of online atlases and training for oncologist including as part of clinical trial quality assurance are likely to be crucial [78,79].

A potential advantage of MR simulation would be the ability to refine the primary CTV. Current consensus guidelines suggest that the whole uterus should be included within the primary CTV [27,41,42] although 7 of 17 experts in guidelines by Lim et al would consider excluding the uninvolved uterus [41]. Large series of patients with early stage disease undergoing radical trachelectomy [43–47], where the uterus is not removed, have reported low risk of uterine relapse which suggests that excluding the uterus may be safe at least in early stage disease. MR has been shown to be accurate in assessing uterine involvement [48] although Van Schoot suggested, by comparing MR contouring to fused photos of pathological specimens, that MR could underestimate the GTV volume [49]. Excluding the uninvolved uterus would reduce the primary CTV volume and also reduce the impact of pelvic organ motion on the primary CTV as the uterine corpus is the most mobile component.

A recent retrospective single institution study of 53 patients treated with a CTV excluding the uninvolved uterus showed excellent local control. The mean volume of the uterus included was 66% (range 18-100%). Only one patient had isolated local failure and no recurrence in the unirradiated uterus was seen [80]. A prospective, non-randomised phase 2 study, will combine external beam radiotherapy without brachytherapy, excluding the uninvolved uterus, followed by a hysterectomy. This will allow for histopathological and clinical correlation of uterine involvement and response to radiotherapy treatment [81].

It remains important to consider CTV volume carefully as in some cases, inadequate CTV margins may have been compensated for by generous PTV margins or the lack of conformality in radiotherapy delivery. Potentially, retrospective analysis of large number of patients could give information on the required field size.

MR guided external beam radiotherapy

MR guided external beam radiotherapy was first delivered in 2014, using a 0.35T MR cobalt-60 machine, the Viewray MRIdian, (ViewRay, Oakwood Village, OH) and a large number of patients have now been treated [82]. This system has now been upgraded to a 6MV 0.35T MR–linac. The other commercially available system is the Elekta (AB, Sweden) / Philips (The Netherlands) Unity, a 7MV 1.5T MR-linac, which is in clinical use since 2018 [83]. Both these systems allow for daily online adaptive radiotherapy based on MR imaging taken on the treatment couch. Currently set sequences are used for online imaging; these are shorter than those for diagnostic images as is image quality requirements for online adaption are not the same as for diagnostic imaging.

A phase 1 study of stereotactic body radiotherapy (SABR) in patients with inoperable or oligometastatic intra-abdominal malignancies has shown MR guidance to be safe, clinically feasible and to provide dosemetric benefits [84]. Excellent outcomes have been observed in patients with inoperable pancreatic cancer with patients receiving BED_{10} greater than 70Gy, with a 2 year overall survival of 49% in a selected cohort [85].

The basic MR guided workflow commences with the patient undergoing an initial planning CT, as well as MR simulation, which is used to develop the baseline radiotherapy plan. They then have a daily MR scan on the treatment couch; contour position is assessed and adapted as required. If necessary a new radiotherapy plan is created and delivered, with varying degrees of adaptation. This includes merely changing the position of the radiotherapy plan to match the current position or adapting its shape, changing the contours of the target or organs at risk (OARS.) Varying degrees of plan optimisation are also possible [86]. The Viewray MRIdian system can also allow online treatment gating based on Cine MR images [82]. There is also potential to perform multi-parametric imaging on the MR linac systems although care will need to be taken to standardise parameters [87,88]. Treatment time is currently around 40 minutes and multiprofessional teams including physicists and doctors may be required to be present for each treatment. This means that MR guided radiotherapy treatment is very resource intensive at present. Other considerations include the electron return effect which may introduce dose alterations especially at the air-tissue interface and there is a requirement for quality assurance and patient monitoring [89]. Despite long treatment times, with a third of patients experiencing discomforts such as parathesia, noise and cold, it is generally reasonably well tolerated [90].

A number of patients with cervical cancer have been successfully treated using the Viewray MRIdian system, tolerating daily MR scans. Daily imaging was acquired with offline replanning in a number of patients but without online adaption [91].
In cervical cancer, it is important to define the best patient group for initial implementation of MR guidance.

	CT	MR
Availability	Widely available (usually no long waiting times)	May be limited (usually long waiting times) especially in low resource countries
Speed	Fast (standard scan obtained in ~ 1 minute [92])	Multiple sequences required (at least 10 minutes) – 3D sequences (~7 minutes) [93] Online sequences shorter
Distortion and artefacts	Distortions may occur due to metallic hip implants Limited motion artefact	There is the potential for distortion artefacts due to disruption of the magnetic field by the equipment or the patient but these can be minimised More frequent motion artefact (5.5-7.5%) [94]
Soft tissue contrast	Poor Primary tumour not clearly visualized [3,4,95]	Excellent Primary tumour clearly visualized [3,4,95]
Contraindications	None	Presence of metallic fragments/implants
Tolerability	Good	High rates of claustrophobia (0.5-14.5%) [94]
Additional radiation exposure	Yes	Nil
Use for simulation	Standard	Not standard but guidelines available [44] (co-registration with CT recommended)
Use for planning	Standard	Estimated electron density map required using techniques such as pseudo CT [52]
Use during treatment	Cone beam CT commonly used (poor resolution)	In clinical use but very limited availability and allows for the use of online adaption [82]

TABLE 2 ADVANTAGES AND DISADAVANTAGES OF THE USE OF CT AND MR IN RADIOTHERAPY

Anatomical position and morphological tumour changes during external beam radiotherapy for cervical cancer

The first study assessing cervical motion during external beam radiotherapy was performed in 2002 [96]. This confirmed that despite small inter-fraction changes in bony position, there was independent motion of cervical fiducial markers. This finding has been confirmed in multiple studies, summarised in a recent systematic review by Jadon et al [97].

The mean inter-fraction motion of the cervix reported between studies varied between 1-16mm (anterior/posterior), 1.5-8mm (superior/inferior) and 0.3-10mm (lateral) [98–100]. Motion may be much greater in individual patients with the maximum posterior motion of 63mm in one study [101] . Within individual studies, uterine motion is greater than cervical motion [101–105]. Motion of the nodal CTV has often been assumed to be insignificant as it is contoured based on pelvic vessels which run close to bony structures. However, this may not necessarily be the case, especially in patients treated prone [67,68]. Nodal CTV motion may also move independently to the primary CTV meaning that "on treatment" couch shifts to improve primary coverage may adversely affect nodal CTV coverage [108].

Intra-fraction motion of the primary CTV is small with most studies reporting mean motion between 0.1-3mm, with displacement of >5mm being unusual. However, use of adaptive radiotherapy is often targeted to patients with substantial motion noted on planning scans and intra-fraction motion may be greater in these patients [109].

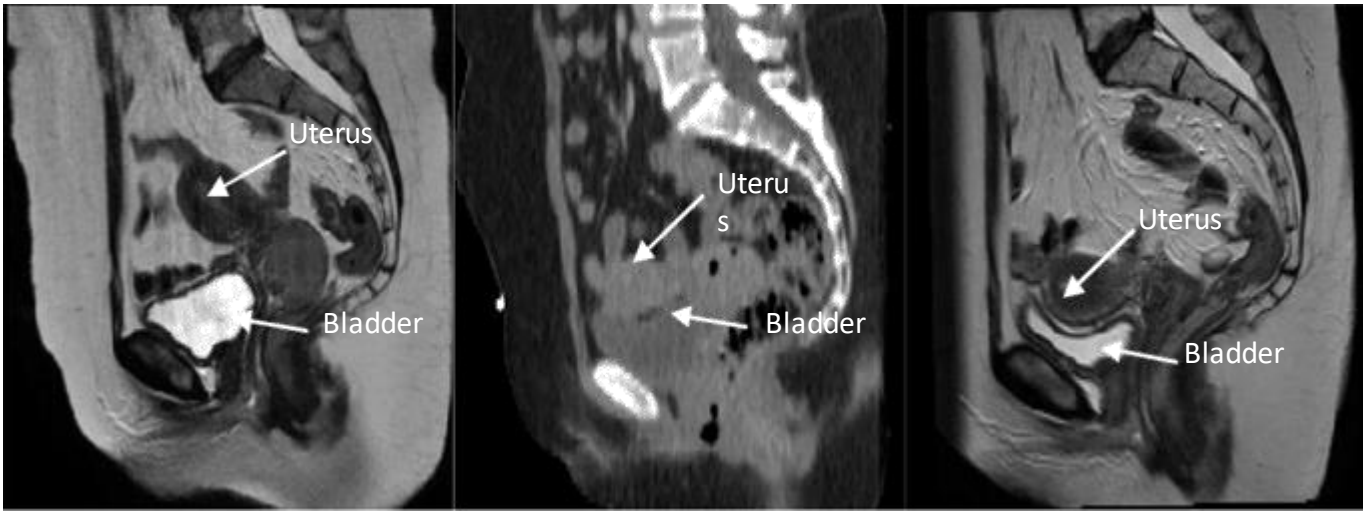

FIGURE 3 IMAGE OF INTRA-PATIENT VARIATION IN UTERUS AND CERVIX POSITION AT THREE TIME POINTS
1. Diagnostic MR 2. Planning CT 3. Mid-treatment MR
The uterus has moved away from the bladder in image 1, where as in image 2 and 3 it is lying superior to the bladder and will be affected by bladder filling. This figure also highlights the difference in soft tissue contrast between CT and MR.

Most studies have found moderate association of pelvic organ motion with bowel and bladder changes [97] The potential relationship is illustrated in figure 3, showing different causes of motion of the uterine cervix and fundus. The change between 1 and 2 is related to small bowel changes at the fundus and rectal changes at the cervix. The changes between 2 and 3 are related to bladder filling at the fundus and rectal changes at the cervix.

There is a stronger association between bladder filling and uterine motion, while rectal volume has a bigger impact on cervical motion [110,111]. Bladder volume has been shown to reduce over the course of radiotherapy, which may lead to a systematic change in uterine position over the course of treatment [101,104,105]

There can be significant tumour regression over the course of external beam radiotherapy, with studies reporting a mean reduction of 59% – 74% in the primary GTV [110,112,121,113–120] and 58% in nodal GTV [106]. The primary CTV volume reduces less than the GTV with a mean reduction of 9.7-39% [110,113,115,118] but for individual patients there can be dramatic changes in shape and position.

Set up error must also be considered. Online CBCT allows correction of translational position changes [122–124], but large rotational changes occur which are difficult to correct even with a 6D couch, because it only allows for up to 3 degrees of rotation [125]. It is unclear whether prone positioning, which allows small bowel sparing but is less stable, is better than supine positioning [126–128].

Even though organ motion has been widely studied, a better understanding of the sources of cervix and uterus motion is required which may be derived from quantitative and qualitative analysis of large number of patients.

Current strategies to account for organ motion and the potential uses of MR guided external beam radiotherapy

A variety of imaging techniques can be used for assessing and managing organ motion. Initial image guidance was based on portal imaging but CBCT is now the most commonly used technique, often in combination with fiducial markers [129]. It is quick, widely available and has been used to select daily plans for a plan of the day approach [130]. Disadvantages

of CBCT include poor tissue contrast, and the additional ionising radiation dose [131,132]. The development of on treatment MR will produce images with higher soft tissue contrast but protocols will need to balance image quality, field of view and speed.

Although there is some sparing of OARs using adaptive radiotherapy techniques, the main benefit is ensuring optimal coverage of the primary CTV. However, such an improvement may facilitate safe reduction of the IM component of the CTV – PTV margin, which can reduce radiotherapy dose to the organs at risk [133–135].

Many studies have reported population margins based on small studies with sporadic imaging [96,103,140–142,105,106,110,129,136–139]. Suggested margins were often anisotropic and varied from 8mm [138] to 32mm [137]. The use of standard margins to provide adequate coverage for patients displaying significant motion leading to unnecessary irradiation of normal tissue for patients with minimal motion [143,144]. Maintaining strict bladder and bowel filling protocols is a simple way of reducing primary CTV motion [111] but the majority of studies have found clinical implementation is very difficult [101,143,145–147].

There are three main approaches to managing anatomical changes during radiotherapy: an internal target volume (ITV) based approach, using a plan of the day (PoD) approach and a replanning approach. The published studies on strategies to overcome organ motion are summarised in table 3.

First author and reference	Number of patients	Clinical/ theoretical	Imaging modality	Method	Reported outcomes	Limitations
[115] Kerkhof et al	11	Theoretical 'online adaption'	Assessment –MR (weekly) Planning – MR	'Online' IMRT based on 4 MR scans (performed weekly) with a primary CTV-PTV margin 4mm Compared with standard IMRT with primary CTV-PTV margin 15mm	Online IMRT reduces the OAR volume irradiated to dose levels between 20-45Gy Adequate coverage of PTV maintained	Only assessed at 4 time points Theoretical CTV-PTV margin 4mm (may not allow for setup and other uncertainties)
[118]Stewart et al (2010)	33	Theoretical	Assessment –MR (weekly) Planning – MR	IMRT plans with primary CTV-PTV margin 3mm	Statistically significant reduction in the	Only assessed at 4 time points

		Weekly replanning		Automated weekly replanning based on MR Compared with no replan	dose to the CTV with no replan. 9/33 did not meet CTV D98>95% No difference in dose to OARs overall but benefits noted for individual patients	Standard plan had 3mm margin and excluded part of uterus (not standard clinical practice)
[148] Bondar et al (2012)	14	Theoretical PoD Model based ITV	Assessment – CT 5 full to empty bladder scans at 2 time points Planning – CT Model based approach internal target volume (mbITV) constructed using variable bladder filling CT	Comparison of IMRT plans with standard margin, mbITV and PoD approach (using 2 or 3 mid-range plans) and daily adaptive plan	38mm CTV-PTV population based margin required to maintain CTV coverage. mbITV approach reduced CTV-PTV volume by 48% PoD further reduced CTV-PTV volume and reduced volume of OARs inside PTV	Assessed using variable bladder filling CTs at only 2 time points it is unclear how representative this is of daily radiotherapy changes
[149] Ahmad et al 2013	14	Theoretical PoD Margin of the day (MoD)	Assessment – Bladder volume on ultrasound (US) (twice weekly) linked to variable bladder filling CT Planning – CT	IMRT approach MoD approach with uniform margin from 5mm increasing by 5mm as required Online approach Compared to standard population margin of 15 mm	40% of patients had inadequate CTV coverage with standard population margin. CTV coverage was adequate with MoD approach Average dose to the OARs were not increased	Assessed using bladder volume on US linked to variable bladder filling CT Large increase in CTV-PTV volume for some patients
[133]Lim et al 2014	30	Theoretical Replanning – set time point vs	Assessment – MR (weekly) Planning – MR	Standard IMRT plan with 3mm primary CTV-PTV margins Compared to a single mid point replan (A-IMRT)	Standard IMRT failed to meet GTV/CTV thresholds for 23% of patients	Assessment based on imaging at 5 time points

		dosemetrically triggered		and a dosimetrically triggered replan (D-IMRT)	A-IMRT failed in 10% of patients D-IMRT maintained coverage for all patients 23 replans for D-IMRT vs 30 for A-IMRT Minimal reduction in dose to OAR for A-IMRT none for D-IMRT	Standard plan had 3mm margin and excluded part of uterus (not standard clinical practice)
[134] Oh et al 2014	15 (including 5 patients with inadequate CTV coverage with a single midpoint replan)	Theoretical Replanning – varying time-points Bony vs soft tissue matching of online imaging	Assessment – MR (weekly) Planning – MR	Online soft tissue matching +/- replanning at up to 4 time points compared with standard IMRT plan with bone matching	Soft tissue matching improved target coverage compared with bone matching Offline replanning also increased target coverage Only soft tissue matching and 4 offline replans achieved coverage for all patients	Assessment based on imaging at 5 time points Standard plan had 3mm margin and excluded part of uterus (not standard clinical practice) Nodal CTV not formally assessed
[130]Heijkoop et al 2014	64 (11 treated with plan of the day)	Clinical PoD Model based ITV	Assessment – CBCT (daily) Planning – CT (variable bladder filling)	Clinical implementation of an IMRT ITV based approach (with a robust back up plan) 11 patients with motion greater than 2.5cm at the tip of uterus treated with PoD approach	IMRT plans were used for more than 80% of fractions Plan selection was robust and quick PoD technique was practical for clinical use	Did not perform full dosemetric assessment 1cm ITV-PTV margin
[150] O'Reilly et al (2016)	10	Theoretical	Assessment – CT (weekly)	Comparison of a fixed margin approach compared	Fixed margin of 15mm was required to	Small number of patients

		Online vs offline MoD approach	Planning – CT (4 time points prior to treatment)	with an online MoD approach and an offline approach using dosemetric assessment to select the smallest appropriate margin	achieve adequate CTV coverage. Online MoD allowed excellent tumour coverage with some sparing of OARs Offline approach achieved satisfactory tumour coverage but greater OAR sparing	Dose accumulation assessed using equivalent uniform dose
[151]Seppenwolde et al (2016)	10 patients	Theoretical PoD vs ITV based approach	Assessment – CBCT (daily) Planning – CT (variable bladder filling)	Comparison of two fixed margins 5-6mm and 15mm with an ITV based approach on first 5 CBCT and a variable bladder based plan of the day approach	Target coverage was improved with ITV or PoD approach. PoD approach reduced high dose to OAR by a small amount eg V40Gy to bladder reduced by 15%	Small sample size with discussion about individual patients. Dose calculation based on daily dose volume histogram parameters
[152] Buschmann et al (2017)	16 (9 treated with plan of the day)	Clinical PoD Model based ITV	Assessment – CBCT (daily) Planning – CT (variable bladder filling)	Clinical implementation of a VMAT ITV approach with 9 patients with motion greater than 2.5cm at the tip of uterus treated with PoD approach	PoD approach is possible in clinical practice. 84% agreement in plan selection. Small decrease in 95% dose volume treated median reduction 87 cm^3.	Small sample size. Dose calculation based on daily dose volume histogram parameters.
[153] Heijkoop et al (2017)	138	Clinical PoD for patients with motion greater than 2.5cm ITV for other patients	Assessment – Patient reported outcomes for acute radiotherapy side effects	Patient reported outcomes, with weekly reports during treatment and less frequently till 1 year.	Symptoms increased during radiotherapy but although some returned to baseline, other	No comparison with standard radiotherapy techniques

					symptoms such as sexual or vaginal dysfunction, dysuria and diarrhoea persist.	
[154] Van De Schoot et al (2017)	10	Theoretical PoD Model based ITV	Assessment – CBCT (daily) Planning – MR variable bladder filling	Dosemetric assessment of a model based ITV PoD approach	PoD improved daily coverage of CTV ($D_{98\%}$>95%) benefits noted for individual patients. POD lead to small increasein dose to bladder and reduction in dose to rectum and bowel	Small sample size, dose accumulation using deformable registrationand CBCT
[155] Nováková et al (2017)	14	Theoretical PoD Model based ITV	Assessment – CBCT (daily) Planning – CT (variable bladder filling)	Assessment of optimal number of model based ITV plans for plan library. Development of measurement of uterine motion 99th percentile of the Hausdorff distance (HD99)	Confirmed benefit of 2 plan approach with patients with HD99 >30 benefiting from 3 plans	Small number of patients with 2 excluded as outliers. Dose calculation based on daily dose volume histogram parameters
[156] Rigaud et al (2017)	20	Theoretical 5 different models – standard, ITV, mid treatment replan, PoD, PoD with additional plans basedon CBCT as required	Assessment – CBCT (biweekly) Planning – CT (variable bladder filling)	Geometric comparison of 5 different models - mid treatment replan, PoD, PoD with additional plans based on CBCT as required a PoD plus approach	An POTD plus approach combined with a reduced margin (from 10mm – 7mm) ensured good CTV coverage and maintained OAR coverage	Dosimetric analysis only performed for one patient. Small sample size. Bi weekly CBCT
[157] Jagt et al (2019)	6	Theoretical Proton PoD vs PoD with	Assessment – four weekly repeat CT scans	Comparison of no replanning, a 1 to 2 plan library approach and a benchmark of full	Fast and automated prior -plan was feasible and reduced	Limited number of patients involved Proton specific

		automated replanning	Planning – full and empty bladder CT	reoptimisation with dosemetric target coverage and dose to OARs	reoptimization time	Re-segmentation not considered
[158] Visser et al (2019)	14	Theoretical PoD vs Online adaption	Assessment – weekly MR scans (greater than 3) Planning – full and empty bladder CT	Dosemetric assessment of OARs and target coverage Comparison of PoD Assessment of coverage on a transverse MR scan (10 mins after sagittal scan used for online adaption)	Reduction in volume of reference dose increasing compliance with bowel bag constraint. 5mm online planning approach allowed coverage of CTV allowing for intrafraction motion	Limited number of scans used to assess – 3-5 Bladder filling

TABLE 3 A SUMMARY OF PUBLISHED STUDIES TO ACCOUNT FOR ORGAN MOTION DURING EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER

An ITV-based approach allows individualised margins to account for primary CTV motion within patients. In some disease sites, such as lung cancer where motion is based on reasonably predictable changes with respiration, techniques such as the use of 4D CT can allow development of an ITV. In cervical cancer, motion is complex with random aspects; inter-fraction motion is greater than intra-fraction motion and is harder to predict prior to starting radiotherapy.

The simplest technique to create an ITV and the minimum requirement for the EMBRACE 2 protocol, is to use information from different imaging studies (PET, MR and CT planning scan) to estimate motion [63].

Although a margin of the day strategy has been explored [98,99], the majority of studies use an individualised model, based on full and empty bladder CTs, to predict the cervix/uterus complex motion [159,160]. This accounts for motion based on bladder filling but not rectal filling, tumour shrinkage or other random changes. In initial PoD studies, patients with minimal motion of the cervix/uterus complex had a single plan while others had two plans; a full to mid bladder and a mid to empty bladder plan [155]. A robust back up plan was also included, which was used in around 20% of cases [111]. Using fiducial markers, 98.2% of the

CBCTs were of adequate quality for plan selection and post treatment CBCTs confirmed that the PTV covered the primary CTV in all cases, suggesting that a 1cm margin was adequate [69]. Full dosimetric analysis was not reported for the clinical implementation study meaning that potential benefits were not quantified [112]. A similar approach has been replicated by another group, confirming PoD leads to excellent primary CTV coverage and may lead to a small reduction in dose to OARs [152]. Further work has focused on predetermining the optimum number of plans for each patient [155] and a plan of the day plus strategy, which uses images acquired on treatment to develop additional plans as required based on anatomical changes outside those covered by available plans [154].

An alternative approach to PoD is offline replanning, with the simplest strategy of a routine offline re-plan for all patients, at a pre-defined point part way through treatment [113]. Lim et al [133,134] carried out two studies assessing different re-planning strategies combined with a primary CTV excluding the body of the uterus and a 3mm primary CTV to PTV margin. They found that a combination of soft tissue matching plus weekly offline re-planning or simulated online re-planning provided the best target coverage. Unfortunately, the CBCT field of view did not cover the entire nodal CTV so it was impossible to accurately assess the impact of these strategies, but it did appear to reduce coverage of the nodal CTV [134]. Kerkhof et al undertook a similar planning study of 11 patients using weekly MR scans [115] These studies used a very small primary CTV to PTV margin, did not account for the set-up margin (SM) component of the PTV and excluded the most mobile part of the primary CTV. Therefore the direct relevance of these studies to clinical practice is doubtful but they do provide a theoretical model for a replanning approach. The combination of PoD and an offline replanning after 2 weeks may lead to further reduction in dose to OARs [161].

There is no clinical application of online adaption of external beam radiotherapy, other than a PoD approach. [162]. Clinical implementation requires steps, including auto-segmentation [163] and fast re-optimisation[164], which are currently in development. Even with automated techniques, there will be some increase in time taken to deliver treatment, to allow for rigorous quality control.

In order to focus resources, it would be useful to select patients with significant motion of the primary CTV, but no predictive factors have been identified [165]. The use of variable bladder filling to select patients is a reasonable strategy, with around a quarter to a half of patients identified as having clinically significant motion of the primary CTV [152,166].

However it may not identify all patients with changes in the position of the CTV due to other causes.

Current evidence is based on small retrospective studies, with clinical studies focussing on the practicality of the approach. [152,167] A further clinical study has reported on the quality of life during PoD based radiotherapy but this is not compared with standard techniques so it is difficult to assess the clinical impact [153]. Studies with larger number of patients are urgently needed.

Potential for MR guided external beam radiotherapy for cervical cancer

Radical external beam radiotherapy including elective nodal volume

Currently, although a small number of patients have been treated using the Viewray Meridian system, use of online adaption has not yet been reported [91]. Plan of the day techniques have been successfully implemented using CBCT, with minimal problems due to imaging quality [130,168]. Alternative approaches including the combination of CBCT and ultrasound have also been proposed [169]. Radiographer led plan of the day selection and soft tissue matching has been shown to be practical in a number of settings but training is required [170,171]. It is unclear if there would be any benefit of MR over CBCT guided plan of the day, although improved image quality could increase confidence, especially if part of the uterus was excluded from the CTV and training requirements could potentially be reduced.

Full online adaption has the potential to improve coverage compared to a plan of the day approach and facilitate margin reduction [115]. The major hurdle to practical implementation is the need for online recontouring of the CTV and OARs due to time as well as resource constraints. Other studies have only recontoured a volume of 2 cm around the CTV [84] but even this limited approach would not be feasible for cervical cance because the CTV is so large. Both the stability of patient set and organ position will reduce as treatment time increases. Auto segmentation or non-rigid contour propagation could be used to aid recontouring, however the large geometric changes make any technique challenging [172]. A combination 'plan of the day plus' approach could provide an efficient workflow solution [173]. This would combine a pre-prepared library of plans, based on planning imaging but if the available plans did not provide adequate CTV coverage, the daily MR could be used to add plans to the library. The improved imaging quality of MR over CBCT would mean no

additional imaging would be required and either an offline or online approach could be used. The daily images could also be used to develop an additional plan to account for the shrinkage of the CTV, either at a set time point or triggered by geometric or dosimetric targets [133]. In the future, functional imaging could be used to deliver biologically targeted radiotherapy, increasing dose in areas of hypoxia or adjusting dose based on treatment response.

The main barrier to the delivery of MR guided radiotherapy for cervical cancer is the treatment field length, which can be greater than 25cm. It has been suggested that only 60% of patients treated with cervical cancer, at our institution, would be suitable for treatment on the Elekta Unity, with a field length limit of 22cm[9]. The field length of the Mridian system is 24cm, and although formal assessment has not been carried out, it is likely that treatment will not be possible for a similar proportion of patients [174]. Potential solutions involve a dual isocentre approach to extend the field length and this method is currently under investigation. The EMBRACE 2 protocol also has a risk stratified approach to nodal coverage, with low risk patients treated with a smaller elective field covering the true pelvis [175,176]. These patients may be suitable for treatment on the Elekta unity.

Use of MR for integrated boost/SABR

Brachytherapy remains the gold standard for boost delivery following pelvic radiotherapy [177]. However, patient factors, volume of residual disease or technical difficulties [178] can mean that a brachytherapy boost is not possible. Outcomes with conventional external beam boost are poor [178] and efforts to improve outcomes have included the use of IMRT and SABR. SABR can be used either alone or in combination with brachytherapy, for a pelvic or paraaortic node boost as well as for treatment of recurrence [179,180]. A number of small retrospective case series have reported with good short term local control rates after a SABR boost to the primary tumour [181–183]. A recent systematic review of SABR in patients with any gynaecological malignancy highlighted the limited evidence but suggested that rates of grade 3-4 toxicity are low, apart when re-irradiating [179].

Although there is no currently published literature, the use of MR in this setting is of great interest as it will allow for precise delineation of residual or recurrent tumour and ensure accuracy during treatment delivery. MR guidance also potentially allows for an isotoxic

approach with daily assessment of organs at risk and daily plan adaption to maintain dose to the target.

There has been a recent case series of MR guided multifractionated stereotactic treatment of isolated pelvic lymph nodes, which confirmed the feasibility of the technique [83].Such boost techniques could potentially allow for dose escalation to nodal disease or primary in patients unfit for brachytherapy or with local recurrence. This is likely to be the main initial setting for MR IGRT as the limited number of fractions and small field size reduce the impact of current technological limitations.

The optimal patient group for an initial trial with MR-guidance has yet to be defined.

Palliative radiotherapy

Almost 10% of patients with cervical cancer present with metastatic disease [12]. The standard of care for these patients is chemotherapy using a combination of cisplatin, paclitaxel and bevicuzimab [184], although carboplatin is sometimes substituted [185]. Radiotherapy has an important role in both to improve symptoms and for control of pelvic disease.

There is a lack of evidence on the impact of radiotherapy on survival. A propensity matched analysis of the SEER database suggested a survival benefit for patients who received radiotherapy; however this included radiotherapy to all sites, not just the pelvis [186] and failed to account for guarantee time bias, meaning that those who lived longer were more likely to receive radiotherapy [187]. The use of radical chemoradiotherapy followed by brachytherapy in patients with para-aortic lymph node metastases, now defined as FIGO (2018) stage 3C2, is generally accepted. Disease free survival reported as between 50-60% at 2 years [188]. This approach has also been used in patients with more extensive metastatic disease, with evidence of good local disease control. However, overall survival for these patients remains poor and there is no convincing evidence of that radical radiotherapy is better than shorter palliative fractionations in this situation [189,190]. There is no standard palliative regimen reported in the literature or in the Royal College of Radiologists dose and fractionation guidelines [191]. Both moderately hypofractionated daily regimens, such as 20Gy/5# [192] as well as alternate day or weekly regimens such as the 0-7-21, delivering 8Gy on day 0, 7 and 21 [193] have been reported.

In the non-metastatic setting, patients who are not fit for or decline radical treatment may still benefit from palliative treatment. Patients with other symptomatic gynaecological malignancies such as endometrial or ovarian cancer can also benefit from palliative radiotherapy with similar treatment fields and schedules. This can be used to treat common symptoms such as pain, bleeding and vaginal discharge.

Although palliative schedules are generally well tolerated, with few long term side effects in the era of conformal radiotherapy, there is a potential to investigate MR guidance. In a palliative situation, it is important to minimise even short term toxicity as much as possible to preserve quality of life.

Palliative treatments do not usually include elective volumes, so field lengths would be suitable for treatment using the Unity or Meridian. As treatment schedules are generally hypofractionated, fewer fractions are required. Treatment of palliative patients also forms part of the R-ideal framework for initial investigation of a new technology, informing the development of treatment with curative intent [194]. A single arm phase 2 study, assessed the impact of image guided adaptive radiotherapy using an weekly hypofractionated regimen in patients with bladder cancer unsuitable for radical radiotherapy [195] and has led to the development of a randomised multicentre trial. This is a potential approach to develop MR guided radiotherapy for cervical cancer.

In summary, although there have been improvements in the treatment of locally advanced cervical cancer, in particular image guided brachytherapy, long term toxicity remains a problem for a proportion of patients. The importance of interfraction motion of the uterine funds and cervix has been demonstrated in a number of studies and a variety of motion management techniques explored. However, the causes and clinical impact of this motion have not been fully assessed, with the majority of techniques based on changes in bladder filling. There are fewer studies of intrafraction motion and the causes of motion have not been directly studied.

MR imaging plays an important role in the diagnosis and monitoring of cervical cancer as well as in image guided brachytherapy due to the difficulties in visualising soft tissues in the pelvis using CT based imaging. This makes MR guided radiotherapy for cervical cancer an attractive target, although as highlighted, technical barriers including a limited field length remain meaning the optimal use of MR guided radiotherapy remains unclear.

This leads us to the following aims of the thesis:

Aim

To assess causes and implications of target motion in cervix cancer to support the development of novel image guided radiotherapy.

Objectives

1. The overall aim of the project is to assess causes and implications of target motion in cervix cancer to support the development of novel image guided radiotherapy.
2. Assess the impact of motion at the uterine fundus on clinical outcomes including survival
3. Assess the causes of interfraction motion at uterine cervix and fundus
4. Assess the causes and magnitude of intrafraction motion at uterine cervix and fundus
5. Assess the benefit of moderately fractionated palliative radiotherapy for gynaecological cancer as first candidate for MR-guided therapy

Chapter 1

A novel method of assessing motion of the uterine fundus and cervix, is it useful?

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Part of this work was presented as an E-poster at ESTRO Barcelona April 2018 [196].

Conception or design of the work: AAC, PH, MvH, AC, AmcW

Acquisition of data: AAC, GP

Contouring of images: AAC, SM

Analysis of data: AAC, AmcW

Interpretation of data: AAC, AmcW, MvH, AC, PH

Drafting and editing text: AAC, AmcW, MvH, AC, JL, LB, PH

Abstract

Introduction

The gold standard treatment for locally advanced cervical cancer is concurrent chemo-radiotherapy followed by image guided brachytherapy. This has led to improved survival outcomes; however, rates of long-term toxicity remain high. There is evidence that the cervix and uterus can move during external beam radiotherapy, even exceeding the CTV (clinical target volume) to PTV (planning target volume) margin in many patients. However, the majority of studies have been carried out in small groups of patients and the impact of motion has not been assessed on a, larger, population level.

Aims

To develop a quick and reproducible method to assess motion of pelvic organs in patients undergoing external beam radiotherapy for cervical cancer in mixed CT and MR scans.

Methods

80 patients with imaging at 3 time-points and clinical data were identified. MR image two weeks prior to radiotherapy, the radiotherapy planning CT and end of treatment MR. The uterus/cervix complex was contoured, and the motion of 7 points identified on a single mid-plane slice was assessed. The reliability of the method was assessed for each of the 7 points.

Results

The method was reliable for use with points at the tip of the uterus but this analysis was not able to confirm reliability for points in the inferior part of the uterus. Mean motion at the uterine fundus was 2.38 cm, which exceeds the clinical target volume to planning target volume.

Conclusion

The novel method developed to assess motion in the large cohort study is reproducible for the uterine fundus and motion seen is consistent with previous studies.

There is strong evidence that motion of the cervix and uterus can exceed the clinical target volume (CTV) to PTV margin for a proportion of patients with large inter-patient variation [97]. The use of conformal radiotherapy techniques such as intensity modulated radiotherapy (IMRT) is increasing [36]. The benefits and safety of these techniques depend on both accurate delineation of the CTV as well as adequate on-treatment image guidance. There is no consensus regarding the correct CTV-PTV margin but 1.5 – 2cm has been suggested in consensus guidelines [15]. The CTV includes the cervix, whole of the uterus, parametrium, part of the vagina as well as an elective nodal volume. Most studies have reported that tip of the uterus is the most mobile part of the CTV [197].

Long term toxicity remains a problem despite treatment with external beam radiotherapy and image guided brachytherapy, with late, persistent, substantial, treatment-related symptoms (LAPERS) present in 11% of patients for urinary frequency, 7% for diarrhoea and 4.6% for bowel control [42]. Reducing the dose to OARs (organs at risk) such as the bladder, rectum and small bowel should reduce toxicity [36].

A variety of techniques to improve coverage have been developed, including replanning during treatment, soft tissue matching on treatment and a plan of the day (PoD) approach. The PoD approach uses at least 2 different plans based on different CTV positions, with the best plan selected using online imaging each day. Most PoD models have been based on CT planning scans with variable bladder filling as this is the easy to adjust using a drinking protocol [167]. However, this does not account for bowel motion and or random variation. The use of adaptive radiotherapy techniques is labour intensive and there is little guidance to select patients who will benefit most [155]. A study of the clinical outcomes of PoD radiotherapy has been published [153], there is no comparison arm so it is difficult to assess the impact of the approach.

There have been a number of previous studies looking at motion summarised in a review by Jadon et al [97]. Initially, portal imaging and fiducial markers were used, which only allowed assessment of motion the uterine cervix. Later studies used 3D imaging including CBCT and MRI, to quantify motion of the entire uterus; however this more detailed assessment was usually carried out at fewer time-points. The majority of studies have been carried out in

small numbers of patients, and as there is a lot of inter-patient variation, this may not reflect the overall population. There is also a lack of studies combining uterine motion with clinical outcomes.

The aim of this study was to develop a simple method of measuring uterine motion and assess its reliability and reproducibility across the course of treatment.

This methodology was specifically developed to allow for a rapid estimation of motion, to complement conventional detailed contouring studies. These studies provide an accurate assessment of motion but are very time consuming and therefore are not suitable to assess a large number of patients. Automatic motion estimation of soft tissue structures is also possible, but local registration methodology is not well suited for mixed CT and MRI scan data, due to the very different contrasts of these scans. Our methodology is designed to be quick and easy to use and to provide an estimation of motion across the course of treatment for a large number of patients. This would allow for motion to be compared to clinical factors, both to assess outcomes and also to assess if any patient related factors increased motion.

The sagittal plane was selected for assessment of motion as previous studies have demonstrated that lateral motion is smaller than motion in other planes [97]. The uterus can also rotate, with the potential for a change from an anteverted to a retroverted position, which can lead to a dramatic change in position in the superior/inferior and anterior posterior planes of motion which is best demonstrated in the sagittal plane.

An important reason that makes lateral motion of the primary CTV less important is this motion is unlikely to cause underdosage as the elective volume includes the parametrium, lateral to the cervix and the elective lymph node areas (obturator, internal, external and common iliac) are lateral to the primary CTV and irradiated to high dose levels. This is clearly demonstrated in figure 4.

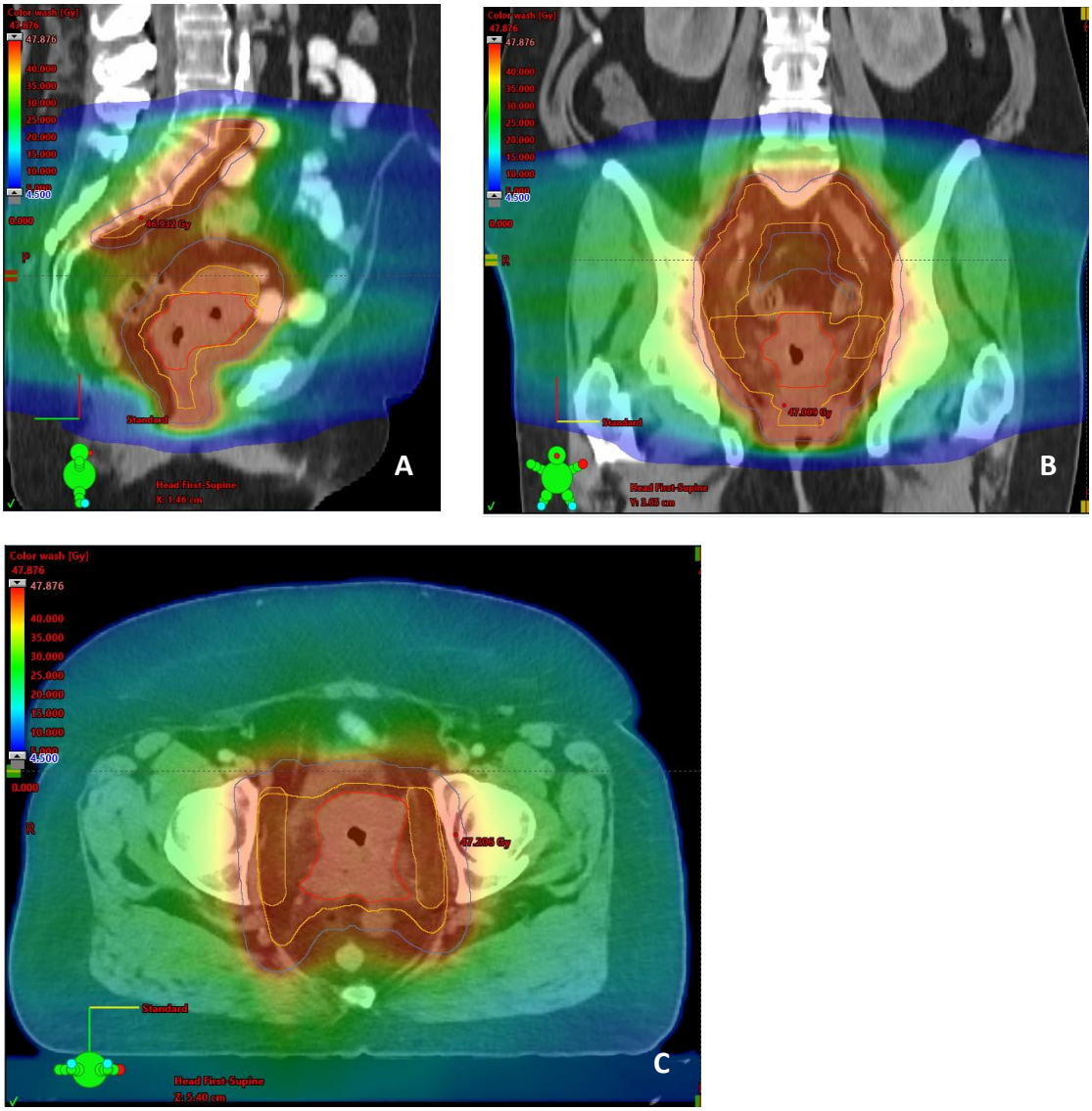


FIGURE 4 VMAT PLAN FOR A PATIENT UNDERGOING RADIOTHERAPY FOR CERVICAL CANCER. THE COLOURWASH INDICATES DOSE WITH AREAS IN RED RECEIVING AT LEAST 45GY/25#. THE GTV IS OUTLINED IN RED, THE CTV IS OUTLINED IN YELLOW AND THE PTV IS OUTLINED IN BLUE.

A The sagittal view showing the primary CTV, with lower dose areas in the anterior, posterior, superior and inferior region. The pre sacral nodal elective region is also seen at the level of the lower lumbar spine and superior sacrum.

B The coronal view shows the parametrial and elective nodal CTV outlined in yellow, showing that in the mid coronal plane, lateral motion is unlikely to lead to reduced coverage as the high dose region extends to the pelvic side wall.

C The axial view at the level of the cervix shows the parametrial and elective nodal CTV, with high dose coverage extending to the bony pelvis. The dose coverage reduces anteriorly and posteriorly to spare the organs at risk.

The aim of this study was to develop a simple method of measuring uterine motion and assess its reliability and reproducibility across the course of treatment.

Methods

This study is based on anonymised patient imaging at three time-points, pre-treatment MR

scan (1), radiotherapy planning CT scan (2) and MR scan in the final week of treatment (3). The time interval between scan (1) and (2) is approximately 4 weeks with 7 weeks between scan (2) and scan (3). The patients included were treated between 2006 and 2016, as the pre-treatment MR scan was not available for all patients. This is linked to a database of patients with cervical cancer treated with radical radiotherapy. Local ethical approval was granted to use anonymous data under a global ethics approval for a hospital wide theragnostics database.

Data was extracted from our locally developed electronic patient record system, the Christie Web Portal, which includes prospectively completed forms with patient demographics, tumour information and previous treatment. Treatment, disease status and physician reported toxicity is collected at every patient attendance. Information is crosslinked with the radiotherapy system, MOSAIQ, Elekta AB, Stockholm, Sweden, and the chemotherapy system, Ascribe, EMIS healthcare, Leeds, United Kingdom.

Patients received external beam radiotherapy with a dose of 40/20Gy or 45/25Gy followed by brachytherapy or an external beam boost. The radiotherapy technique was either 3D conformal or VMAT. The primary CTV consisted of the GTV, cervix, whole uterus, parametria, upper third of the vagina, or 2cm below involved disease and patients also received elective nodal irradiation. The CTV to PTV margin was between 1.5 -2 cm. No formal adaptive techniques were used and no patients were re-planned during treatment. The majority of patients had on–treatment cone beam CT, at least weekly, used for bony matching. Patients were treated in the supine position.

The T2 weighted sagittal sequence was selected in the MR scans, with the CT scan viewed in the sagittal plane. Images identified were exported into Worldmatch, an in-house software programme. All images were automatically fused to scan 1, using rigid fusion based on bony landmarks to ensure that measurements of organ motion were not affected by setup error and that the same plane was analysed for all scans. The mid uterine slice on scan 1 was next selected and contours were made on the corresponding slice for each scan. The uterus and cervix, including visible tumour, were contoured.

7 points were then located on 7 identifiable extrema of the shape of cervix/uterus complex at each time-point, see figure 5. These points were selected to describe the different parts of the cervix/uterus complex as accurate identification of the internal anatomical structures is difficult especially on CT. Points A, B and G define the tip of the uterus, the inflection points are C posteriorly and F anteriorly and points D and E are the lowest part of the cervix or tumour. Note that these points were chosen based on the expectation that they could be identified more reliable than, for instance points on the surface between B and C. However, the reliability of identifying these points will be established below.

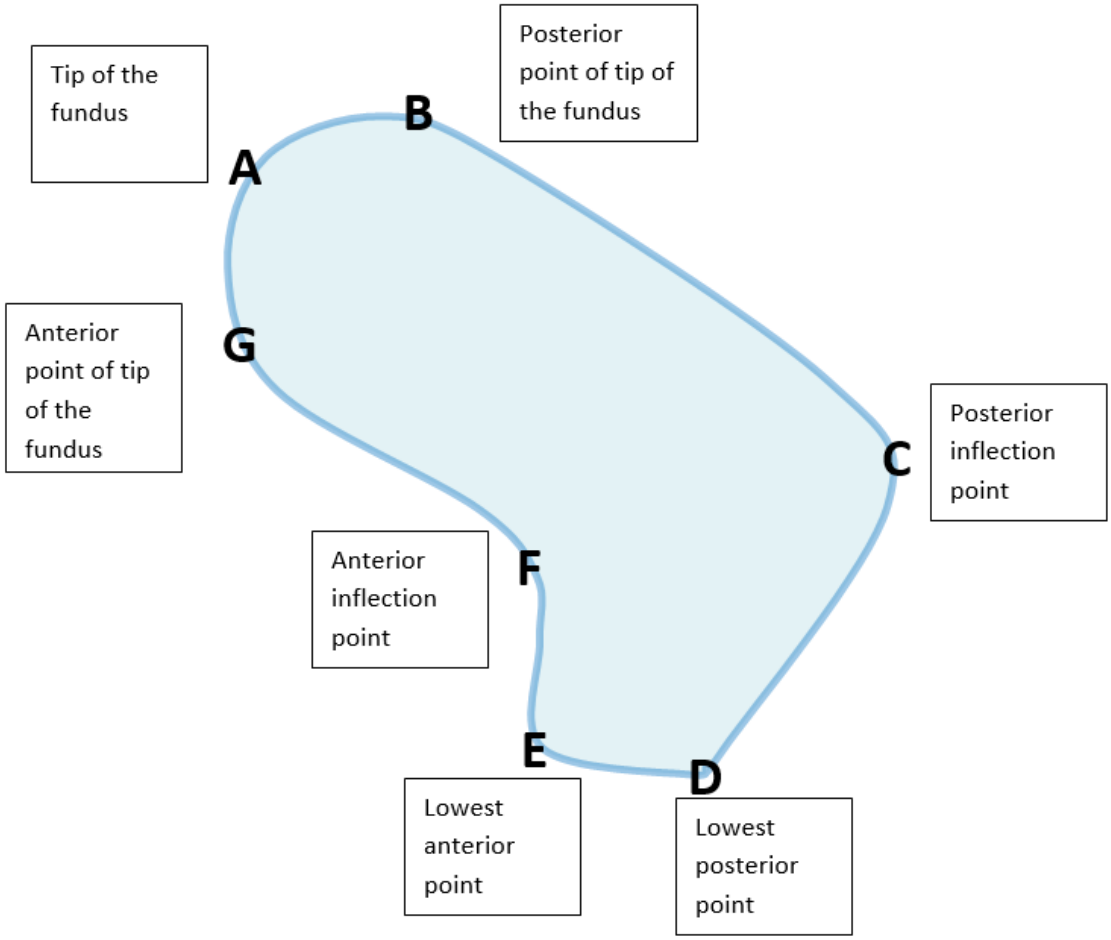


FIGURE 5 SCHEMATIC SHOWING LOCATION OF POINTS

The absolute distance at each point between each scan, i.e. 1-2, 1-2 and 2-3 was recorded, see figure 4. A comparison was made between motion at timepoint 1-2 (pre-treatment) and timepoint 2-3 (including response to treatment.) See figure 6

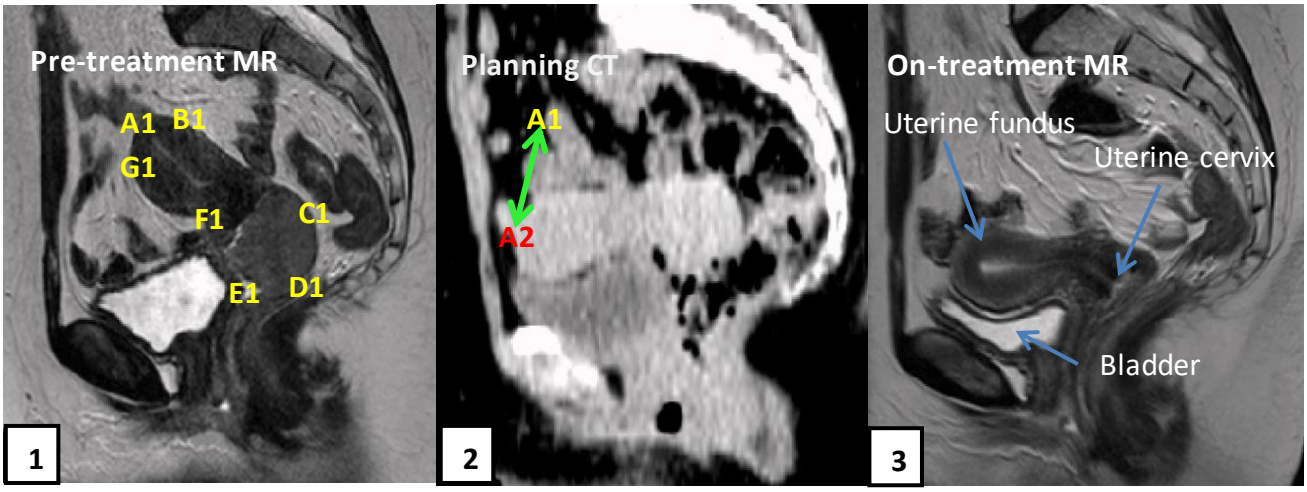


FIGURE 6 SCAN IMAGES

1 Pre-treatment MR – shows location of points a1-g1

2 Planning CT – shows location of a1 and a2 with the green arrow indicating the distance between them

3 On treatment MR – with labels to demonstrate uterine fundus, cervix and bladder

We chose the sagittal plane because we expected lateral motion to be small. In order to assess lateral motion, the uterus and cervix were contoured in all axial slices for 5 patients at three timepoints using Raystation v6, Stockholm, Sweden. The mean lateral motion at the tip of the uterine fundus was calculated.

Method reliability

To assess the reliability of point selection, landmark placement was repeated by the same observer (AC) for 10 patients (12% of cohort). The absolute distance between points on initial and repeat assessment was calculated. The difference in motion between time-points for each point was calculated and comparison was made between the initial and repeat assessment. The impact of imaging modality was also assessed; comparing intraobserver variability between timepoints 1 (MR) -3 (MR) and timepoints 1 (MR) -2 (CT). Interobserver variability was assessed by a second observer, an oncology registrar (SM), selecting points for 5 (6%) patients. The difference in motion between time-points for each point was calculated and a comparison was made between points selected by the first and second observer.

In order to assess whether motion at 3 time-points was representative of motion across the course of radiotherapy, Cone Beam CT (CBCT) images were obtained for 12 (15%) patients. CBCT scans were registered to the planning CT and points were identified as described in the initial method. Mean motion across all time-points for each point on CBCT was compared to mean motion for each point at the initial 3 time-points.

Landmarks were considered reliable if their inter- and intra-observer variation was less than 32% of the measured organ motion, e.g. inter- and intra-observer variation would cause less

than 10% inflation of the determined standard deviation of motion.

Another assessment performed was to measure if there was a correlation between motion at points that were close to each other and would be expected to move together, for example, points **A**, **B** and **G**.

Statistical analysis

Databases were developed in Microsoft Excel, Version 14.0 and statistical analysis was carried out using R Studio, Version 1.1.463. Overall survival was calculated using Kaplan Meier survival curves and median follow up was calculated using the reverse Kaplan Meir method. Summary statistics were calculated for each point and the mean motion for all time – points. Pearson's correlation coefficient was used to assess correlation between motion in the analyses described above.

Results

Images were identified for 91 patients who underwent radical radiotherapy for cervical cancer and 80 patients were included in the final analysis. 3 patients were excluded as it was not possible to contour the uterine fundus and cervix on all three scans. For one patient this was due to large lateral motion of the uterus, which was not seen on the scan 3. The other patients had very large uteri which were not fully visible on all the scans. Inability to find a satisfactory anatomical rigid registration between timepoints, led to the exclusion of 5 patients. Overall survival was not available for three patients who were excluded from the analysis. Progression free survival was not available for one patient.

The patient characteristics are outlined in table 4. Median follow up was 55 months, with an interquartile range of 41 to 72 months. Median overall and progression free survival was not reached as shown in figure 7.

Characteristic		**Number (range)**
Stage (FIGO 2008)	IB1	15
	IB2	6
	II (unspecified)	4
	IIA2	3

	IIB	38
	IIIA	3
	IIIB	2
	IVA	7
	IVB	1
	Unknown	1
Tumour size	1-3 cm	18
	4-6 cm	51
	7-10 cm	11
Age	Median (range)	45 (23-84)
5 year Overall Survival		0.79 95% CI (0.71-0.89)
5 year Progression free survival		0.73 95% CI (0.63-0.84)

TABLE 4 Patient Characteristics

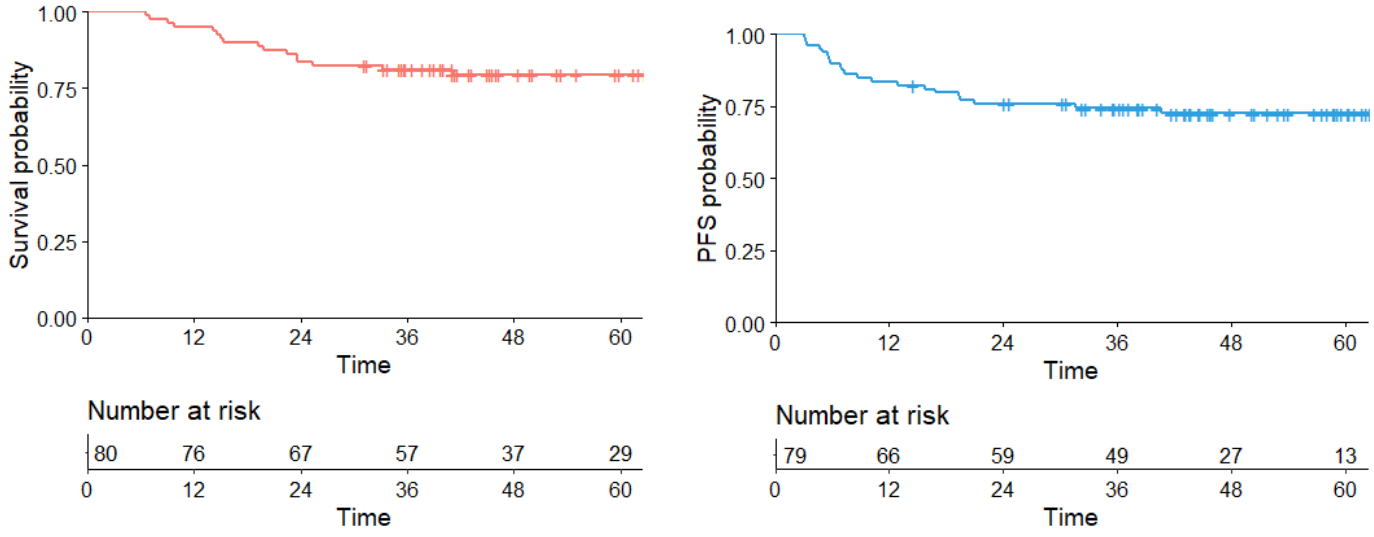


FIGURE 7 OVERALL SURVIVAL (RED) AND PROGRESSION FREE SURVIVAL (BLUE)

Summary of mean motion at each point is shown in table 5. This shows mean motion of greater than 1 cm at each point, with maximum motion of 7.3 cm at point **A**. Motion was greatest at points **A**, **B** and **G**, which represent the uterine fundus.

Point	Median (cm)	Mean (cm)	SD (cm)	Min (cm)	Max (cm)
A	2.15	2.42	1.36	0.56	7.37
B	1.95	2.10	1.18	0.43	6.35
C	1.24	1.30	0.55	0.38	3.06
D	1.28	1.30	0.57	0.24	3.48
E	1.29	1.29	0.55	0.33	2.63
F	1.50	1.48	0.59	0.51	3.67
G	2.08	2.23	1.10	0.43	5.51

TABLE 5 Summary of motion at 3 time-points

In the 5 contoured patients, mean motion lateral motion at the tip of the uterine fundus, corresponding to point A, was median 0.6cm, mean 0.64cm, standard deviation 0.29cm, max 1.1cm and minimum 0.4cm. This is much less than motion recorded between at point A with a median 2.42cm, mean 2.15 and less than the CTV to PTV margin in all cases.

In order to assess if there were differences between motion from prior to radiotherapy and during radiotherapy, motion from time-point 1-2 (initial MR scan and CT planning scan) and motion from time-point 2-3 (CT planning scan and on treatment MR scan.) These are summarised in tables 6 and 7. They show the same pattern as the motion at 3 time points, and mean motion is within one standard deviation for all points.

Point	Median (cm)	Mean (cm)	SD (cm)	Min (cm)	Max (cm)
A	1.98	2.62	1.88	0.41	9.37
B	1.73	2.19	1.67	0.09	8.74
C	1.06	1.22	0.63	0.28	2.77
D	1.11	1.23	0.74	0.05	3.63
E	1.01	1.21	0.73	0.10	3.26
F	1.20	1.40	0.82	0.19	4.69
G	1.87	2.40	1.52	0.17	7.41

TABLE 6 SUMMARY OF MOTION AT TIME-POINT 1-2 (PRIOR TO TREATMENT)

Point	Median (cm)	Mean (cm)	SD (cm)	Min (cm)	Max (cm)
A	1.77	2.26	1.69	0.19	8.34
B	1.66	1.94	1.39	0.04	6.57
C	1.16	1.31	0.72	0.15	3.69
D	1.26	1.37	0.84	0.15	5.23
E	1.34	1.41	0.78	0.18	3.56
F	1.34	1.49	0.84	0.11	3.91
G	1.87	2.15	1.41	0.31	6.97

TABLE 7 SUMMARY OF MOTION AT TIME-POINT 2-3 (AFTER TREATMENT)

Method reliability assessment

Interobserver and intraobserver variability

The initial assessment measured absolute distance between initial and repeat points. The mean distance between points was between 0.3 cm and 1 cm, with a larger distance seen at points **C**, **D**, **E** and **F**. The distance between points on each scan was then calculated and the difference between initial and repeat observations was recorded. The difference in distance between time-points was smaller with a range of 0 to 0.5 cm but a similar pattern was seen with a bigger difference at points **C**, **D** and **E**.

The results are summarised in table 8. When compared with table 5, it shows that the mean inter-observer variation in points C, D and E exceed 32% of the measured motion. For this reason, these points will be rejected as unreliable.

Point	Absolute distance			Difference in distance between time-points		
	Mean (cm)	SD (cm)	Max (cm)	Mean (cm)	SD (cm)	Max (cm)
A	0.31	0.28	1.31	0.00	0.37	0.91
B	0.36	0.29	0.96	0.02	0.48	1.12
C	0.39	0.47	2.43	0.29	0.60	2.31
D	0.99	0.80	3.42	0.53	1.00	2.85
E	0.56	0.38	1.58	0.10	0.52	1.14
F	0.57	0.73	2.57	0.05	0.44	1.50
G	0.50	0.35	1.47	-0.14	0.42	0.54

TABLE 8 ABSOLUTE DISTANCE BETWEEN POINTS ON INITIAL AND REPEAT ASSESSMENT AND DIFFERENCE IN MEAN DISTANCE BETWEEN SCANS ON INITIAL AND REPEAT POINT ASSESSMENT SD STANDARD DEVIATION

In order to assess the impact of imaging modality, the mean difference in point selection was compared between timepoints 1-2 (MR and CT) and timepoints 1-3 (MR and MR) for all points. Difference in points was assessed directly as this was the most direct methodology to assess impact of imaging methodology. The results are summarised in table 9. The difference between the two assessments was small but for most points the mean difference was greater between scans 1-3, where the imaging modalities were the same, but time difference was larger. This suggests that imaging modality did not influence point selection, although the number of patients included was small.

Point	Absolute difference between points scans 1-2 (cm)	Absolute difference between points scans 1-3 (cm)	Difference (cm)
A	0.24	0.51	-0.27
B	0.44	0.41	0.03
C	0.33	0.31	0.02
D	0.99	1.21	-0.22
E	0.49	0.56	-0.08
F	0.52	0.46	0.06
G	0.40	0.60	-0.21

TABLE 9 MEAN ABSOLUTE DISTANCE BETWEEN POINTS ON INITIAL AND REPEAT ASSESSMENT AND BETWEEN SCANS ON INITIAL AND REPEAT POINT ASSESSMENT SD STANDARD DEVIATION

Intraobserver variability was assessed using the difference in distance between points. The results are summarized in the table below. They were larger than the difference in distance between timepoints in the interobserver assessment however in general the pattern was the same with smaller differences between point **A** and **B** and larger differences at points **C**, **D**, **E** and **F**. There was a large difference at point **G** and **C** but this may represent outliers, as the maximum and standard deviation was very large. This is summarised in table 13.

Point	Difference in distance between time -points		
	Mean (cm)	SD (cm)	Max (cm)
A	0.18	0.09	0.4
B	0.24	0.14	0.75
C	2.55	2.40	7.72
D	1.33	0.92	3.81
E	0.72	0.49	1.81
F	0.54	0.31	1.40
G	1.24	1.36	4.46

TABLE 10 SUMMARY OF INTRA OBSERVER VARIABILITY SHOWING THE DIFFERENCE IN DISTANCE BETWEEN TIME-POINTS BETWEEN THE FIRST AND SECOND OBSERVER

Motion comparison of nearby points

There was very strong correlation between magnitude of motion at points **A** and **B** (R=0.98 p<0.0001), points **A** and **G** (R=0.86 p<0.0001) and points **B** and **G** (R=0.91 p<0.0001). These points are all at the uterine fundus. There was no or minimal correlation between motion at points **B** and **C** (R=0.097 p=0.39), points **C** and **F** (R=0.18 p=0.1) and point **D** and **E** (R=0.22 p=0.049). There was moderate correlation between motion at point **C** and **D** (R=0.44 p<0.0001) and strong correlation between point **D** and **E** (R=0.74 p<0.0001). See figure 1 in supplementary material.

Comparison with motion on CBCT imaging

A mean of 8.4 CBCT scans (range 4 – 12) were identified for 12 patients. A summary of the motion is shown in table 11, which also includes the difference in motion on initial scans for comparison. Motion was lower across CBCT for all points, with a mean difference between of 0.37 cm (range 0.27 to 0.48), however mean motion across CBCT was within the SD of mean motion across 3 time-points in all cases.

Point	Mean motion across CBCT				Initial scans (difference)		
	Median (cm)	Mean (cm)	SD (cm)	Max (cm)	Median (cm)	Mean (cm)	Max (cm)
A	1.92	1.98	0.94	4.25	2.15 (0.23)	2.42 (0.54)	7.37
B	1.57	1.69	0.78	3.59	1.95 (0.38)	2.10 (0.41)	6.35
C	1.01	1.02	0.36	1.61	1.24 (0.23)	1.30 (0.26)	3.06
D	0.93	0.92	0.31	1.45	1.28 (0.35)	1.30 (0.36)	3.48
E	0.92	0.92	0.36	1.40	1.29 (0.37)	1.29 (0.37)	2.63
F	1.08	1.13	0.47	1.82	1.50 (0.42)	1.48 (0.49)	3.67
G	1.71	1.73	0.74	3.27	2.08 (0.37)	2.23 (0.50)	5.51

TABLE 11 SUMMARY OF MOTION AT INITIAL 3 TIME-POINTS WITH MEAN MOTION ACROSS 3 TIME –POINTS FOR THE CORRESPONDING PATIENTS AND THE DIFFERENCE BETWEEN THE TWO METHODS

SD standard deviation

Overall correlation between mean motion across initial 3 scans and mean motion across CBCT was strong with R = 0.84 p=0.00054 (see figure 2 in supplementary material.)

However, when correlation was assessed across individual points, this was not consistent. There was strong correlation at points **A**, **B**, **D** and **G** but there was no correlation at points **C**, **D** and **F**. This is illustrated by the individual scatter plots shown in figure 8.

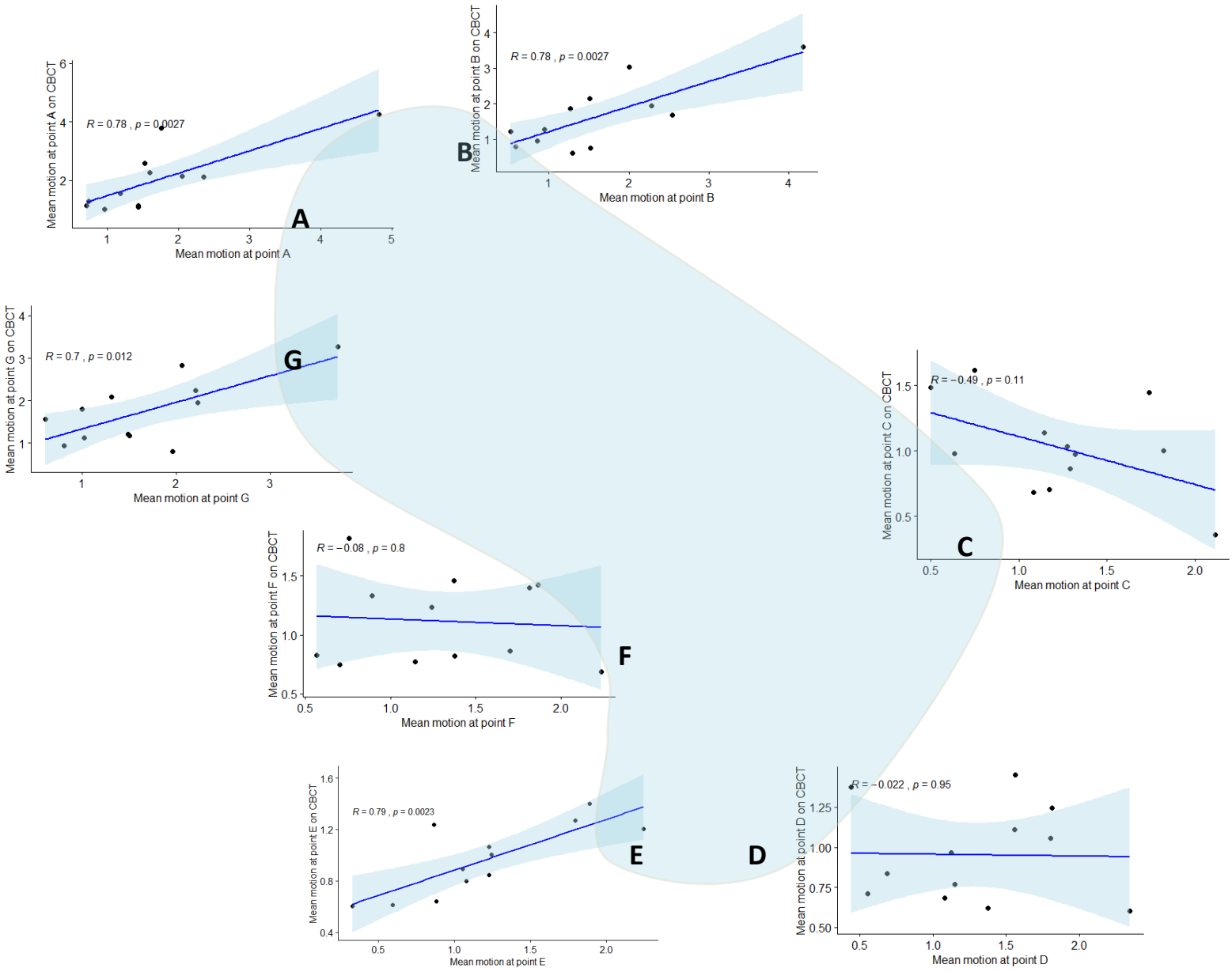


FIGURE 8 SCHEMATIC OF UTERUS SHOWING SCATTERPLOTS ASSESSING CORRELATION BETWEEN MEAN MOTION ACROSS 3 TIME-POINTS AND MEAN MOTION ACROSS CBCT
SCATTERPLOTS ARE DISPLAYED AT THE APPROPRIATE POINT ON THE UTERUS

Point reliability assessment

This is an exploratory analysis as there was no a priori formal definition of point reliability. However, by comparing the measured motion with the intraobserver variation, and the other analyses in this chapter, , point **A** appears to be most reliable. There is good inter and intra observer reliability, with differences in distance between points of under 2mm in both cases, there is good correlation with motion at points **B** (R = 0.98 p<0.0001) and **G** (R = 0.86 p<0.0001) and good correlation with motion at CBCT (R = 0.78 p0.003). Points **B** and **G** were

similar but less reliable. None of the lower points were reliable across all measures, point **E** had good correlation with CBCT but inter and observer reliability were not as strong.

Discussion

There has been significant variation in the motion recorded in previous studies, which is likely due to the heterogeneity of the studies and small numbers of patients included. The majority report motion separated into anterior/posterior and superior/ inferior components. This makes direct comparison with this cohort difficult; however the use of a single measurement of motion simplifies comparison with clinical endpoints. As the study was using three time points, the absolute distance was used rather than the vector as it was the variability of position as a surrogate for motion rather than the direction of motion which was considered.

The mean inter-fraction motion of the cervix reported between studies varied between 0.01-0.16cm (anterior/posterior), 0.15-0.8cm (superior/inferior) and 0.03-0.10cm (lateral) [98–100]. Motion may be much greater in individual patients with the maximum posterior motion of 6.3cm in one study [101] . Within individual studies, uterine motion is greater than cervical motion [101–105] with a mean motion of 0.33-0.14cm (anterior/posterior),0.6-0.9cm (superior/inferior) and 0.07- 0.65cm (lateral)[101,137].

Limitations of this study include the limited number of patients included, although this is the largest cohort of this type. This was due to the difficulty of accessing pre-treatment scans, which are often not transferred onto the local radiology system and therefore not included in the anonymised database.

Another limitation, is the fact that it was not possible to quantify lateral motion. This was an intrinsic part of the methodology as only a single slice was contoured as was considered a reasonable trade off to allow assessment of a large cohort of patients. Lateral motion is generally reported to be smaller than motion in other planes, as shown in this study, and maybe covered as part of the parametrial or nodal CTV. Indeed, a small sub-study we

showed that the mean lateral motion was about 25% of the mean motion in the sagittal plane.

Chan et al, used a similar approach, with points located along the uterine canal on a single MRI slice as part of a cine MRI study. Reproducibility was good in this study with mean differences of point identification of less than 1 mm in all cases [105]. This could be because points in the uterine canal were selected, providing a fixed reference point. This is consistent with the fact that point A was the most reproducible in the current study. Using points at the centre of the region of interest may underestimate motion, with motion at the centre of mass less than motion as a whole [97]. The study by Chan et al, only included MRI images and it is more difficult to accurate the uterine canal on CT and likely to be impossible on many CBCT images.

Reproducibility in the current study was good for points at the uterine fundus but poor for points in the lower part of the uterus, especially point **D** . Point selection was difficult as the aim was to identify a consistent extremal point along a curve that is quite smooth. In all cases, the actual location of the point was less reliable than the distance between points. This was due to the fact that scans for all three time-points (and CBCT) were displayed at the same time increasing consistency of point selection.

It was hard to identify the lower extent of the tumour even using MRI. This had an impact on the reproducibility of the lower points, although point **E** appeared better than point **D**. This could be due to chance as the numbers were small or could potentially reflect the fact that it was easier to identify point **E** due to its location next to the bladder. Points **C** and **E** were at points of inflection, rather than at fixed anatomical points and therefore there was a larger potential for uncertainty. Repeat difference in motion was less than 2mm, apart from at points **C** and **D**. There was strong correlation between the points at the fundus of the uterus and also points **D** and **E**. There was limited correlation between points **B** - **C** and **F** - **G**, which would be expected due to the rotational changes of the uterus with points **C** and **F** approximate points of rotation. There was however only moderate correlation or low correlation between points **C** - **D** and **E** - **F**, which should potentially move together.

The analysis of CBCT again confirmed that the points at the uterine fundus were reliable with good correlation with motion on CBCT. There was poor correlation with CBCT at points **C**, **D** and **F**. This may relate to the difficulty of identifying the lower aspect of the uterus on CBCT due to the poor soft tissue contrast. Motion on CBCT was slightly greater than at on the 3 initial scans for motion at the tip of the uterus but smaller for the points on the lower part of the uterus. This may relate to the fact that there was approximately 11 weeks between scan 1 and 3 or that because scan 3 was at the end of treatment, tumour shrinkage had a disproportionate effect.

It could also be due to the fact that the poor soft tissue contrast on CBCT meant that points selected were conservative and underestimated motion. Maximum motion was greater on 3 initial scans but other studies have confirmed that dramatic changes do occur with one study reporting change in uterine position from anteversion to retroversion in 11% of patients [102].

In summary, there was excellent correlation between motion at associated points at the uterine fundus (**A**,**B** and **G**) with good intra observer variability and strong correlation with motion on CBCT. The results for points at the bottom of the uterus were more variable and it is not possible based on the current study to recommend their use without further assessment.

The addition of fiducial markers in the cervix would be an excellent way to expand this methodology as it would allow for accurate assessment of motion at both the uterine fundus and cervix. However, this is an invasive procedure and therefore may not be possible in all cases. Alternative strategies could include conventional contouring, but this is very time consuming. Autocontouring may make this more realistic in the future and methods such as contour registration could provide automatic assessment of motion.

Conclusion

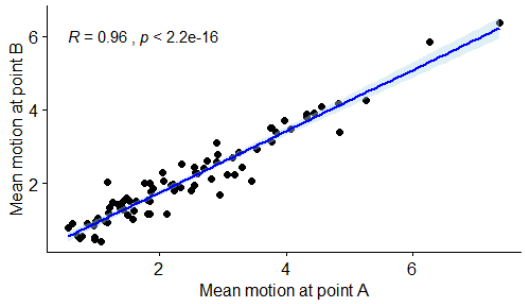
It is possible to accurately represent motion of the uterine fundus during radiotherapy using visually identified points on imaging at 3 time-points. However, it is not significantly

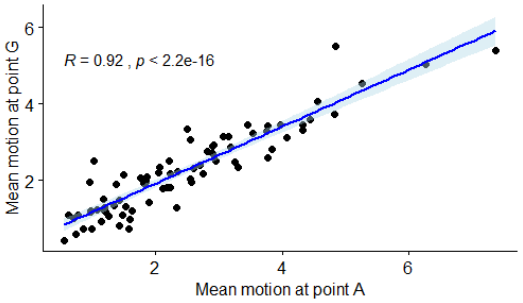
accurate to estimate motion in the lower uterine segment or cervix. The addition of fiducial markers could allow estimation of motion of the whole uterus.

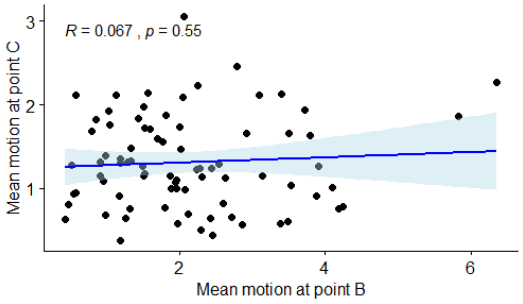
Motion at the uterine fundus is large with the mean motion greater than the CTV to PTV margin. The implications of this finding must be explored. Either adaptive measures should be considered to ensure coverage or if coverage at the fundus does not impact clinical factors, either the CTV should be redesigned or an informal approach to allow some underdosage at the fundus could be used.

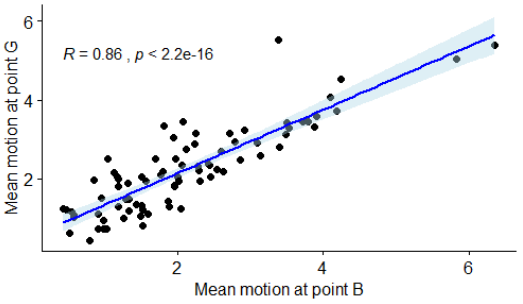
The development of adaptive MR guided radiotherapy will also provide an excellent opportunity, not only to potentially improve treatment delivery, but also to accurately quantify inter-fraction motion across a large cohort of patients.

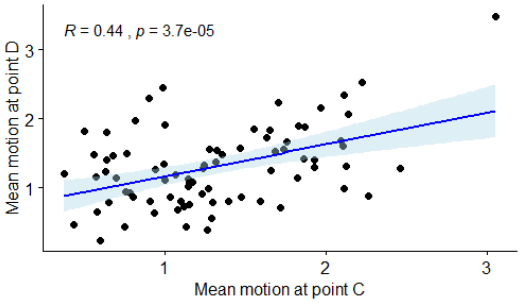
Supplementary material - 1

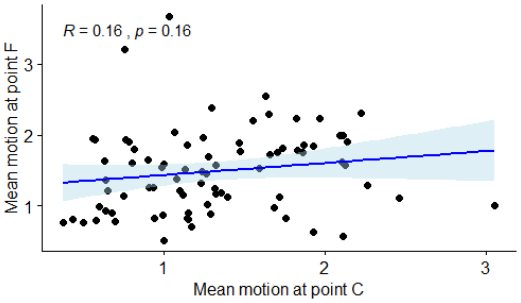


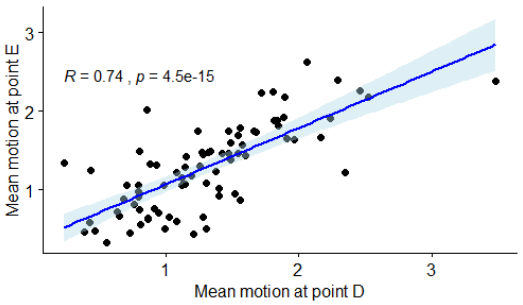


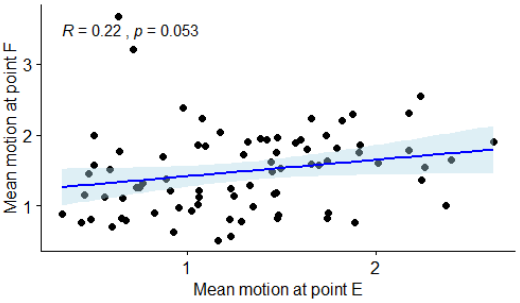


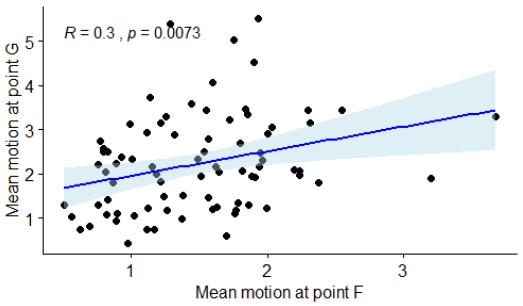








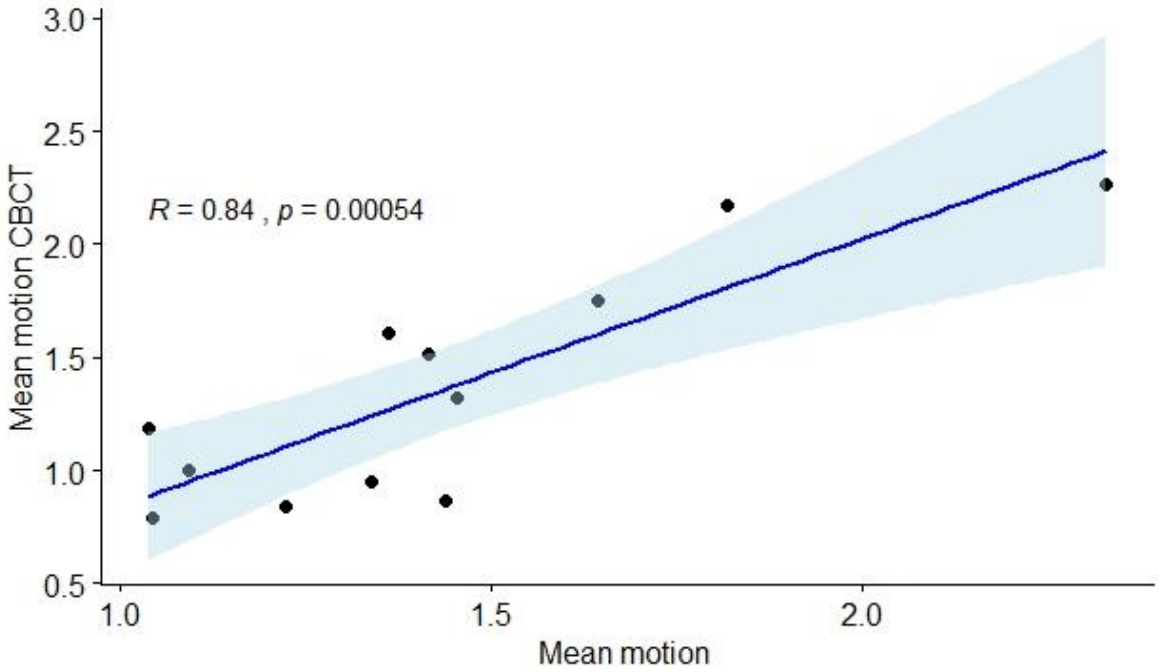




SUPPLEMENTARY FIGURE 1

Scatter plots showing the correlation between different points

a) A-B **b)** A-G **c)** B-G **d)** B-C **e)** C-D **f)** C-F **g)** D-E **h)** E-F **i)** F-G



SUPPLEMENTARY FIGURE 2

Scatter plot showing the correlation between mean motion on CBCT and at 3 time-points

Chapter 2

Is motion at the uterine fundus associated with overall survival in a cohort of patients treated with external beam radiotherapy for cervical cancer?

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Part of this work was presented as an E-poster at ESTRO Barcelona April 2018 [196].

Conception or design of the work: AAC, PH, MvH, AC, AMcW

Acquisition of data: AAC, GP

Contouring of images: AAC, SM

Analysis of data: AAC, AMcW

Interpretation of data: AAC, AMcW, MvH, AC, PH

Drafting and editing text: AAC, AMcW, MvH, AC, JL, LB, PH

Abstract

Introduction

The gold standard treatment for locally advanced cervical cancer is concurrent chemo radiotherapy followed by image guided brachytherapy. This has led to improved survival outcomes; however, rates of long-term toxicity remain high. There is evidence that the cervix and uterus can move during external beam radiotherapy, exceeding the CTV (clinical target volume) to PTV (planning target volume) margin in many patients. The majority of studies have been carried out in small groups of patients and the impact of motion has not been assessed on a population level.

Aims

To assess the impact of motion at the uterine fundus and rectal volume on clinical outcomes

Methods

80 patients with imaging at 3 time-points and clinical data were identified. A single point was used to estimate motion at the uterine fundus. The impact of motion on factors such as overall survival, progression free survival, and toxicity was assessed. The impact of rectal volume was also analysed.

Results

The median motion at the uterine fundus was 2.15 cm (0.56-7.37cm), which was greater than the CTV to PTV margin of 1.5-2cm. There was no association between motion and overall survival or progression free survival. There was a small difference in mean motion between patients with high and low toxicity but this was not statistically significant. The median rectal diameter at the lower cervix was 3.1 cm (1.0-3.5cm) with a median difference of 0.88cm across the three scans for each patient. There was no association between rectal diameter at the lower cervix and overall survival or progression free survival.

Conclusion

Despite median motion at the uterine fundus being greater than CTV to PTV margin, there was no association between overall survival and motion. This develops the hypothesis that under dosage of the uterine fundus does not have a negative impact on survival.

Introduction

It has long been recognised that the uterine fundus and cervix are mobile and can change position during the course of external beam radiotherapy [96]. This magnitude of motion varies from patient to patient and between different parts of the uterus with the fundus being the most mobile [197]. It can exceed the clinical target volume (CTV) to planning target volume (PTV) margin, with the use of a standard margin leading to under-dosage of part of the CTV in a proportion of patients [148].

A variety of strategies have been developed to manage motion in this situation, with the plan of the day (PoD) approach most widely used. A number of plans are developed based on variable bladder filling at radiotherapy planning and the most appropriate is selected on daily imaging [167]. There is little evidence regarding which patients may benefit from a very resource intensive technique [155]. The majority of published strategies do not specifically account for changes related to bowel motion, rectal changes or variation due to other causes. In patients with prostate cancer receiving 3D conformal radiotherapy, rectal distension was associated with worse outcome in some patients [198,199]. This finding was not replicated in a more recent study using image guided radiotherapy [200]. The link between rectal size and outcome has not been explored in cervical cancer.

There has also been interest in redefining the CTV by treating the GTV with a margin instead of the whole uterine fundus [15]. This approach would both reduce the overall CTV volume and also exclude the most mobile part of the uterus. However, the clinical evidence to support this remains limited and it also depends on an accurate delineation of the GTV [80].

A number of studies have been carried out to quantify motion, but they often include small numbers of patients and a limited number of time-points. Although the PoD technique has been assessed on dosimetric outcomes such as dose volume histograms (DVHs), the only paper reporting patient reported outcomes did not have a comparator arm.

The aim of the study was to assess if motion of the uterine fundus and changes in rectal volume are associated with patient outcomes including survival and toxicity.

Methods

This study used pseudonymised patient images at three time-points, pre-treatment MR scan (1), radiotherapy planning CT scan (2) and MR scan in the final week of treatment (3). The time interval between scan (1) and (2) is approximately 2 weeks with 7 weeks between scan

(2) and scan (3). This is linked to patient outcome data. For a full description of data extraction methods and radiotherapy treatment, see chapter 1.

The T2 weighted sagittal sequence was selected in the MR scans, with the radiotherapy planning CT scan viewed in the sagittal plane. Images identified were exported into World Match, an in-house software programme. All images were fused to scan 1, using rigid fusion based on bony anatomy. The mid uterus slice on scan 1 was selected and contours were made on the corresponding slice for all scans. The uterus and cervix, including visible tumour, were contoured. 7 points were identified; however this analysis focuses on point A, which is representative of motion at the uterine fundus, and was the most reproducible to be identified. Points at the lower part of the uterus were not as reproducible and therefore not felt to be reliable for inclusion in survival analysis, for a full discussion see chapter 1.

Point A1 was defined as point A on scan 1, with point A2 on scan 2 and point A3 on scan 3, see figure 9. The rectum was not always visible on the mid uterus sagittal slice and therefore rectal diameter was measured manually at the lower and upper uterine cervix border on the appropriate axial slice, see figure 10.

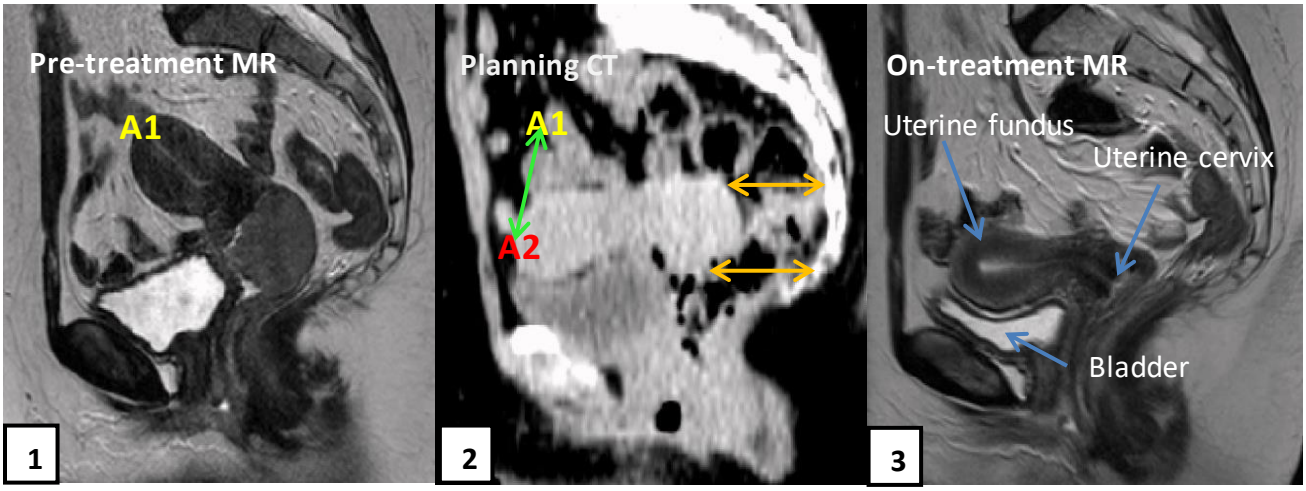

FIGURE 9 LOCATION OF POINTS AND DISTANCES BETWEEN POINTS
1 Pre-treatment MR – shows location of point A1 (point A on scan 1)
2 Planning CT – shows location of A1 and A2, with the green arrow indicating the distance between them. Superior and inferior rectal diameter illustrated by orange arrows
3 On treatment MR – with labels to demonstrate uterine fundus, cervix and bladder

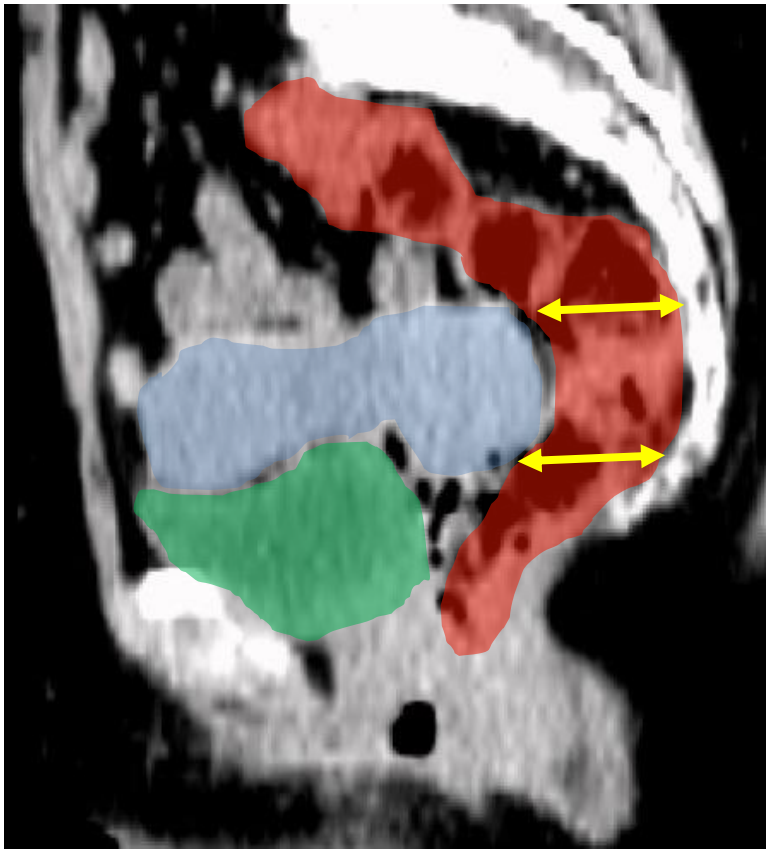

FIGURE 10 CT SCAN SHOWING UPPER AND LOWER LEVELS RECTAL DIAMETER MEASUREMENT WITH THE UPPER LEVEL AT THE INFLECTION POINT OF THE UTERINE CERVIX CONTOUR (IN BLUE) CLOSE TO THE RECTUM (IN RED) AND THE LOWER LEVEL AT THE INFERIOR OR POSTERIOR ASPECT OF THE UTERINE CERVIX CONTOUR. THE BLADDER IS SHADED IN GREEN.

The images were analysed using World Match, an in-house software program. The distance between point A between pairs of scans was automatically calculated with in-house software, and recorded i.e., as A1-A2, A1-A3 and A2-A3. The direction of motion was not considered. Mean motion for each point was calculated across the three scans. The current analysis only considers point A, as a representative point for motion of the uterine fundus. The association between motion at point A and factors such as age, tumour size and stage were also assessed. Toxicity was defined as highest late (greater than 3 months following radiotherapy) clinician recorded impact on quality of life, using a four-point scale. This is a non-standard local scale with impact described as none, minimal, moderate or severe.

Statistical analysis

Statistical analysis was carried out using Microsoft Excel 2010 and R v 3.6.1. Summary statistics were calculated for motion at point A. The association between motion at point A; stage, tumour size and age was assessed using Kruskal Wallis and Wilcoxon test respectively.

Kaplan Meier survival analysis was performed to assess overall survival and progression free survival. Motion at the uterine fundus and the rectal diameter using defined cut offs were considered as variates with significance assessed using log rank testing. A Cox proportional hazard model was used to assess motion as a continuous factor but multivariable analysis was not performed as the event rate was low.

An a priori power calculation was not performed but a post hoc calculation was done.

Results

80 patients were included in the analysis; progression free survival data was not available for one patient. For full patient characteristics, see table 4 in chapter 1.

Motion at point A is summarised in table 12.

Point	Median (cm)	Mean (cm)	SD (cm)	Min (cm)	Max (cm)
A	2.15	2.42	1.36	0.56	7.37

TABLE 12 SUMMARY OF MEAN MOTION AT POINT A. SD (STANDARD DEVIATION)

The mean and median motion exceeded the largest CTV – PTV margin of 2cm. This was validated with a subset of patients by assessing motion on CBCT, see chapter 1.

There was no association between motion at point A and patient age, tumour stage or size, see figure 11.

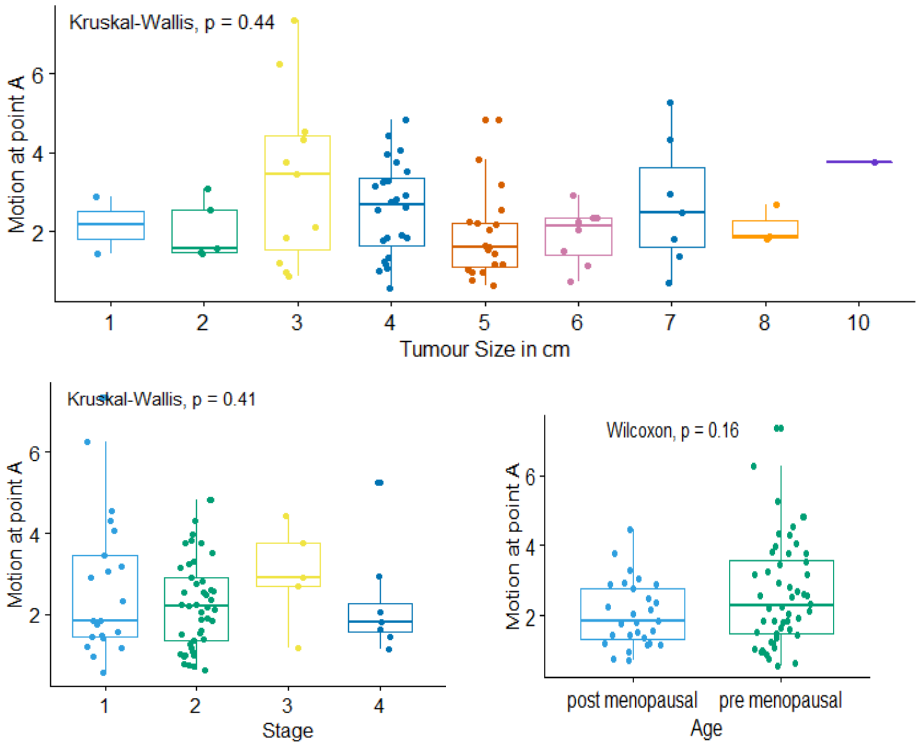

FIGURE 11 BOX PLOTS SHOWING MOTION AT POINT A CATEGORISED BY TUMOUR SIZE, FIGO (2009) TUMOUR STAGE AND AGE, WITH PATIENTS OVER 55 YEARS CONSIDERED POST- MENOPAUSAL.

Age was divided into pre or postmenopausal with a cut off at 55 years. There was also no association between age or tumour size on a continuous scale and motion at point A.

Survival analysis

As mean and median motion at point A exceeded the CTV – PTV margin, this will lead to under-dosage of the uterine fundus in a proportion of patients. If there is tumour there such under-dosage would lead to a geometric miss and a reduction in progression free survival. The impact of motion overall and progression free survival was therefore explored both as a dichotomous variable using the median motion, 2.15cm, as the cut point, and also as a continuous variable.

There was no statistically significant difference in overall or progression free survival see table 16 and figure 12.

Motion at point A	Overall survival at 5 years	Progression free survival at 5 years
Less than median	79% (67-93%)	76% (63-91%)
Greater than the median	80% (68-93%)	70% (57-85%)

TABLE 16

Summary of overall and progression free survival at 5 years split by median motion at point A

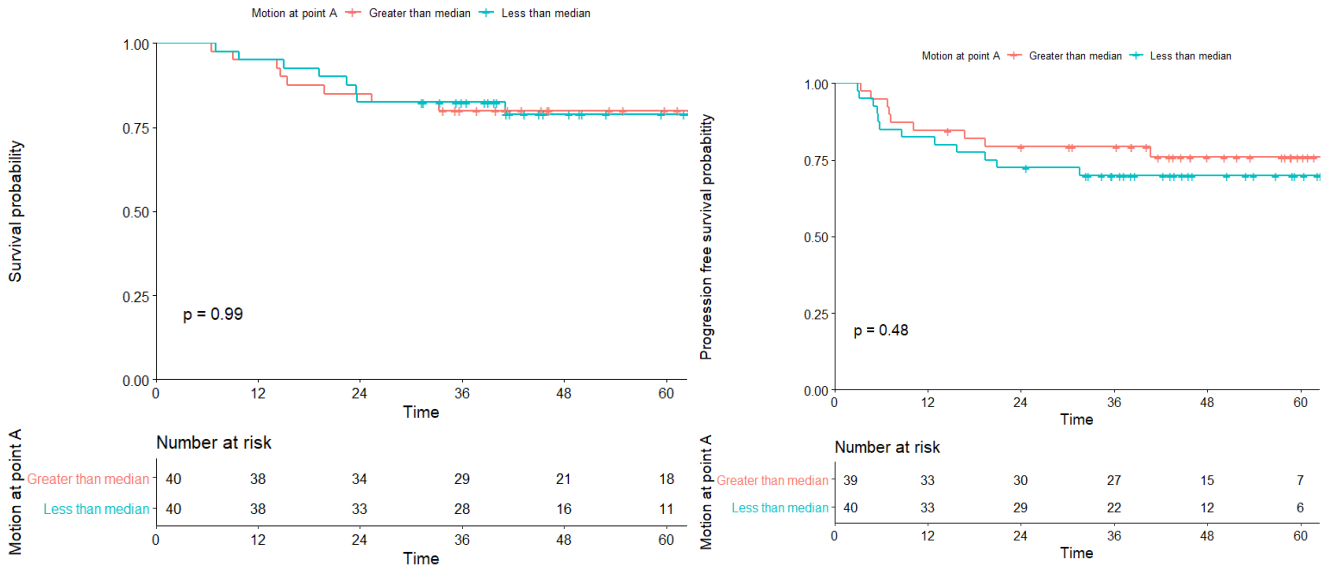

FIGURE 12 KAPLAN MEIER CURVE SHOWING OVERALL AND PROGRESSION FREE SURVIVAL COMPARING MOTION AT POINT A GREATER OR LESS THAN THE MEDIAN (2.15CM)

In patients who had died, median motion at point A was 2.02 cm and mean motion was 2.15cm; in patients who were still alive median motion was 2.15cm and mean motion was 2.45cm.

Toxicity was recorded by physicians, on an ordinal scale with 4 groups. This is a locally derived scale and has not been prospectively validated. These were no impact on quality of life, low impact on quality of life, moderate impact on quality of life and high impact on quality of life.

These were subdivided into two groups, none or low impact into low toxicity and moderate to high into high toxicity. The box plot is shown in figure 13.

The median and mean motion at point A was 3.16cm and 2.98cm for high late toxicity group and 1.88cm and 2.23cm for the low late toxicity group. The difference in the means for each group did not reach statistical significance with a p=0.11.

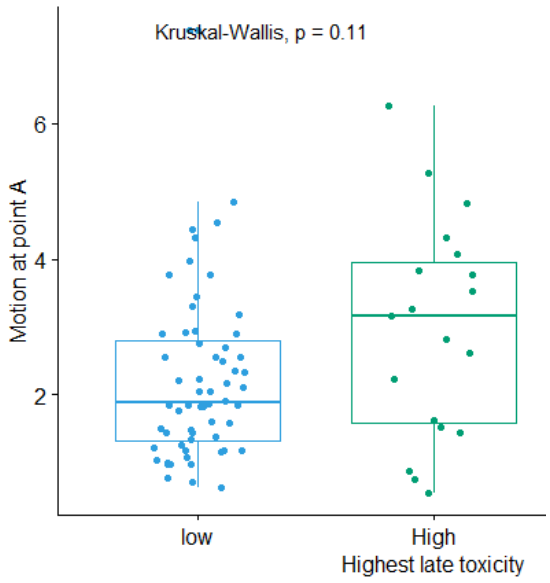

FIGURE 13 BOX PLOT SHOWING MOTION AT POINT A FOR PATIENTS REPORTED TO HAVE HIGH AND LOW TOXICITY

Rectal diameter

The rectal diameter was measured at two levels, see figure 1. In keeping with previous research in patients treated with radiotherapy for prostate cancer [199], rectal diameter on the radiotherapy planning scan (scan 2) was used for analysis, see table 13.

Rectal diameter	Median (cm)	Mean (cm)	SD (cm)	Min (cm)	Max (cm)
Upper	3.30	3.50	1.36	1.30	7.50
Lower	3.10	3.10	1.15	1.00	6.50

TABLE 13 RECTAL DIAMETER ON RADIOTHERAPY PLANNING

The mean change between rectal diameter across all scans was calculated for each patient; at the upper level mean difference was 0.95cm and the median difference was 0.88cm; at the lower level, the mean was 1.01cm and the median was 0.90cm. There was no difference in survival with rectal diameter at either level, either considered as a categorical or continuous variable, see figure 14. There was no statistically significant difference between mean rectal diameter on planning scan in patients with high and low toxicity.

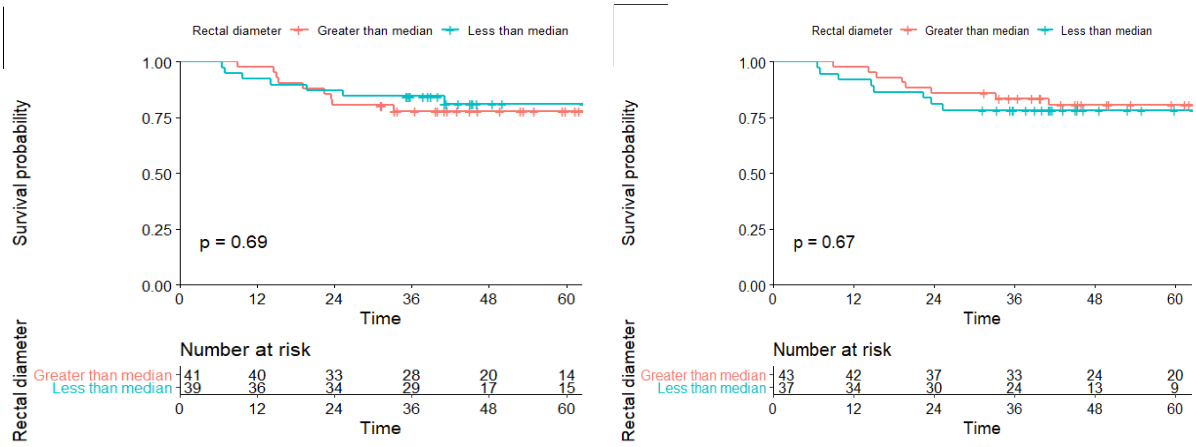

FIGURE 14 KAPLAN MEIER CURVE SHOWING OVERALL SURVIVAL AT POINT A WITH CUT OFF AT MEDIAN RECTAL DIAMETER UPPER (A) AND MEDIAN LOWER RECTAL DIAMETER (B

Power calculation

A post hoc power calculation has been included for the difference in overall survival for motion at Point A. With 40 patients in each group and an alpha of 0.1, there would be a power of 81.5% to detect a 25% difference in survival. In order to detect a 10% difference in survival, with a power of 80% and an alpha value of 0.1, a sample size of 462 would be required.

Discussion

This is the first study to look at the impact of uterine fundal motion and rectal diameter on clinical outcomes including survival, progression free survival and toxicity. There was direct estimation of motion at the uterine fundus and rectal diameter was used as a surrogate estimate of motion in the lower portion of the CTV as it proved impossible to locate robust points in that area. There was no association between motion at the uterine fundus or rectal diameter on overall survival or progression free survival.

The study has a number of limitations including no assessment of lateral motion. One patient was excluded from the study as lateral motion meant that analysis was not possible but this was less than 2% of the patients included. Lateral motion has generally been reported to be smaller [97] and due to the shape of the CTV, lateral motion at the level of the tumour is likely to be covered by the parametrial portion of the CTV. Another limitation is that patients treated in this study were treated with a mix of IMRT and 3D conformal

radiotherapy with margins of 1.5 – 2cm. However, median motion at point A was greater than the largest margin.

The assessment of motion was based on a snapshot rather than motion across the course of treatment, including imaging when the patient was not receiving radiotherapy. Work done in chapter 1 does suggest that there was good correlation (R=0.78 p=0.003) between motion at 3 timepoints and on CBCT. There is a trade-off between the accuracy of measurement and time taken to obtain the measurement. This methodology was designed to be carried out in a large cohort of patients and provide an estimate of motion.

Another limitation is that, although this is the largest cohort of patients with both motion and survival data available, the overall number of events was small. This means that small differences will not be detected as the power of the study is low as demonstrated by the post hoc power calculation. The inclusion of patients was limited by the availability of pre-treatment MR scans, which are carried out in peripheral hospitals and not always transferred to the central system.

The lack of a direct measure of cervical motion is also an important limitation of the study. It was impossible to select reproducible points in the lower portion of the CTV. As it was felt to be very important to evaluate motion in this area, as the part of the CTV most likely to contain tumour, an indirect approach was developed, using rectal diameter as a surrogate marker for motion at the cervix. This approach has been used in patients treated for prostate cancer before and therefore felt to be a reasonable approach. As shown in chapter 3, interfraction motion at the cervix is mainly related to rectal changes, although tumour shrinkage also impacts tumour positon. Fiducial markers in the cervix could be used in the future to provide a more accurate assessment of cervix motion.

There was no statistically significant difference in mean motion at point A between patients with high and low physician reported toxicity. However, the median value of motion in the group with high physician reported toxicity was 3.16 cm compared to 1.88 cm in the low toxicity group. The measure of toxicity used was not a validated score, because only retrospective data was available, which is a limitation of the study. The study also focussed

on overall and progression free survival, rather than local control, which is likely to be more closely related to radiotherapy dose. This was again due to the use of anonymised retrospective data.

Relating motion to clinical outcome in cervix cancer does seem to be an area that would benefit from further investigation as there has been no previous work in this area. As shown by the post hoc power calculation, in order to detect a difference in survival of 10% over 400 patients would be required. This highlights the benefit of a quick and easy way to estimate motion. A combination of fiducial markers in the cervix and measurement of Point **A** at 3 timepoints would be viable for a large cohort of patients and would provide a reliable estimation of motion.

The use of trial cohort with a standardised radiotherapy protocol, as well as validated toxicity assessment as assessment of progression free and overall survival would be an ideal. As assessment of motion point **A** seems to have good intra observer variability, measurements could be carried out locally, meaning that images would not have to be transferred. A formal assessment of reliability with a pre-hoc definition of acceptable reliability would need to take place before large scale assessments were done.

To measure the impact of inadequate dose at the uterine fundus and cervix directly would require contouring at additional time points, either on pre and on treatment MR scans or cone beam CTs. CTV coverage could be assessed as well as dosimetric analysis to estimate the impact of changes. This would be very time consuming to perform for enough patients for the study to have adequate power to detect even relatively large differences. In the future, auto contouring and automatic image registration could be used to rapidly define motion.

Patients treated with adaptive radiotherapy, have daily contours that could be used to assess CTV motion but they will be amended ensure that the whole CTV is covered and therefore would not be suitable for this analysis.

The study results do generate an interesting hypothesis. Although median motion of the tip of the uterus exceeds the CTV to PTV margin implying inadequate CTV coverage of the upper uterus in a proportion of patients, there is no evidence that motion of the uterine fundus is associated with survival.

It may therefore be possible to exclude the uterine fundus from the CTV in the absence of uterine body infiltration by the primary tumour, reducing toxicity without affecting overall survival. This would be particularly important if a link between toxicity and motion at point A was confirmed. This hypothesis is also supported by the outcome data from trachelectomy, the removal of the cervix leaving the uterus in situ, in early stage disease, with little evidence of isolated relapse within the uterus [201–205]. However, this is a highly selected cohort of patients with small tumours and there is evidence that risk of uterine involvement increases with tumour size and stage.

This approach is being studied with a recent retrospective review in 53 patients treated with reported no isolated uterine relapse [80] and there is an ongoing prospective phase 2 study [81]. The use of MR planning is likely to be required to support this, to fully assess the extent of uterine involvement [206].

Rectal diameter at radiotherapy planning scan did not correlate with survival in this cohort. This is in keeping with a recent study in patients with prostate cancer [200], although not others [198,199] and is unsurprising as the median change in mean rectal diameter was less than one centimetre. It may mean that smaller margins could be considered in the lower part of the CTV, as this is the least mobile part [97].

Conclusion

This study shows that motion on sequential imaging is greater than the PTV margin. However, there is no relation to clinical outcomes including overall and progression free survival or toxicity. This requires confirmation in a larger dataset but should be used to inform future protocols of fundal sparing in chemo radiotherapy for cervical cancer.

Chapter 3

What are the main causes of inter-fraction motion of the uterine fundus and cervix?

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A version of this work was accepted as an abstract at ESTRO 2020 as a poster highlight

Conception or design of the work: AAC, EVO

Acquisition of data: AAC, GP

Contouring of images: AAC,

Analysis of data: AAC, AMcW

Interpretation of data: AAC, AMcW, MvH, AC, PH, EVO

Drafting and editing text: AAC, AMcW, MvH, AC, PH

Abstract

Introduction

Inter-fraction motion of the uterus and cervix can be large and often exceeds applied CTV-PTV margins. There is variation between patients and different parts of the uterus move differently. Most strategies accounting for this are based on bladder filling. However, we hypothesise that there are other anatomical causes of uterine motion.

Aims

To provide a qualitative assessment of causes of motion of the uterine fundus and cervix in a large cohort of patients.

Methods

Anonymised scans were retrospectively obtained for 80 patients who received radical radiotherapy for cervical cancer, with imaging at 3 time points; diagnostic MRI scan (scan 1), planning CT, ~2 weeks later (scan 2) and final week MRI scan, ~8weeks later than scan 1 (scan 3). Scans were registered on bony anatomy to the diagnostic MRI for each patient. The uterus was contoured by a single observer for all 240 scans on a single sagittal slice identified as mid of the uterus on scan 1. The main cause and direction of motion of the cervix and uterine fundus was evaluated between scans 1-2 and 1-3 based on visual interpretation.

Results

Between scan 1 and 2 motion (>1cm) was seen in 43 cases (54% of cohort) at the cervix and 56 cases (70%) between scan 1 and 3. The most common cause of motion between scan 1 and 2 was rectal change with 29 cases (36%) and for scan 1 and 3 was tumour regression, also with 29 cases (36%). Bladder filling differences only accounted for cervix motion in 5 cases (6%) in scan 1-2 and 1 case (1%) in scan 1-3. At the cervix, in scan 1-2, there was a superior/inferior component of motion in 20 cases (24%), mainly related to rectal changes. In scan 1-3, there was a superior/inferior component of motion in 38 cases (45%), mainly related to tumour regression.

Motion was seen in 62 cases (78%) at the uterine fundus between scans 1 and 2 and in 61 cases (76%) between scans 1 and 3. The main drivers of motion at the fundus were bladder filling with 22 cases (28%) in scan 1-2 and 18 cases (23%) in scan 1-3. However, motion was

also related to rectal changes in 12 cases (15%) in scan 1-2 and 13 (16%) scan 1-3, to bowel changes in 21 cases (26 %) in scan 1-2 and 13 cases (16%) in scan 1-3, and to tumour regression in 15 cases (19%) in scan 1-3.

Conclusion

The main causes of cervical motion are changes in rectal filling and tumour regression, with bladder filling playing a limited role. Motion at the uterine fundus is affected by bladder filling but other factors also have an important role. This suggests that current radiotherapy motion management strategies based on bladder filling may not account for the most important causes of cervix motion. Alternative approaches such as online adaption may be beneficial.

Introduction

Concurrent chemo-radiotherapy followed by image guided brachytherapy is the standard of care for the majority of patients with locally advanced cervical cancer. Over the last 10 years, it has been appreciated that motion of internal organs can alter the position of the clinical target volume, with both intra and inter-fraction motion recorded. A number of studies have been carried out to quantify this motion, but they often include small numbers of patients and a limited number of time-points [197]. The focus has often been on the impact of bladder filling as this is easy to manipulate [97]. However, it is recognised that there is at best moderate correlation of bladder filling with uterine motion and this is mainly at the uterine fundus [110,111]. There is no literature specifically exploring the other potential causes of uterine motion and as the motion is complex, it is difficult to classify it using a purely quantitative approach.

The focus on bladder filling has also influenced the approach to manage motion during radiotherapy. The most widely used strategy is the plan of the day (PoD) approach, although library of plans may be a more appropriate name. A number of plans are developed based on variable bladder filling at radiotherapy planning and the most appropriate is selected based on daily on-treatment imaging [167]. This leads to a focus on motion driven by the bladder and doesn't account for other potential causes of motion including bowel motion, rectal motion and tumour shrinkage. Other approaches have been proposed such as re-planning at various time points during treatment. This will have an impact on progressive changes such as tumour shrinkage but would not be effective for random changes such as bowel or rectal changes. Another proposal is an adaptive library of plans, adding plans based on images obtained during treatment [173]. However, there are currently no reports of clinical implementation of these techniques.

To best select the appropriate motion management techniques, we first need a full understanding of what drives the motion during treatment. In this study, we aim to describe the causes of motion in the initial and final stages of treatment based on qualitative assessment.

Methodology

A cohort of 91 patients, who were treated for cervical cancer with external beam radiotherapy +/- chemotherapy +/- brachytherapy was collected. Scans at three time points were obtained, all with the patients supine; the diagnostic MR scan (scan 1) , the radiotherapy planning CT scan obtained around two weeks later (scan 2) and an MR scan (scan 3) during external beam radiotherapy approximately seven weeks following the planning scan. The scans were fused based on bony anatomy using World Match, an in-house software and the mid-uterine slice was selected on scan 1.

A full description of the methodology is available in chapter 1, including a table of patient characteristics.

Qualitative assessment of motion

The diagnostic MRI scan (scan 1) was used as the reference image and was compared to scan 2 and 3. The uterine fundus and cervix were considered independently. Manual measurement was used from the contour of the scan 1 to the comparison scan to select patients with motion greater than 1 cm in either area. In these patients, visual inspection was used to determine the predominant cause and the direction of motion between scans. The causes of motion were defined as related to bladder, rectum, bowel, tumour shrinkage, hydrometrium or other reasons. The direction of motion was defined visually, based on an estimation of the centre of mass and the predominate direction recorded. For example, if the bladder reduced in volume between scan 1 and 2 and a manual measurement showed the uterine fundus moved inferiorly by more than 1 cm along the boundary of the bladder, this would be recorded as inferior motion at the fundus due to bladder changes.

Figure 15 illustrates the different causes of motion.

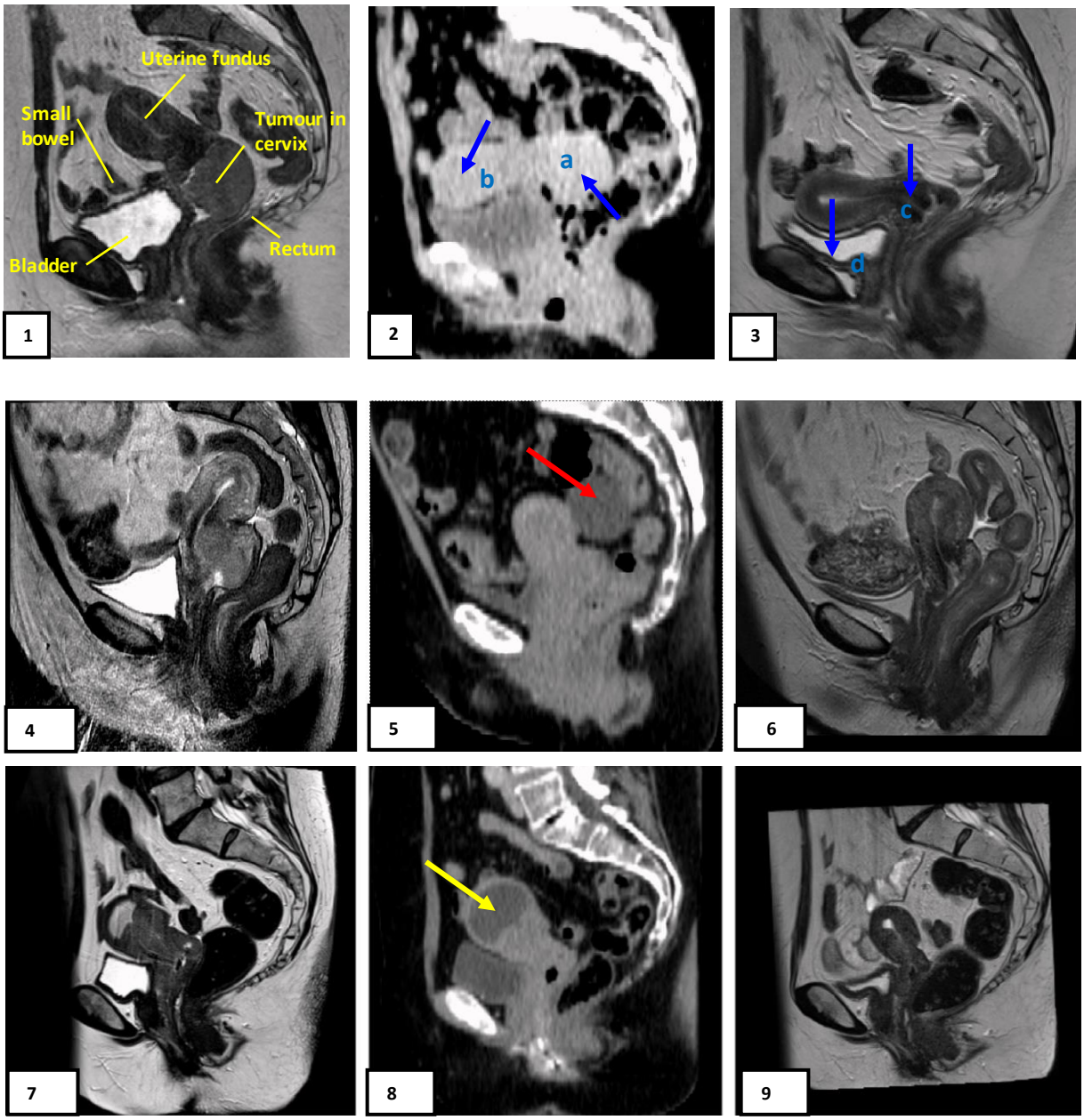

FIGURE 15 ILLUSTRATION OF CHANGES IN POSITION OF THE UTERINE CERVIX AND FUNDUS BETWEEN IMAGES

1-2 a. Cervix motion due to rectal changes; b uterine fundus motion due to small bowel changes

1-3 c. Cervix motion due to tumour shrinkage; d uterine fundus motion due to small bowel and bladder changes

2-3. Here bladder filling changes drive the motion of the uterine fundus

4-5. Cervix motion due to rectal changes; uterine fundus motion due to other cause, cystic structure highlighted by red arrow

8-9. Cervix motion less than 1 cm; uterine fundus motion due to reduction in hydrometrium highlighted by yellow arrow

Results

80 patients were included in the analysis with a total of 240 images assessed. 3 patients were excluded as it was not possible to contour the uterine fundus and cervix on all three scans. For one patient this was due to lateral motion of the uterus, which was not seen on the scan 3. The other patients had very large uteri which were not fully visible on all the scans. Problems with World Match analysis, including poor image fusion, led to the exclusion of 5 patients. Overall survival was not available for three patients who were excluded from the cohort. A summary of motion is shown in table 14.

		Scan 1 to 2		**Scan 1 to 3**	
		Number	*%*	**Number**	*%*
Uterine cervix	**Motion <1cm**	37	*46*	24	*30*
	Motion >1cm	43	*54*	56	*70*
Uterine fundus	**Motion <1cm**	18	*23*	19	*24*
	Motion >1cm	62	*78*	61	*76*

TABLE 14 NUMBER OF PATIENTS WITH MOTION GREATER THAN 1CM AT THE UTERINE CERVIX AND FUNDUS FOR EACH TIME POINT

Between scan 1-2 the majority of patients with motion at the uterine cervix also had motion at the uterine fundus, only 3 (7%) patients of the 43 with motion greater than 1 cm at the uterine cervix did not have motion greater than 1 cm at the uterine fundus. Between scan 1-3, 9 (18%) of 56 patients with motion greater than 1 cm at the uterine cervix did not have motion greater than 1cm at the uterus. This suggests especially at the start of treatment, it is unlikely for patients to have motion at the cervix without motion at the uterine fundus. This data is summarised in table 19.

	1 to 2		1 to 3	
	uterine motion < 1cm	**uterus motion >1cm**	**uterine motion < 1cm**	**uterus motion >1cm**
cervix motion < 1cm	15	22	10	14
cervix motion >1cm	3	40	9	47

Table 19 Comparison of motion at the cervix and uterine fundus at timepoint 1 to 2 and 1 to 3

The causes of motion are illustrated in figure 16. For the cervix, the most common cause of motion between scan 1 and 2 was rectal change with 29 cases (36%) and scan 1 and 3, it was tumour regression, with 29 cases (36%). Bladder filling differences only accounted for cervix motion in 5 cases (6%) in scan 1-2 and 1 case (1%) in scan 1-3.

The main drivers of motion at the fundus were bladder filling with 22 cases (28%) between scan 1-2 and 18 cases (23%) in scan 1-3. However, motion was also related to rectal changes in 12 cases (15%) in scan 1-2 and 13 (16%) scan 1-3, to bowel changes in 21 cases (26 %) in scan 1-2 and 13 cases (16%) in scan 1-3, and to tumour regression in 15 cases (19%) in scan 1-3. This highlights the number of causes of the complex motion and the relative unimportance of bladder filling on motion at the cervix.

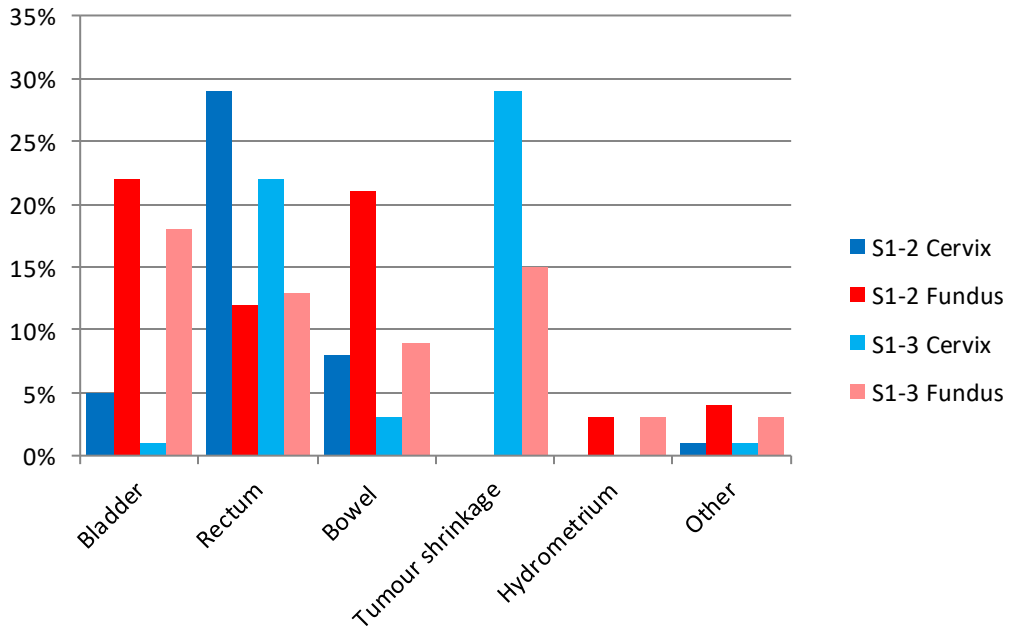

FIGURE 16 FIGURE 16 CAUSES OF MOTION GREATER THAN 1CM AT THE UTERINE CERVIX AND FUNDUS FROM SCAN 1 TO 2 (S1-2) AND 1 TO 3 (S1-3) (EXPRESSED AS A PERCENTAGE OF THE TOTAL NUMBER OF PATIENTS)

The direction of motion is summarised in figure 17. At the cervix, in scan 1-2, there was a superior/inferior component of motion in 20 cases (24%), mainly related to rectal changes, with anterior/posterior component of motion in 34 cases (43%). In scan 1-3, there was a superior/inferior component of motion in 38 cases (45%), mainly related to tumour regression, with the anterior/posterior component in 46 cases (56%). Motion at the fundus showed greater motion in the inferior direction between scan 1-2, potentially related to changes in bladder filling. Between scan 1-3, the predominant motion was inferior and posterior, which could relate to changes as the cervix contracted due to tumour shrinkage. The causes of motion for each time-point for the cervix and uterus are summarised in the tables 15.

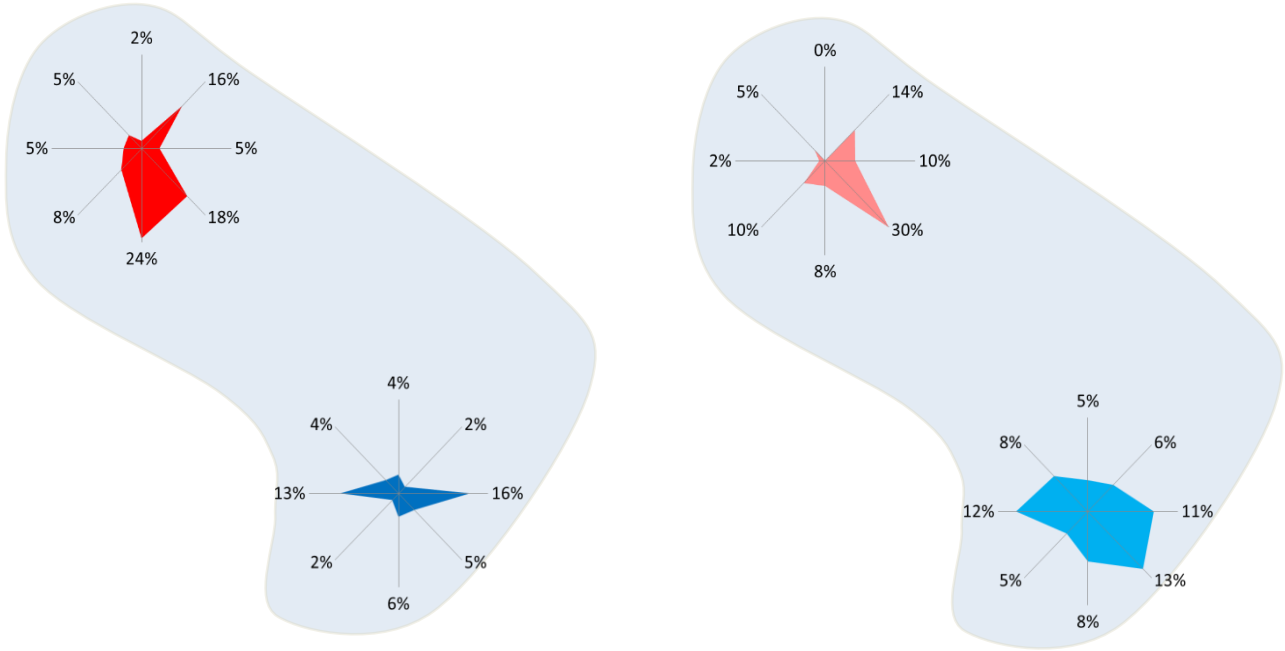

FIGURE 17 DIRECTION OF MOTION GREATER THAN 1CM AT THE UTERINE CERVIX AND FUNDUS FROM SCAN 1 TO 2 AND SCAN 1 TO 3

Cervix 1-2	**Cause**					
Direction of motion	**Bladder**	**Rectum**	**Bowel**	**Tumour Shrinkage**	**Hydrometrium**	**Other**
Anterior	0	10	0	N/a	0	1
Anterior/inferior	2	1	1	N/a	0	0
Anterior/superior	0	3	0	N/a	0	0
Posterior	1	7	5	N/a	0	0
Posterior/inferior	1	2	1	N/a	0	0
Posterior/superior	1	1	0	N/a	0	0
Inferior	2	1	1	N/a	0	0
Superior	0	3	1	N/a	0	0

Uterus 1-2	**Cause**					
Direction of motion	**Bladder**	**Rectum**	**Bowel**	**Tumour Shrinkage**	**Hydrometrium**	**Other**
Anterior	0	3	0	N/a	1	0
Anterior/inferior	3	2	1	N/a	0	1
Anterior/superior	0	0	0	N/a	0	0
Posterior	1	2	1	N/a	0	0
Posterior/inferior	6	2	4	N/a	1	1
Posterior/superior	1	2	8	N/a	0	1
Inferior	10	1	6	N/a	1	1
Superior	0	2	1	N/a	0	0

Cervix 1-3	**Cause**					
Direction of motion	**Bladder**	**Rectum**	**Bowel**	**Tumour Shrinkage**	**Hydrometrium**	**Other**
Anterior	0	2	1	7	0	0
Anterior/inferior	0	0	0	4	0	0
Anterior/superior	0	5	0	2	0	0
Posterior	1	2	1	5	0	0
Posterior/inferior	0	6	1	3	0	0
Posterior/superior	0	2	0	4	0	0
Inferior	0	3	0	4	0	0
Superior	0	0	0	2	0	1

Uterus 1-3	**Cause**					
Direction of motion	**Bladder**	**Rectum**	**Bowel**	**Tumour Shrinkage**	**Hydrometrium**	**Other**
Anterior	1	1	0	0	0	0
Anterior/inferior	2	1	2	0	0	1
Anterior/superior	1	1	1	0	1	0
Posterior	0	1	1	5	0	1
Posterior/inferior	5	6	0	9	2	0
Posterior/superior	4	4	3	0	0	1
Inferior	5	0	1	1	0	0
Superior	0	0	0	0	0	0

TABLE 15 THE CAUSES OF MOTION BY DIRECTION AT TIME POINT 1-2 AND 1-3 FOR CERVIX AND UTERUS

Discussion

This is the first study to qualitatively assess the causes of motion of the uterine fundus and cervix separately. This has highlighted that although bladder filling is an important cause of motion of the uterine fundus, motion at the cervix is predominantly due to other causes such as rectal and bowel changes. The uterine cervix is less mobile than the uterine fundus

in agreement with previous studies. This is important as in many patients, with smaller tumours, the probability of disease at the fundus is small.

Previous studies have noted that there is only moderate correlation between bladder filling and motion of the uterine fundus and cervix [110,111]. Van de Bunt et al suggested weak correlation with change in bladder filling relative to the radiotherapy planning scan, with increasing bladder volume moving the GTV superiorly. However no correlation was seen for the CTV[3]. Eminowitz et al suggest that a change of greater than 130ml in bladder volume relative to the radiotherapy planning scan always led to the CTV not being covered by the PTV but could only estimate that increased bladder filling lead to superior motion of the upper part of CTV as the cervix and uterus were not analysed separately [4]. The majority of studies were also carried out with a bladder filling protocol, so that change related to bladder filling were highlighted [97]. This evidence and the fact that bladder filling is easily manipulated mean that the majority of motion management strategies have only been based on this factor. The initial plan of the day studies were developed on patients treated in the prone position [130], which may alter the impact of the bladder filling. However, other groups have used a similar approach with patients treated supine [152].

This study also shows that the causes of motion change over time, with more patients displaying motion at the end of treatment. Previous studies have suggested classifying patients into movers and non-movers, prior to treatment to select those who require motion management strategies[130]. The current study suggests that this may exclude a proportion of patients who could benefit.

This study has emphasised the importance of rectal changes as a major cause of motion at the cervix. Cervical tumours are often located near the rectal cervical border and therefore changes in this area are particularly important as they may lead to under treatment of the tumour. Rectal changes were important both between scan 1-2 and scan 2-3. The impact of rectal filling has been noted previously, for example in the definition of the ITV in the EMBRACE II protocol. This recommends that rectal filling is taken into account when defining the posterior and anterior border of the ITV [63]. However, rectal filling can also lead to motion of the target in other directions, especially superiorly and inferiorly. Van de

Bunt also showed a weak correlation between rectal volume, anterior posterior and superior inferior changes in the CTV position[3]. They did not specify which part of the CTV was influenced. Rectal motion is also random, supporting the argument for online adaption, as it would be difficult to correct using a library of plans approach.

The major limitation of this work was that in order to analyse a large number of patients, only a single slice on three scans were used. This meant it was impossible to classify lateral motion and in a small number of cases the cause of motion may have been different if all slices were analysed, although gross lateral motion would be easy to identify and only one patient was excluded due to this. Lateral motion is reported to be smaller [207] than other directions and may be less important as it may be covered by the parametrial part of the CTV. It was also difficult to determine one predominate direction in the case of tumour shrinkage, however to select only one reference edge would mean that motion would be lost.

Scan 1 was chosen as the reference image, with changes between scan 1 and 2 roughly representing changes at the beginning of radiotherapy, before tumour shrinkage and scan 1 to 3 representing changes in the final week of treatment. Although there may have been some tumour growth between scans 1 and 2, it was not apparent in the images, and the timing also roughly represents the time between the radiotherapy planning scan and start of treatment. As scan 3 was performed towards the end of the course of radiotherapy tumour shrinkage may have a disproportionate impact, compared to assessment throughout the treatment course.

This study illustrates the additional value of qualitative assessment, as the complexity of motion can be lost when summarised using a quantitative approach and a cause cannot be attributed. Although bladder filling is an important factor in the motion of the uterine fundus, it plays less of a role at the cervix, which as it includes the GTV must be the priority for coverage.

Motion management strategies are complex and time consuming and it is important that they are directed at the most important causes of motion. This work highlights the need to consider other causes of motion than bladder filling and therefore there are limitations of the current library of plans approach. Offline replanning could address changes due to

tumour shrinkage, however only an online adaptive approach could account for important random changes such as rectal motion.

Conclusion

Current strategies for managing motion of the CTV in patients with cervical cancer focus on changes related to bladder filling. This is the first study to highlight the importance of the other causes of motion including rectal and bowel changes, especially for the cervix. These changes are difficult to predict or simulate prior to treatment and therefore support a potential role for online adaptation.

Chapter 4

The potential impact of intra-fraction motion during MR guided external beam radiotherapy for cervical cancer

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A version of this work was presented as an E-poster at ASTRO, September 2019 [208]

Conception or design of the work: AAC, AMcW

Acquisition of data: AAC, MD, AMcW

Contouring of images: AAC

Analysis of data: AAC, AMcW, HM

Interpretation of data: AAC, AMcW, MvH,

Drafting and editing text: AAC, AMcW, MvH, AC, PH

.

Abstract

Introduction

During external beam radiotherapy (EBRT) for cervical cancer, large planning target volumes are required to account for potential pelvic organ motion during treatment. These large margins drive treatment toxicity. The introduction of online adaptive MR guided EBRT will enable plan adaption to daily anatomical position, minimising the impact of inter-fraction changes. Therefore, intra-fraction motion becomes the larger source of residual uncertainty.

Aim

This study assesses the magnitude and variation of intra-fraction motion at multiple points over an estimated treatment delivery time.

Methods

A prospective MR imaging study acquired scans on a 1.5T diagnostic scanner at 4 time-points over the course EBRT (45Gy/25#). 6 patients were included in this analysis. At each time-point, motion was captured with 5 alternating axial and 5 sagittal fast T2 Turbo Spin Echo sequences (acquisition time 1min), over approximately 10 minutes. Patients were instructed to empty their bladder and drink 300ml water prior to the scan.
The bladder, rectum and a target volume; uterus, cervix and gross tumour were contoured on the initial axial sequence by a single observer. Contours were propagated on the subsequent axial sequence using deformable registration and manually corrected (RayStation vr7.99). This was repeated in a stepwise manner. The mean distance to agreement (DTA), which is the mean of measuring the shortest distance for all points on one surface of one structure to another, was calculated for the target volume with reference to the initial axial sequence for each time-point. The standard deviation (SD) and maximum DTA was also calculated. A qualitative assessment of motion was also carried out as well as an estimation of motion in individual planes.

Results

The mean DTA was small with a mean of 0.04cm, however the maximum DTA was larger with a mean of 0.52cm. Bladder filling was the most important cause of motion, and tended to be a gradual change in motion. Rectal changes were less common but were unpredictable. Motion at the uterine fundus was predominately in the superior and

posterior direction and large motion was exclusively due to bladder filling. Motion at the uterine cervix was mainly due to bladder filling, motion was mainly anterior and posterior. Lateral motion was smaller than motion in other planes and motion at the cervix was smaller than motion at the cervix.

Conclusion

This is the most detailed assessment of intra-fraction motion during EBRT for cervical cancer. The mean of mean maximum DTA for all patients was 0.52cm, however site of maximum motion changed between time-points. This means that for fractionated radiotherapy, it is likely that this motion may not have a large impact, however for hypofractionated regimens strategies such as appropriate anisotropic margins or gating should be considered.

Introduction

The standard treatment for locally advanced cervical cancer is concurrent chemoradiotherapy followed by surgery [209]. Delivery of external beam radiotherapy is complicated by internal pelvic organ motion [97], which can lead to changes in position of the clinical target volume (CTV) both between and even during fractions of radiotherapy. This motion can be related to changes in bladder and rectal filling as well as random changes [210]. A variety of approaches have been developed to account for these changes including adaptive radiotherapy with a plan of the day approach based on changes in bladder filling [167]. The development of commercial MR linacs [82,83] will allow the development of true online adaption, to account for interfraction changes in CTV. However, these techniques are currently complex and as they increase the treatment time it increases the likelihood of changes in the CTV during radiotherapy delivery. Intrafraction motion is therefore an increasingly important component of residual uncertainty.

Intrafraction motion has not been widely assessed, previous studies have suggested that mean motion is small, less than 0.3cm but that for individual patients maximum motion may exceed 1cm [105,211–213]. The majority of previous work has assessed motion at two time-points, for example using changes on cone beam CT before and after treatment, with a timeframe of approximately 20 minutes [109]. This may miss changes that happen over a period of minutes and then revert, such as the passage of rectal gas.

The anatomical causes associated with motion have not been explored nor whether motion occurs gradually, for example, due to bladder filling or represents random change. There may be the potential to develop individual predications of intrafraction motion for each patient and therefore adjust the CTV to PTV margins to account for specific changes.

This study uses MR imaging to determine interfraction motion over 5 time- points across an estimated treatment delivery period of 10 minutes. This detailed analysis aims to provide information about the variation of intrafraction motion over time and between patients. A qualitative approach is also used to describe the causes of motion.

Methods

A prospective imaging study was performed (clinical trials.gov NCT03101306), in patients undergoing radical external beam radiotherapy (+/- chemotherapy and brachytherapy) for locally advanced cervical cancer. Patients were recruited between September 2017 and

November 2018. Ethics approval was obtained from the North West - Greater Manchester South Research Ethics Committee (17/NW/0300) and informed consent was obtained from all participants.

The 10 patients included in this analysis were treated with external beam radiotherapy (45Gy in 25 fractions) followed by brachytherapy, 9 patients also received concurrent cisplatin 40mg per m^2.

A research MR scan was carried out in the first week of treatment, with two further research MR scans performed between weeks 2-4. Patients were scanned on a 1.5T MRI scanner (MAGNETOM Aera; Siemens Healthcare, Erlangen, Germany). These scans were carried out in the treatment position with a flat couch top, and no anti-motility agents were administered. In the final week of treatment, patients had a standard of care scan with additional research sequences, on a standard couch top with IV hyoscine butylbromide. Patients followed a bladder filling protocol, drinking 300ml water 15 minutes prior and empting their bladder straight before each scan.

Scan sequences included a series to capture motion with 5 alternating axial and 5 sagittal fast T2 Turbo Spin Echo sequences (acquisition time around 1min), over approximately 10 minutes. These motion sequences were available for each of the 4 MR scans over the course of treatment. Therefore, a total of 40 series comprising a total of 200 individual sequences were contoured.

A primary CTV, comprising of the cervix, gross tumour, and entire uterus as well as the bladder and rectum were contoured by a single observer, AC, a senior clinical fellow in gynaecological clinical oncology. All images in each series were registered to the initial axial sequence using rigid registration to bone. Contouring was carried out on the initial axial sequence and contours were propagated using deformable registration using Raystation v6, Stockholm, Sweden followed by manual correction in a stepwise manner.

DTA, measures the shortest distance between the surface of one structure to the surface of another structure. DTA is calculated for all points on the reference surface to the closest point on the test surface. Figure 18 shows a schematic measuring the distance between every point on surface one to the nearest point on surface two. DTA produces a histogram

which can then be summarised into various measures. Mean DTA summarises these values into the mean and describes the mean change of the contour.

The maximum DTA is the largest distance to agreement between the reference and test surface.

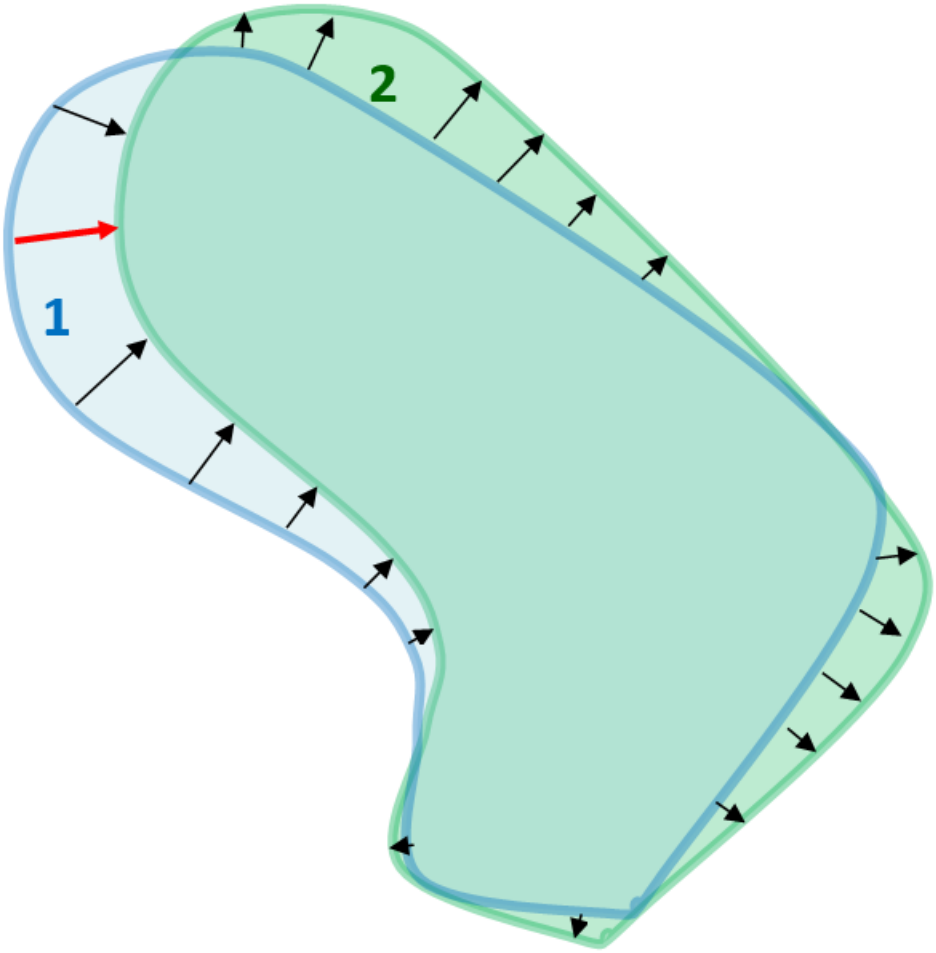


FIGURE 18 SCHEMATIC ILLUSTRATION SHOWING THE DISTANCE BETWEEN POINTS ON SURFACE 1 TO THE NEAREST POINT ON SURFACE 2. THE DTA IS CALCULATED ON A PER VOXEL BASIS. THE MAXIMUM DTA IS HIGHLIGHTED IN RED

Time-point one was set as the reference time-point and measured to each following time-point to allow investigations of the progression across time. The mean DTA, standard deviation (SD) of the DTA and maximum DTA was also calculated. The mean maximum DTA was calculated for each time point and the mean of the mean DTA was calculated for each patient, as well as the mean of the mean DTA across all patients. The mean and maximum DTA were plotted as bar graphs for individual patients to allow visualisation of changes over time.

Next, in order to assess motion of the CTV in different planes, an alternative methodology was implemented. Images within each timepoint were rigidly registered to the first timepoint using two regions of interest. The translations from the registration allows the motion in each direction to be assessed. For each of the uterine body and cervix, a clipbox focused the registration on this anatomical region allowing each to be considered separately. Each subsequent image for that timepoint was rigidly registered and the translations in each plane were recorded. Rotations were not permitted. Motion for each patient at each timepoint over 10 minutes was calculated.

Additionally, a qualitative methodology was applied to identify the area of the CTV which was main site of motion, and the causes of that motion. For each time-point, the five images were displayed in the sagittal plane at the mid uterine slice, both as still images as well as an animated gif. The CTV was contoured on the initial scan for each patient. The uterine fundus and cervix were considered separately and motion was classified as none, minimal or present. Minimal motion was a defined a visual change between images, estimated to be less than 2 mm. Motion present was defined as an obvious change between images, estimated to be greater than 2 mm.

Three causes of motion were seen during the qualitative assessment; bladder, rectal and small bowel changes. The predominant cause of motion was recorded as well as the site of greatest motion, which was assessed subjectively. For example if the bladder had increased in volume and the uterus had moved superiorly more than 2mm, this was recorded as superior motion of the uterus due to bladder filling. Another example is if the rectum has increase in size and the cervix has moved anteriorly less than 2mm, this was recorded as minimal anterior motion of the cervix due to rectal changes.

Results

10 patients were included in the analysis, with assessment of 5 scans at 4 time-points and a total of 200 contours. In one time-point it was not possible to assess motion at the uterine fundus because it was not included in the scan.

The patient details are shown in table 16.

Patient number	Histology	FIGO stage (2009)	Nodal status	ECOG Performance status	Differentiation	Maximum transverse tumour size (cm)
1	Squamous cell carcinoma	IIB	Positive	0	2 - Moderately differentiated	5
2	Squamous cell carcinoma	IB2	Negative	0	Not recorded	5
3	Adenocarcinoma	IIB	Positive	1	3 - Poorly differentiated	7
4	Squamous cell carcinoma	IIB	Negative	0	Not recorded	6
5	Squamous cell carcinoma	IIB	Negative	0	2 - Moderately differentiated	8
6	Adenocarcinoma	IB2	Negative	0	1 - Well differentiated	5
7	Undifferentiated carcinoma	IIB	Positive	0	3 - Poorly differentiated	6
8	Adenocarcinoma	IIB	Positive	1	1 - Well differentiated	3
9	Squamous cell carcinoma	IIB	Positive	0	3 - Poorly differentiated	5
10	Adenocarcinoma	IB2	Negative	0	3 - Poorly differentiated	6

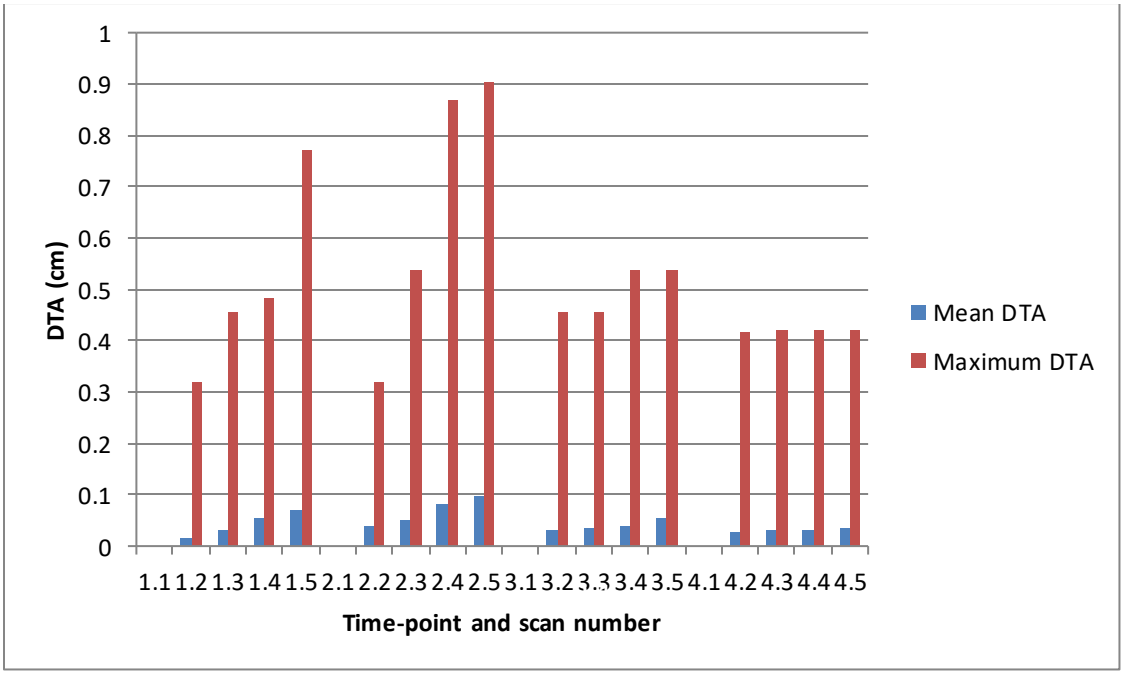
TABLE 16 PATIENT CHARACTERISTICS

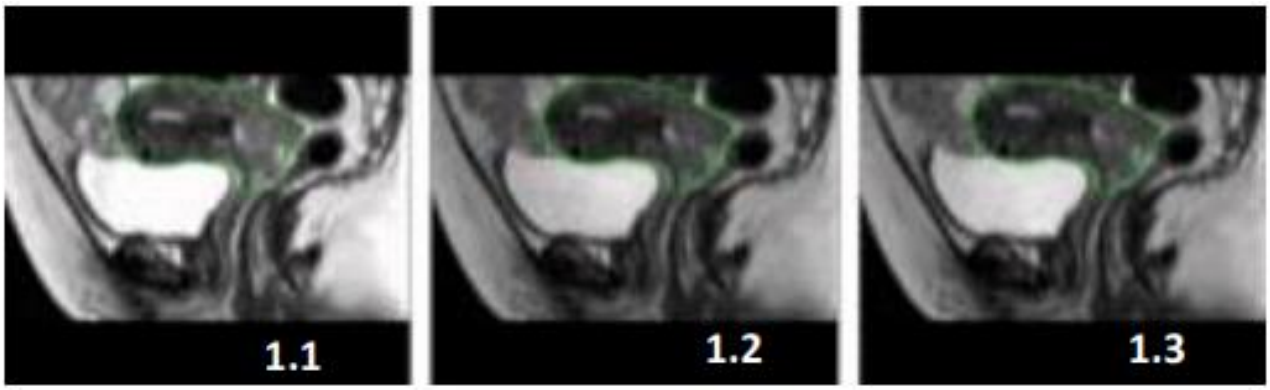
The mean DTA was small for all patients with a range of 0.01-0.15cm, median of 0.03cm, mean of 0.04cm and a standard deviation of 0.03cm. The max DTA was an order of magnitude larger with a range of 0.17- 1.27cm, highlighting the local extent of motion on a single scan. The median for all patients was 0.46cm, with an overall mean of 0.52cm and a standard deviation 0.24cm.

The mean of the mean max DTA of the individual time-points for each patient, ranged from 0.29cm to 0.67cm, with a SD of 0.11cm. This is important as it represents the average change from the intial scan for each time-point.

An example of motion for an individual patient (Patient 1) is shown in figure 19. This shows the mean and maximum DTA grouped by time-point, with each scan compared to the initial

one. This is shown with a sagittal slice of the final scan for each time-point with the contour of the initial scan overlaid (an animated gif is available in the supplementary material.) This highlights the different causes of motion and the patterns observed. At time-point 1, there is a steady increase in both the mean and maximum DTA, which is due to a progressive increase in bladder filling. At time-point 2, there was a gradual increase followed by a sudden rise in the maximum DTA due to changes in bowel gas. Smaller changes were seen at time-point 3 and 4, with the biggest difference in maximum DTA occurring between the first and second time-point. Animated Gifs for all patients are uploaded as a separate attachment to the thesis.





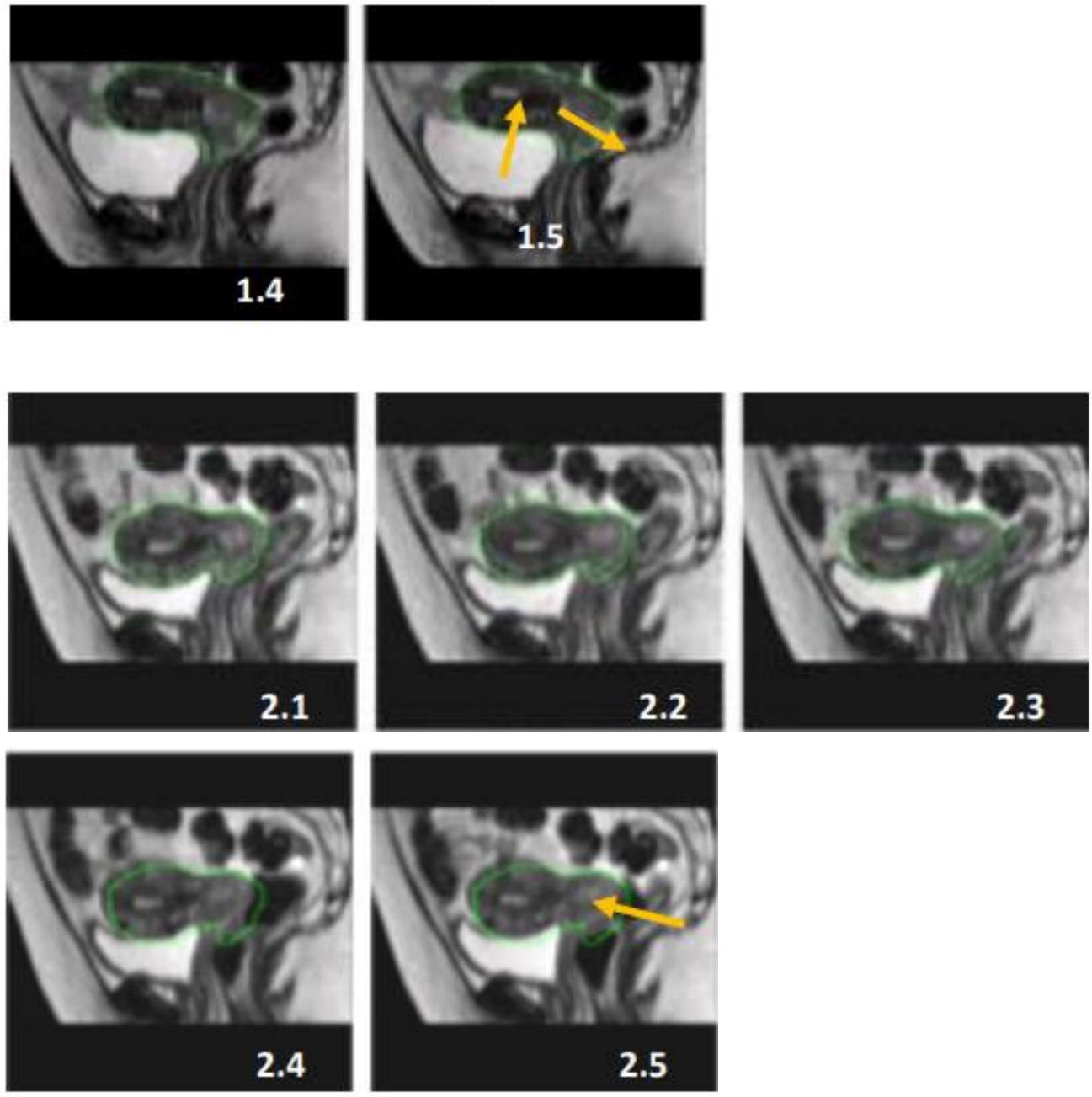


FIGURE 19 A bar chart with mean DTA in blue and maximum DTA in red separated by time-point for patient 1, the images are a single saggital slice of the scans at time point, with a contour based on the initial scan for each time-point. The yellow arrow highlights the direction of motion.

The maximum DTA over all time-points is shown for each patient with the box plot in figure 20. The motion in patient number 6 is smaller than other patients as the uterus is retroverted, meaning that there is minimal impact of bladder filling on uterine motion. The uterus of patient number 3 was in a midpoint position, and motion was still seen but was not related to bladder filling. The remainder of patients had an anteverted uterus. Motion greater than 1cm was seen in at one time-point in three patients and in three time-points in one patient. A max DTA greater than 1cm was related to bladder filling in all cases. The

outliers with a large maximum motion were generally from a single time-point, however for patient 10, the outliers were related to 3 different time-points. This was due to large motion related to bladder filling.

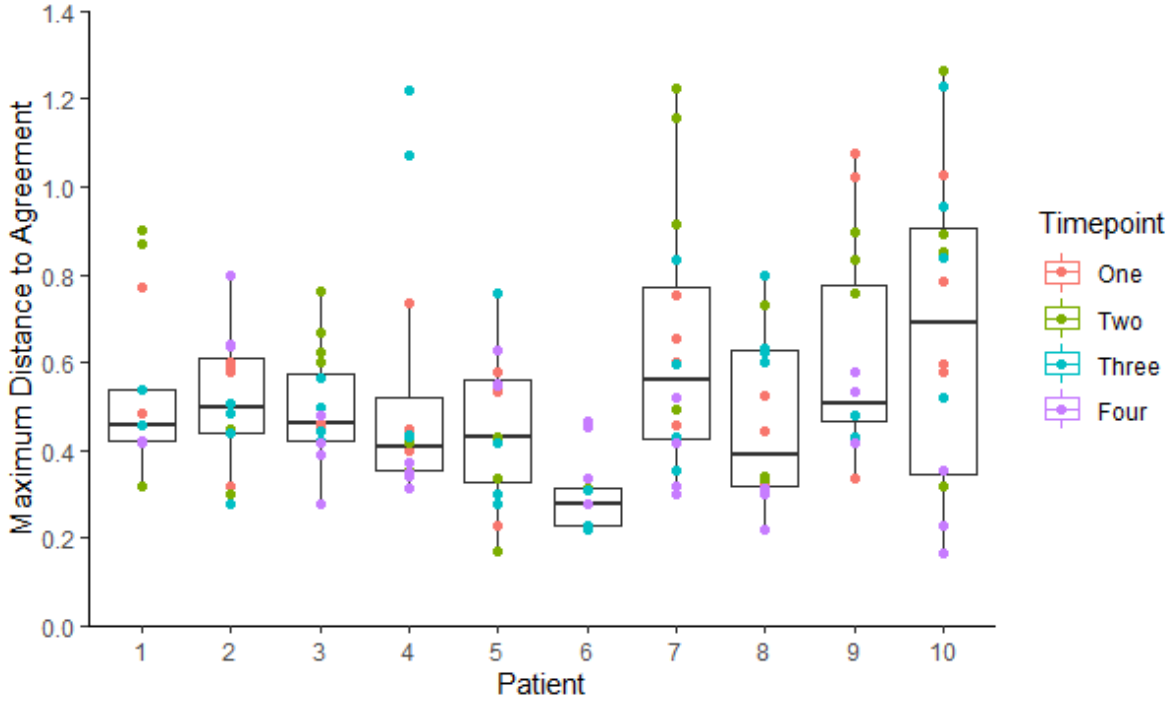


FIGURE 20 BOX PLOT OF MAXIMUM DISTANCE TO AGREEMENT BY PATIENT WITH COLOURS SHOWING DIFFERENT TIME-POINTS.

Intrafraction motion in individual planes

The motion in individual planes has been summarised for the cervix and uterus individually. The mean motion, standard deviation and maximum motion was recorded for the Anterior/posterior, Superior/Inferior and lateral planes for each patient. This is summarised in table 17.

Motion at the cervix for individual patients

	Lateral Mean (cm)	Lateral SD (cm)	Lateral Max (cm)	Sup/inf mean (cm)	Sup/inf SD (cm)	Sup/inf max (cm)	Ant/post mean (cm)	Ant/post SD (cm)	Ant/post Max (cm)
1	-0.01	0.01	-0.05	0.00	0.03	0.09	0.07	0.03	0.21
2	0.03	0.02	0.10	-0.03	0.02	-0.08	0.03	0.03	0.09
3	0.01	0.03	0.08	0.03	0.06	0.20	-0.07	0.08	-0.36
4	0.01	0.01	0.06	-0.01	0.02	-0.06	0.03	0.02	0.09
5	0.02	0.03	0.12	-0.02	0.09	-0.49	0.10	0.06	0.26
6	-0.02	0.04	0.11	-0.03	0.03	0.10	0.06	0.04	0.22

7	-0.03	0.02	-0.08	-0.02	0.07	0.22	0.16	0.06	0.40
8	-0.01	0.04	-0.23	-0.10	0.10	-0.47	-0.05	0.06	-0.24
9	-0.02	0.02	-0.08	0.01	0.05	-0.20	0.14	0.07	0.41
10	0.03	0.02	0.10	-0.08	0.05	-0.41	0.09	0.07	0.24

Motion at the uterus for individual patients

	Lateral mean (cm)	**Lateral SD (cm)**	**Lateral Max (cm)**	**Sup/inf mean (cm)**	**Sup/inf SD (cm)**	**Sup/inf Max (cm)**	**Ant/post mean (cm)**	**Ant/post SD (cm)**	**Ant/post Max (cm)**
1	-0.05	0.04	-0.19	-0.11	0.11	-0.35	0.09	0.08	0.25
2	-0.02	0.05	-0.26	-0.12	0.12	-0.45	0.11	0.11	0.40
3	0.03	0.03	0.11	0.04	0.04	0.11	-0.03	0.09	-0.23
4	0.02	0.02	0.06	-0.09	0.04	-0.24	0.05	0.03	0.08
5	0.03	0.04	0.13	-0.14	0.11	-0.54	0.03	0.05	0.20
6	-0.03	0.03	-0.13	-0.04	0.04	-0.10	0.03	0.03	0.08
7	0.01	0.07	0.17	-0.25	0.22	-0.96	0.17	0.14	0.52
8	0.05	0.05	0.19	-0.13	0.10	-0.48	-0.03	0.10	-0.23
9	-0.05	0.09	-0.35	-0.19	0.19	-0.69	0.23	0.17	0.56
10	0.06	0.06	0.23	-0.33	0.26	-0.99	0.18	0.14	0.54

TABLE 17 MOTION AT THE UTERUS AND CERVIX FOR INDIVIDUAL PATIENTS

Lateral motion is smaller than motion in other directions, both at the cervix and the uterus with the maximum lateral motion of – 0.35 cm seen at the uterus.

Superior/inferior motion was largest at the uterus with the largest maximum motion recorded as -0.99cm, the largest motion recorded for any patient in any direction. The maximum motion at the cervix was -0.49 cm in the superior/inferior plane.

Maximum mean lateral motion at the cervix was 0.03cm, superior/inferior motion was 0.10cm and anterior/posterior motion was 0.14cm. Maximum mean lateral motion at the uterus was 0.06cm, superior/inferior motion was 0.33cm and anterior/posterior motion was 0.11cm.

Qualitative assessment of motion

At the cervix, 11 time-points (28%) showed large motion, 14 (35%) showed minimal motion and the remainder, 15 (37.5%) no motion. In those with large motion, this was due to bladder changes in 8 cases, rectal changes in 2 cases and small bowel changes in 1 case. In patients with minimal motion, changes related to the rectum in 4 cases and the bladder in 10 cases. In those with large motion at the cervix, 10 patients had large motion at the fundus and in only one case, there was no motion at the fundus. In those cases with minimal motion at the cervix, 4 had large motion at the fundus, 4 had minimal motion at the fundus and 2 had no motion. In those with no motion at the cervix, 7 cases had large motion at the fundus, 4 had minimal motion and 4 had no motion. One patient had no motion at the cervix seen at any time-point (patient 4), 3 patients had minimal or large motion at all time-points, 3 patients had motion at 3 time-points, 3 patients had motion at 2 time-points. At the uterine fundus, 19 cases (48%) had large motion, which was due to bladder changes in all but one case, which was due to small bowel changes. There were 12 (30%) of cases with minimal motion, with 6 due to bladder changes, 2 to small bowel changes and 4 due to rectal changes. 8 cases had no motion and in one case it was impossible to assess. This is summarised in table 18.

Cervix	Number	Cause of motion	Number	Uterus	Number	Cause of motion	Number
Large motion	11 (28%)	Bladder Rectum Small Bowel	8 (20%) 2 (5%) 1 (2.5%)	**Large motion**	19 (48%)	Bladder Rectum Small Bowel	18 (45%) 0 1 (2.5%)
Minimal motion	24 (35%)	Bladder Rectum Small Bowel	10 (25%) 4 (10%) 0	**Minimal motion**	12 (30%)	Bladder Rectum Small Bowel	6 (15%) 4 (10%) 2 (5%)
No motion	15 (37.5%)	N/a	N/a	**No motion**	8 (20%)	N/a	N/a

TABLE 18 SUMMARY OF QUALATIVE MOTION ASSESSMENT AT THE UTERUS AND CERVIX.

The site of greatest motion was judged to be the cervix in 4 cases, the fundus in 20, both in 10 with no motion seen in 5 cases and not possible to assess in one case (as the fundus was not included in the scan.) Both the site and cause of motion can vary between time-points. The direction of motion at the cervix was posterior in 15 (38%), anterior in 7 (18%), superior anterior in 2 (5%) and superior in 1 (3%). At the fundus, motion was superior in 14 (35%), superior posterior in 10 (25%), posterior in 5 (13%), inferior in 1 (3%) and anterior in 1 (3%). These differences are due to the differential impact of bladder filling, the main cause of motion, which pushes the cervix posteriorly and the fundus superior and posterior. A full summary is shown in table 19.

Patient	Time-point	Motion at cervix	Cause	Direction	Motion at uterus	Cause	Direction	Greatest motion	Mean DTA	Max DTA
1	1	Minimal	Bladder	Posterior	Minimal	Bladder	Superior/ Posterior	Uterus	0.044	0.5
	2	Yes	Rectum	Anterior	Yes	Rectum	Superior/ Anterior	Both	0.067	0.7
	3	Minimal	Bladder	Anterior	Minimal	Rectum	Superior	Uterus	0.04	0.5
	4	Yes	Bladder	Posterior	Yes	Bladder	Posterior	Both	0.032	0.4
2	1	None	-		Yes	Bladder	Superior	Uterus	0.018	0.5
	2	None	-		Yes	Bladder	Superior	Uterus	0.04	0.4
	3	None	-		Yes	Bladder	Superior	Uterus	0.051	0.4
	4	Yes	Bladder	Superior posterior	Yes	Bladder	Superior posterior	Cervix	0.034	0.7
3	1	None			Minimal	Small bowel	Posterior	Uterus	0.029	0.4
	2	Yes	Small bowel	Anterior	None	None		Cervix	0.028	0.7
	3	Yes	Rectum	Anterior	NA	NA		NA	0.005	0.5
	4	None			Minimal	Small Bowel	Superior posterior	Uterus	0.019	0.4
4	1	None			Yes	Small Bowel	Superior	Uterus	0.033	0.6
	2	None			None				0.024	0.4
	3	None			Yes	Bladder	Superior	Uterus	0.036	0.8
	4	None			Yes	Bladder	Superior	Uterus	0.021	0.3
5	1	Minimal	Bladder	Superior	Yes	Bladder	Superior posterior	Uterus	0.044	0.4
	2	None			Minimal	Bladder	Superior	Uterus	0.032	0.3

	3	Yes	Bladder	Superior anterior	Yes	Bladder	Superior	Both	0.029	0.4
	4	None			None				0.03	0.6
6	1	Yes	Bladder	Posterior	None			Cervix	0.027	0.3
	2	None			None				0.033	0.3
	3	None			None				0.024	0.3
	4	Minimal	Bladder	Posterior	None			Cervix	0.022	0.4
7	1	Minimal	Rectum	Posterior	Minimal	Rectum	Posterior	Both	0.016	**0.6**
	2	Minimal	Bladder	Posterior	Yes	Bladder	Superior posterior	Uterus	0.102	0.9
	3	Yes	Bladder	Posterior	Yes	Bladder	Superior posterior	Uterus	0.061	0.6
	4	Minimal	Rectum	Posterior	Minimal	Rectum	Superior posterior	Both	0.017	0.4
8	1	None			Minimal	Bladder	Posterior	Uterus	0.043	**0.4**
	2	Minimal	Bladder	Posterior	Minimal	Bladder	Posterior	Uterus	0.048	0.5
	3	Minimal	Bladder	Anterior	Yes	Bladder	Superior	Uterus	0.101	0.7
	4	Minimal	Bladder	Anterior	None				0.027	0.3
9	1	Yes	Bladder	Posterior	Yes	Bladder	Superior posterior	Both	0.083	**0.7**
	2	Yes	Bladder	Posterior	Yes	Bladder	Superior posterior	Both	0.056	0.7
	3	Minimal	Rectum	Posterior	Minimal	Bladder	Inferior	Both	0.053	0.5
	4	Minimal	Rectum	Anterior	Minimal	Rectum	Anterior	Both	0.035	0.5
10	1	None			Yes	Bladder	Superior	Uterus	0.04	0.7

	2	Yes	Bladder	Posterior	Yes	Bladder	Superior	Uterus	0.072	0.8
	3	Minimal	Bladder	Posterior	Yes	Bladder	Superior	Uterus	0.042	0.9
	4	Minimal	Bladder	Posterior	Minimal	Bladder	Superior	Both	0.03	0.2

TABLE 19 QUALITATIVE ASSESSMENT OF MOTION AT THE UTERINE CERVIX AND FUNDUS WITH CORRESPONDING MEAN AND MAX DTA

Discussion

This is the first study to analyse the motion of the cervix and uterus in all planes on repeated scans over a 10 minute time period. This has shown that although the mean DTA is small, the maximum DTA can be greater than 1cm. This has implications for margins and coverage of the CTV during treatment. The qualitative assessment also allowed for description of the causes of motion, which is important to decide the best strategies to address them. The qualitative study that described the causes of motion was complemented by a quantitative study using local rigid registration where it was not possible to determine the cause of motion.

In this study, bladder filling had the biggest impact on motion with rectal changes and small bowel changes being uncommon, although they could have a large impact especially at the cervix when they occur. Both Hejikoop [109] et al and Kerkhof [212], showed that bladder filling had a moderate correlation with displacement of the uterus and cervix. Neither of these studies looked specifically at motion at different parts of the CTV. This is in contrast to interfraction motion, where rectal changes are a more important cause of motion at the cervix (see chapter 3). Changes due to bladder filling often occur gradually and are therefore potentially predictable, rectal changes however can be large and unpredictable. The overall mean DTA over all patients provides a possible estimate for the margin required to ensure CTV coverage. In this study it was 0.52 cm, suggesting a 5 mm margin would be reasonable to account for intrafraction motion. This may however be an overestimation as it is based on the assumption that the maximum motion occurs at the same place in each fraction of treatment and this is not the case. It is however in line with recommendations from previous studies. Chan et al assessed motion at points along the uterine canal on a sagittal slice with motion over 30 minutes. The suggested margins were in the region of 5mm at the cervix and 10mm at the fundus. A further study by Visser et al, used scans taken over 10 minutes to assess CTV coverage based on a daily plan, recommended a 5 mm margin to ensure adequate CTV coverage [158].

Limitations of the study include the duration of the motion sequence, which at 10 mins may be less than the time needed to plan and deliver a radiotherapy fraction. However, using an online adaptive approach, following treatment planning and prior to delivery, a scan to ensure coverage is taken and final corrections are made if required. Most of the motion

occurs gradually and is in agreement with previous studies. It would be reasonable to extrapolate from the data seen to a longer time frame. There were also a relatively small number of patients included however there were 40 time-points overall, with a total of 200 scans, providing information about a range of different patterns of motion.

Further assessment of management in each plane showed that lateral motion was smaller than the motion in other planes for both the uterus and cervix. Maximum motion at any point was less than 1cm at the uterus and 0.5cm at the cervix. This suggests that anisotrophic margins could be used, with different margins at the cervix and uterus.

This work suggests that intrafraction motion is not negligible but that because location of maximum motion varies between time-points, it is likely that impact in fractionated radiotherapy will be less important than that suggested by the mean mean DTA. Due to the small sample size it was not possible to meaningfully assess if motion at the first fraction predicted motion at further fractions. Using a similar MRI sequence would allow an assessment of potential intrafraction motion. This could potentially be used to develop individualised margins, for example in this study, patient 6 had a retroverted uterus, and intrafraction motion was small at every time-point.

As with interfraction motion, in the majority of patients the greatest motion is seen at the fundus and in patients without fundal involvement, the impact of underdosage in this area may be minimal. The EMBRACE 2 protocol allows underdosage of the fundus by up to 5 Gy during external beam radiotherapy, as there is contribution of dose from brachytherapy [176]. There has been investigation of excluding the fundus from the CTV in cases where there is no tumour infiltration with a small retrospective study, suggesting that this is a safe approach [80].

Strategies to manage intrafraction motion, especially in cases of hypofractionation, where it is more important, include adding a global margin or predicting the direction of motion and anisotropic expansion of the margin superiorly at the fundus. This approach could help to manage predictable motion due to bladder filling, but for unpredictable changes such as rectal motion, gating may be an appropriate approach.

Conclusion

This study provides the most detailed assessment of intra-fraction motion for cervical cancer in the literature. As contouring reproducibility improves and adaptive techniques account for interfraction motion, the impact of intrafraction motion will become the dominant source of uncertainty.

The mean of the mean max DTA at each time-point gives a conservative estimate of the margin required to cover the CTV with a mean value of 0.52cm. This assumes that maximum motion will occur in the same place during every fraction, however as shown in this study, this is not the case. This means that with standard conventionally fractionated radiotherapy, it is unlikely that such a large margin would be required. For hypofractionated radiotherapy, especially stereotactic ablative body radiotherapy (SABR), it is important to consider the impact of this motion. Potential solutions include appropriate margins, the use of gating or an approach to estimate and account for potential changes.

Chapter 5

Palliative radiotherapy to the pelvis for gynaecological cancer

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This work was presented as an E-poster at the British Gynaecological Cancer Annual Scientific Meeting.

Conception or design of the work: AAC, AC, PH

Acquisition of data: AAC, JK, JL, LB, KH

Data collection: AAC, NA

Analysis of data: AAC

Interpretation of data: AAC

Drafting and editing text: AAC, AMcW, MvH, AC, PH

Abstract

Aims

To assess the efficacy and tolerability of modern palliative radiotherapy to the pelvis for advanced gynaecological tumours.

Background

Palliative radiotherapy to the pelvis can be used to treat the symptoms of gynaecological cancers including pain, bleeding and discharge. However, unlike curative treatment, there is no standard dose or fractionation schedule, with patients having between one to five weeks of radiotherapy. This is a single institution retrospective audit of the outcomes of modern palliative pelvic radiotherapy. Palliative radiotherapy is a potential for the first stage of developing MR guided radiotherapy for gynaecological malignancy

Methods

114 patients with cervical, endometrial, vulval or vaginal cancer treated with palliative radiotherapy to the pelvis from 2013 to 2017 were identified. Data including patient characteristics including disease site, stage, PS, comorbidities, clinician reported symptoms, toxicity and radiotherapy details were collected retrospectively.

Results

The median age was 75 (27-98) years. 73 (64%) had PS 2 or greater. 68 (60%) were ineligible for radical radiotherapy due to disease or technical factors, in the remainder palliative treatment was delivered due to poor performance status or comorbidities. 23 (20%) had vulvar cancer, 42 (37%) had cervical cancer, 3 (3%) vaginal cancer and 46 (40%) had endometrial cancer. 105 (91%) of patients were symptomatic, 78 (68%) had bleeding, 62 (54%) pain and 26 (23%) discharge. 15 (13%) received 20 Gy in 5 fractions, 38 (33%) 28-30Gy in 10 fractions and 61 (54%) 35Gy in 15 fractions.

111 (97%) completed their radiotherapy. 28 (25%) experienced grade 2 or higher acute clinician reported toxicity. 88 (83%) of initially symptomatic patients had a clinical response to treatment. The median overall survival from start of radiotherapy was 8 months, with just over 10% of patients alive at 3 years. In 90% of patients receiving palliative treatment including an intact uterus, field length was less than 18cm.

Conclusions

Radiotherapy is an effective and generally well tolerated palliative treatment, even in those with poor performance status. The results of this audit will help support the development of a protocol for palliative radiotherapy for gynaecological cancer using the MR linac.

Background

Palliative radiotherapy for gynaecological cancer is an important treatment modality for patients who are unsuitable for curative treatment. Metastatic disease at presentation is relatively rare [17], however patients may not be able tolerate standard treatment or have disease which results in overlap with previous radiotherapy fields. Patients commonly present with symptoms such as bleeding, pain, discharge as well as bowel and urinary symptoms.

Radiotherapy is generally very effective in reduction of symptoms, at least in the short term [214]. One study, using extreme hypofractionation and 2D planning techniques led to high rates of late toxicity [215], but modern regimens are generally well tolerated [216]. There is no standard dose and fractionation schedule [191] recommended for palliative radiotherapy in gynaecological cancers. A variety of regimens have been reported in the literature, varying between weekly hypofractionated schedules [193] to 'radical' chemoradiotherapy followed by brachytherapy for patients with metastatic cervical cancer [217]. The current local treatment regimen of 35Gy in 15 fractions has not previously been reported in the literature, although a similar but slightly more hypofractionated regimen was used for palliative treatment of patients with bladder cancer and found to be equivalent to 21Gy in 3 fractions [218].

There is little evidence, based on small retrospective case series, to support different schedules and in patients with a limited life expectancy, seven weeks of treatment including brachytherapy is potentially very burdensome. An analysis of the SEER database, seemed to suggest a survival benefit with the use of radiotherapy in patients with metastatic cervical cancer [186]. However, this study included radiotherapy to any site of disease and also did not account for the guarantee time bias, in which patients who received radiotherapy have lived longer allowing them to receive more treatment [187]. Chemotherapy is also an important component of treatment in patients with metastatic disease, with a combination of a platinum based chemotherapy and paclitaxel commonly used [185,219]. There is no guidance to support the timing of treatment and many patients with a performance status of 2 or greater will not be fit for chemotherapy.

Palliative radiotherapy is a possible model for treating patients with gynaecological malignancies using MR guided radiotherapy as the field length is likely to be shorter and therefore will fit within the limited field lengths of an MR linac.

This single centre retrospective audit will evaluate the toxicity and benefit of palliative radiotherapy for gynaecological malignancies, including the potential for MR guided treatment.

Methodology

This is a retrospective audit, which has received institutional approval by the Quality Improvement and Audit Committee, The Christie NHS Foundation Trust (reference 19/2407). Patients were identified using electronic records including the Clinical Web Portal, a locally developed electronic database which contains prospectively recorded information including blood test results, treatment delivered, treatment outcome and clinician reported toxicity. Data was cross referenced with information from the radiotherapy management system; MOSAIQ, Elekta AB, Stockholm, Sweden.

Searches were carried out to identify patients with cervical, endometrial or vulvar cancer, who received a palliative radiotherapy fractionation (defined as less than either less than 40Gy or fewer than 20 fractions) who received radiotherapy and had FIGO (2009) stage 4B disease at palliation. Patients who received radical treatment, for example, an external beam boost were excluded. Patients were identified who received treatment between 2013, when the electronic record system (CWP) was developed and 2017, to allow for at least one year of follow up.

Details collected including patient demographics, performance status, symptoms and comorbidities; tumour details including histology, site, size and stage. Radiotherapy details were recorded including site, dose and fractionation as well as details of previous and subsequent treatment. The length of the radiotherapy field was recorded for patients treated from 2016-2017 as prior to this radiotherapy plans were not available electronically. Objective and subjective treatment response, toxicity details, both late and early and overall survival were collected. A retrospective assessment was made as to whether radical radiotherapy was technically possible, with disease that could be covered in a radical plan and was not precluded by contraindications such as previous pelvic radiotherapy.

Descriptive statistical analysis was carried out using R v3.61, including Kaplan Meier survival assessment.

Results

114 patients who received radiotherapy with palliative intent to both the primary and metastatic disease within the pelvis were identified. Their characteristics are outlined in table 20. Median follow up time using the reverse Kaplan Meier method was 3 years 10 months.

		Number of patients (percentage)
Tumour site	Cervical	42 (37%)
	Endometrial	46 (40%)
	Vulvar	23 (20%)
	Vaginal	3 (3%)
Performance status	0	15 (13%)
	1	26 (23%)
	2	33 (30%)
	3	38 (33%)
	4	2 (2%)
Metastatic disease	Yes	50 (44%)
	No	64 (56%)
Symptomatic	Yes	105 (91%)
	No	9 (9%)
Symptoms present *(patients may more have than 1 symptom so percentage doesn't add up to 100)*	Bleeding	78 (68%)
	Pelvic pain	62 (54%)
	Discharge	26 (23%)

TABLE 20 PATIENT CHARACTERISTICS

The median age was 75 (27-98) years with the majority of patients, 73 (64%) having a PS 2 or greater. The majority were symptomatic with bleeding being the most common symptom.

15 (13%) of patients were treated with 20Gy in 5 fractions, 38(33%) patients received 28-30Gy in 8-10 fractions and the remainder, 61 (54%) 35Gy in 15 fractions. 40 (46%) of patients received palliative treatment even when radical radiotherapy was technically

possible. In the majority of cases this was due to performance status. One patient declined surgery or radical radiotherapy and four patients had a synchronous metastatic lung cancer. Two patients had previously had pelvic radiotherapy overlapping with the proposed treatment field.

Radiotherapy field length was available for 44 patients (37%). The mean field length was 13.5cm, median 12.6cm with a minimum of 7.3cm and a maximum 31.6cm (this included treatment of the lumbar spine.) This included all patients who received palliative treatment to any pelvic site. In those whose treatment was centred on an intact uterus, 20 patients, mean field length was 14cm, median was 13.6cm. In only 2 of 20 patients (10%), did the field length exceed 18cm, in one case due to inclusion of the lumbar spine and in the other because of extensive vaginal disease. Of these 20 patients, 13 had a PS 0-2.

111 (97%) of patients completed radiotherapy, the remaining 3 patients did not complete treatment due to progressive disease leading to a general deterioration. 6 (5%) patients had died before assessment of treatment and 10 (9%) of patients did not receive any symptomatic benefit. Amongst patients with vaginal bleeding, 60 patients had a complete response, 13 had a partial response, 2 were not assessed, 5 died prior to assessment and 1 patient had no response. This is summarised in table 21.

		Number of patients (percentage)
Symptomatic response to treatment	Asymptomatic	9 (8%)
	No response	10 (9%)
	Died prior to assessment	6 (5%)
	Not assessed	2 (18%)
	Response (at least partial)	88 (77%)

TABLE 21 SYMPTOMATIC RESPONSE TO TREATMENT

Acute toxicity was prospectively recording by clinicians although data was missing for 6 patients. Gastrointestinal toxicity was the most common with 34 patients experiencing grade 1 toxicity, 16 grade 2 and 4 grade 3. 14 patients had grade 1 urinary toxicity, 2 had

grade 2 and 2 grade 3. Other toxicity recorded included fatigue in 6 patients (grade 1-2), nausea grade 2 in 2 patients and grade 2 vomiting in 1 patient. 14 patients treated for vulvar or vaginal cancer experienced grade 2 or above skin toxicity.

Median overall survival was 8 months with just over 10% of patients alive at 3 years post completion of radiotherapy. 22 (19%) patients survived less than 3 months following the completion of treatment, see figure 21.

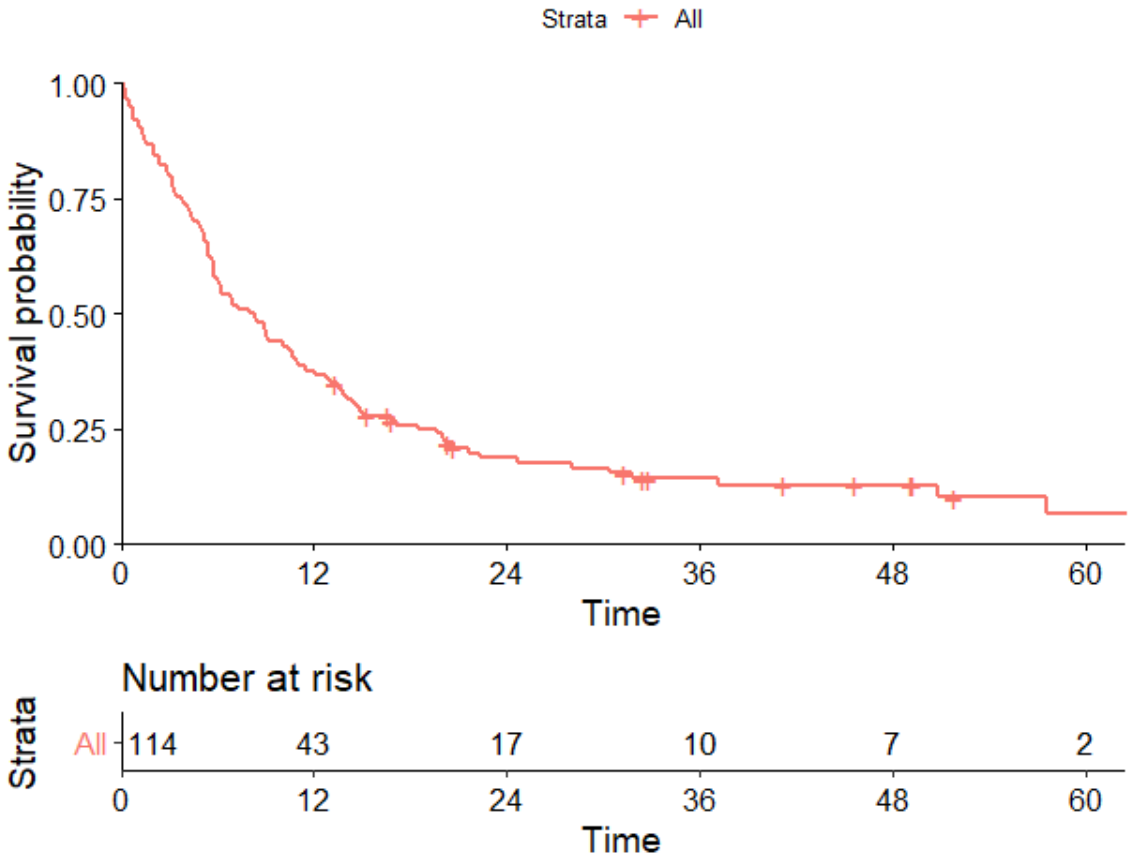

FIGURE 21 KAPLAN MEIR CURVE SHOWING PATIENT SURVIVAL FOLLOWING RADIOTHERAPY

Due to the small numbers and heterogeneity of the patient population, formal multivariable analysis was not performed.

However, two specific subgroups of interest were examined. The first was the patient group who were technically suitable for radical radiotherapy but were not treated as they were considered unfit. This group could potentially benefit from higher dose palliative schedules if their life expectancy is long enough. This group included 40 patients and their median overall survival was 13.6 months with 95% confidence intervals of 6.2 – 28.1, although as

the number is small the 95% confidence intervals are large. This also includes a small number of long-term survivors. See figure 22.

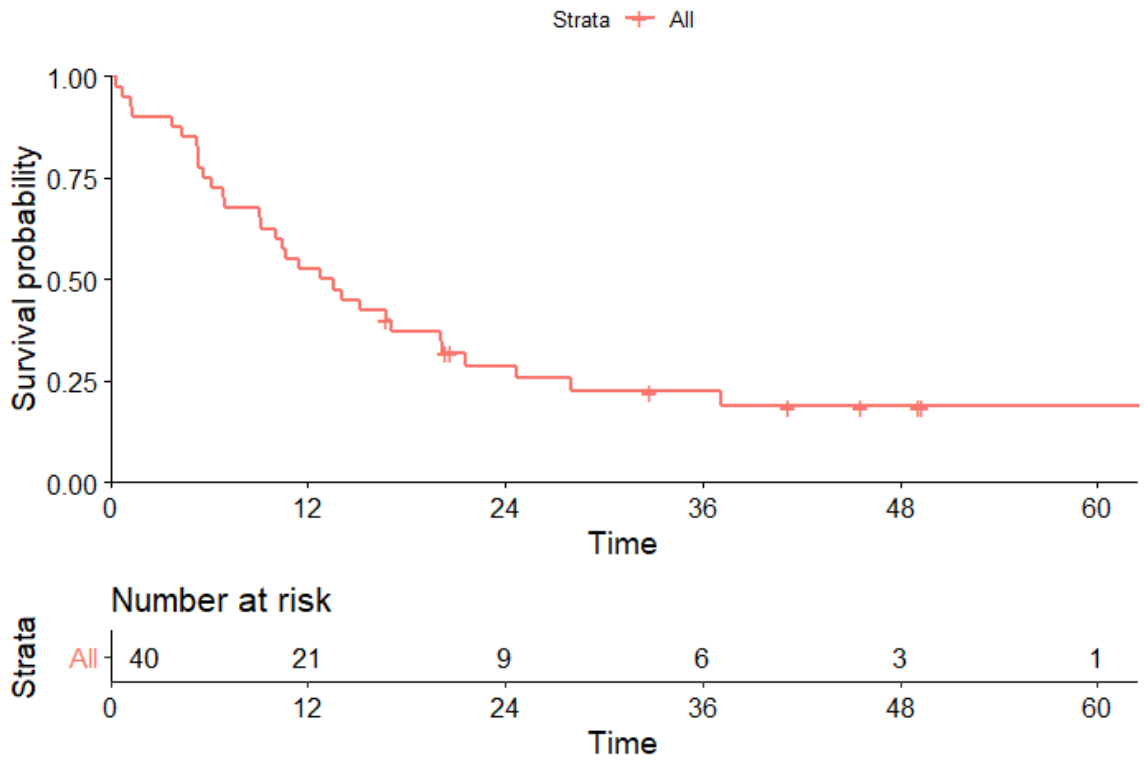

FIGURE 22 PATIENTS TECHNICALLY SUITABLE FOR RADICAL RADIOTHERAPY

The other subgroup analysed was patients treated with the 35Gy/15# schedule. This is an unconventional fractionation, that is specific to the institution and it is unclear if there is any benefit compared to conventional fractionation regimes. This analysis was confined to response and toxicity as overall survival would be very susceptible to selection bias, with fitter patients being selected for the longer treatment regimen.

Symptomatic response assessment was compared between 35Gy/15#, 28Gy/10#, 30Gy/10# and 20Gy/5#. EQD2 (equivalent total doses in 2-Gy fractions) for the tumour was calculated assuming a α/β ratio of 10. Patients who were asymptomatic were excluded and those who died before response assessment were considered not to have responded. This analysis was repeated excluding patients who died before response assessment, as this may also reflect selection bias. This repeat analysis suggests that there is little difference in overall response between patients who received 30Gy/10# and 35Gy/15# in this retrospective series, with 85% of patients responding to 30Gy/10# and 86% of patients responding to 35Gy/15#. See table 28.

		Including patients who died prior to response assessment		Excluding patients who died prior to response assessment	
	EQD2 (α/β = 10)	No response	Response	No response	Response
20Gy/5#	23Gy	5	8 (0.62)	4	8 (0.67)
28Gy/10#	30Gy	3	5 (0.625)	1	5 (0.83)
30Gy/10#	32.5Gy	6	23 (0.79)	4	23 (0.85)
35Gy/15#	36Gy	8	50 (0.86)	8	50 (0.86)

TABLE 22 SYMPTOMATIC RESPONSE TO TREATMENT

Acute toxicity was also compared for different dose fractionations (see table 23 and 24). This suggests that acute gastrointestinal toxicity may be higher in patients treated with a 35Gy/15# regimen compared to 30Gy/10# with little difference in urinary toxicity. The 30Gy/10# group contained a higher proportion of patients with vulval cancer, 9 patients (31%) compared to 4 patients (7%) in the 35Gy/15# cohort.

	EQD2 (α/β = 10)	Nil	G1	G2	G3	Any	G2 and above
20Gy/5#	23Gy	11	1	2	0	3 (0.21)	2 (0.14)
28Gy/10#	30Gy	6	2	0	0	2 (0.25)	0 (0)
30Gy/10#	32.5Gy	15	7	3	1	11 (0.42)	4 (0.15)
35Gy/15#	36Gy	21	24	11	3	38 (0.64)	14 (0.24)

TABLE 23 ACUTE GASTROINTESTINAL TOXICITY

	EQD2 (α/β = 10)	Nil	g1	g2	g3	Any	g2 and above
20Gy/5#	23Gy	13	1	0	0	1 (0.07)	0 (0)
28Gy/10#	30Gy	7	1	0	0	1 (0.13)	0 (0)
30Gy/10#	32.5Gy	21	1	1	1	5 (0.19)	2 (0.08)
35gy/15#	36Gy	48	10	0	1	11 (0.19)	1 (0.02)

TABLE 24 ACUTE URINARY TOXICITY

Discussion

This is the largest reported series of palliative gynaecological radiotherapy in the literature. The majority of patients completed palliative radiotherapy and experienced a symptomatic response. The response rate and overall survival recorded are consistent with those reported in other series [214,216]. Rates of acute radiotherapy side effects were relatively low, however they are likely to be under reported as no patient reported outcomes were recorded. Other limitations of this data were the poor recording and assessment of both objective response and toxicity. This is a common problem with the reporting of palliative series as patients may be frail and often do not receive follow up at the treating centre. It was not possible to accurately assess the duration of response or late toxicity. A high proportion, almost 20%, of patients died within 3 months of treatment and it is important to balance the potential benefits and toxicity of treatment, including time spent in hospital. The regimen of 35Gy/15# is a unique schedule, which is specific to the institution. Any comparisons are susceptible to bias as this is a heterogenous non-radomised case series. However, there was no difference in symptomatic response compared to 30Gy/10# (once patients who had died prior to assessment were excluded.) The raw data also suggest a possible increase in acute gastrointestinal toxicity although there are a number of potential confounding factors including the different case mix. There may also be differences in toxicity patterns, with toxicity during shorter regimens potentially being under reported if it occurred when patients had finished treatment. This case series does not provide any evidence that 35Gy/15# has any benefits over 30Gy/10# in terms of response or toxicity. There could be potential benefits, including improved durability of response or reduced late toxicity but it was not possible to assess this. The impact of additional treatment time should also be considered in patients with limited life expectancy and there is the EQD2 is only slightly higher in the longer fractionation.

A prospective randomised study could be carried out to compare the moderately fractionated regimen, 30Gy in 10 fractions, with a more 'radical' approach in fit patients with low volume metastatic cervical cancer, for example chemoradiotherapy 45Gy in 25 fractions with or without brachytherapy. Less fit patients could be randomised to 30Gy in 10 fractions or an extreme hypofractionated approach for example 21Gy in 3 fractions over a week. Patients who were considered unfit for radical radiotherapy, without metastatic

disease, had a median overall survival of over 1 year. They could potentially benefit from improved radiotherapy techniques to reduce toxicity and increase local control. Unfortunately, the radiotherapy field length was only readily available for just over a third of patients, however these were those who received treatment most recently, from 2016-2017, and are therefore likely to represent current practice. In the majority of cases, the radiotherapy field length was less than 18cm. MR guided palliative radiotherapy could lead to improved techniques, including an online daily adaption. This would allow a reduction in margins and therefore a potential reduction in toxicity. This could also facilitate increased hypofractionation or an increase in dose.

Although all patients could potentially benefit from treatment using the MR-Linac, those receiving radiotherapy targeted on the intact uterus would also provide a useful starting point to develop techniques to treat radical patients. This coincides with the approach suggested in the R –ideal framework , which suggests the initial use of new techniques in a cohort of palliative patients [194].

There are potential difficulties associated with this approach as MR guided treatment is likely to take longer than conventional radiotherapy and MR scans can be difficult to tolerate. However patients who are selected for treatment using an MR linac generally tolerate it well, with noise being the biggest problem [90]. The number of patients identified with an intact uterus and treatment fields suitable for the MR linac and a performance status of 2 or less was relatively small, with 11 identified over 2 years. A multi-centre approach, treating patients with radiotherapy focussed outside the uterine fundus or treating both palliative and radical patients would increase the numbers eligible.

Conclusion

This work has shown that palliative radiotherapy for gynaecological cancer is an effective treatment with low recorded toxicity rates. Palliative radiotherapy for gynaecological cancer is a potential first indication for treatment using the MR linac, although patient numbers are relatively low.

More broadly this study could also provide the background for a prospective study of palliative radiotherapy for gynaecological treatment to provide further evidence in this under researched area. Improving and standardising palliative radiotherapy may be increasingly important in the era of drug – radiotherapy combinations.

Chapter 6
The optimal workflow for adaptive radiotherapy for cervical cancer

Conception or design of the work: AAC

Drafting of text: AAC

Editing text: AAC, AmcW, AC

Locally advanced cervical cancer is an ideal candidate for adaptive external beam radiotherapy techniques. The primary CTV is mobile, the treatment field is large and radiotherapy is associated with high rates of late toxicity despites improvements due to image guided brachytherapy. Dose reduction to the organs at risk has been shown to reduce toxicity in multiple clinical studies [176,220,221].

There are now a variety of possible adaptive strategies including library plan of the day selection and full online adaption utilising both CBCT and MR. Many practical challenges remain with current systems, including treatment delivery times and accurate auto-contouring, however this is a rapidly advancing field. It is likely that the optimal workflow will change within the next 5 – 10 years as these issues are resolved.

Ideally, any innovative radiotherapy techniques should be assessed using an approach such as the R-ideal framework. Where this is not possible, routine collection of standardised response and toxicity data, alongside increased use of PROMs, should provide some support for the use of these techniques. There may be potential for these techniques to be included as part of the Embrace 2 study [176] as well as technology specific prospective cohort studies such as Momentum[222].

The ALARP principle, as defined in Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) also recommends that 'doses to non-target volumes and tissues must be as low as reasonably practicable and consistent with the intended radiotherapeutic purpose of the exposure.' It is vital to monitor techniques which may reduce dose to CTV as there are examples where this has led to local or marginal failures[223]. This risk may be less in patients with cervical cancer, as due to the developments in image guided brachytherapy, isolated local relapse is rare[224], although an interesting study has suggested that reduced coverage of pre-treatment PET hot spots at brachytherapy was linked to increased risk of distant recurrence[225].The risk of nodal recurrence is higher than local , however as adaptive techniques target the primary CTV rather than nodal CTV they may not improve treatments in this region. This is consistent with the change from conformal to IMRT/VMAT which reduced the overall treated volume as shown in the EMBRACE cohorts. This has

allowed extension of nodal fields to include the para aortic area for selected patients without increasing volume and treated areas. [226,227]

As the technology improves and automation increases it is likely that these new techniques will be more widely adopted. An example is the use of IMRT and VMAT, once reserved for complex cases is now considered for the use in even palliative treatments [228]. In some cases, it more time efficient to use new rather than traditional techniques.

It should also be considered that there are other ways that may reduce the treated volume or doses to organs at risk. Proton therapy has been shown to reduce doses to organs at risk in planning studies, but changes in pelvic gas, weight changes, interfraction and intrafraction motion could impact delivered dose distributions [154,229,230]. Other options to reduce treated volume include training to standardise contours as well as changes to the CTV [79] to reduce areas that are less likely to be involved such as the uterine fundus. The EMBRACE protocol defines a HR CTV (including the tumour and whole cervix) as well as a larger intermediate CTV (including the whole uterus, parametrium and 2cm of vagina) [176]. This intermediate risk CTV could be altered to exclude the uninvolved uterine fundus. Improvements in adaptive radiotherapy may support safe alteration of the CTV.

Small incremental benefits can also add up to larger benefits at a population level and techniques may also disproportionately benefit individual patients even if the overall benefit is small.

In this chapter, I will discuss the benefits and disadvantages of the current available online adaptive radiotherapy strategies based on published data as well as the work presented in this thesis. I will also highlight potential solutions that could increase the feasibility of each approach and the benefits of the different image guidance systems.

As adaptive techniques improve, the impact of interfraction motion will decrease, increasing the importance of contouring accuracy as well as intrafraction motion. There is a trade-off between the complexity of the technique, the time it takes to deliver and the need for rapid manual re-contouring, with the risk of inaccuracy. The limited field size of the current MR

linacs is also a barrier to treatment for many patients with locally advanced cervical cancer[9].

I will initially describe each approach, with the current and potential workflow and then compare them with reference to which is likely to be most suitable for use on the MR linac.

The evidence for any adaptive technique

There is evidence from multiple studies that external beam radiotherapy for cervical cancer without accounting for motion either using an ITV or adaptive techniques leads to under-treatment of the CTV for a number of patients [97,111,152,231] [133,134]. All adaptive techniques improve coverage of the CTV whilst maintaining or reducing coverage to the organs at risk. The uterine fundus is the most mobile part of the uterus and therefore most likely to have reduced dose [97]. The impact of this is still uncertain, as brachytherapy contributes an estimated 5Gy to the dose to the uterine fundus [176].

There have also been a small number of dosemetric studies, which have shown in general, that adaptive radiotherapy can led to a reduction of dose to organs at risk [119]. The optimal way to calculate dose to organs at risk is controversial, requiring handling OAR movement across the treatment fractions. It is difficult to calculate it accurately, as even with deformable registration, uncertainties remain. Other options include summing the daily delivered dose to the OARs or assessing dose to the OARs on the planning scan, but this doesn't fully represent the delivered dose [232,233].

More advanced techniques have been shown to allow the safe use of smaller margins[133–135]. The benefit varies between individual patients, with some experiencing very large benefits. There are currently limited methods to select these patients before radiotherapy to make the best use of resources [165]. These techniques are described below, it is difficult to quantify the benefits as multiple different methodologies and comparisons are used.

Standard approach

The current standard approach, which must be considered a baseline to compare techniques is either a standard margin CTV-PTV margin around the primary CTV, usually

between 1 – 2 cm or an ITV approach, which either formally or informally, considers changes in primary CTV positions on different diagnostic or planning scans i.e PET scan, MR (diagnostic or planning) scan and radiotherapy planning CT. An individualised CTV to ITV margin is added, with the largest margin covering areas of potential position change and then a standard ITV to PTV margin is included. Although the use of an ITV, may ensure that CTV coverage is maintained, it can increase doses to organs at risk as the treated volume is greater. A recent abstract, assessed dosemetric coverage on weekly CBCT for 5 weeks, using a variety of adaptive techniques. CTV coverage was maintained even with a standard margin approach, in contrast to previous studies. In this case the ITV approach actually increased dose to the OARs, although the differences were small, with the largest a 12% increase to the bladder V40Gy [234].

In all cases, a bladder filling protocol is recommended, and some centres also implement daily enemas or laxatives at the start of treatment [111]. Daily CBCT is considered standard, with online review by radiographers and correction of bowel, bladder filling and appropriate shifts to ensure adequate CTV coverage. There may be significant time delays if patients cannot be treated following the initial CBCT and need to get off the treatment couch to change their bowel or bladder filling. Ultrasound bladder scanning has sometimes been used to reduce the need for CBCT by checking patient's bladder filling prior to treatment[97,111].

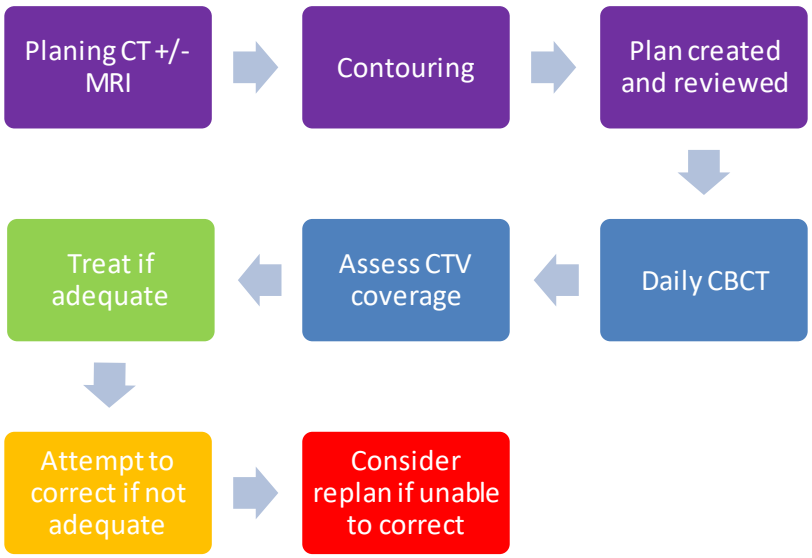

FIGURE 23 STANDARD RADIOTHERAPY PATHWAY

A variation of this strategy is to build in a set replanning strategy, with a variety of options either replanning at a set time point such after two weeks or reserving replanning for those who need it. This can either be done on a geometric or dosimetric basis. Replanning may decrease dose to organs at risk more than adaptive techniques such a plan of the day.

Plan of the day

The plan of the day approach is the only advanced adaptive technique which is in routine practice in a number of centres and is considered the current gold standard approach [151,167]. Daily plan selection is usually quick and radiographer led, adding little to overall treatment time. There is evidence from planning studies that this approach improves coverage of the CTV and can reduce dose to organs at risk, but the benefits vary from patient to patient. A recent study showed only limited reduction, approximately 80cm^3, in treated volume with plan of the day treatment compared to those treated with VMAT based on the EMBRACE 2 study protocol. This was in comparison to a reduction of treated volume from 2500 cm^3 with 3D conformal radiotherapy, 2000 cm^3 with the EMBRACE 1 protocol and 1800 cm^3 with the Embrace 2 Protocol. The team felt that those patients treated with a plan of the day approach were those who displayed more organ motion and therefore an ITV plan would have had a larger volume [227]. This is consistent with the reductions seen by White et al for plan of the day, but the volume of the standard plan was smaller at 1400cm^3 [234] The reduction in dose to organs at risk was greater than the overall volume reduction.

The plans are based on either pre-treatment imaging, with variable bladder filling or based on the CTV from the first week of cone beam CTs. The CTVs can either be created using a model based system, using 2 scans with a full and empty bladder, to produce a simulation of CTV positions with different bladder filling [148] or using a manual approach, combining manually contoured CTVs on 3 scans.

The plans are added to a library and the plan that is the best fit is chosen each day. Initially, there was also a large volume back up plan, but this is no longer considered necessary as it was rarely used. The CTV to PTV margins are usually smaller than using a standardised margin [130,168].

The ideal number of plans for the library is not yet standardised and may vary between individual patients [155]. Some patients with minimal motion between planning scans only have one plan prepared, a basic form of patient selection, although it will miss some patients who may benefit from adaptive radiotherapy. This technique could be combined with a scheduled re-plan for further reduction in dose to OARs. There is evidence that intrafraction motion could have an impact on coverage, with a single study assessing motion by repeating CBCT scans after plan selection and treatment. This took approximately 20 mins and the group mean displacements were 0.1±1.4mm in the left/right direction, 1.8±1.5mm in the caudo/cranial direction and -2.8±1.8mm in the anterior/posterior direction [109]. This is probably a worst case estimate as it was based on patient with changes of greater than 2.5cm between full and empty bladder filling scans. This study was performed a number of years ago and an optimised workflow may reduce the time between initial scan and treatment. There is also the possibility of making allowances for potential intrafraction shifts especially if they are due to bladder filling as described in chapter 4.

There is additional work prior to treatment, with additional scans and contouring (although this is focused on the primary CTV only) as well as the creation of additional radiotherapy plans. Some of this work may be automated, but there is still an added time burden for the department[157,235,236]. It may reduce the need for unplanned replanning but this has not been quantified.

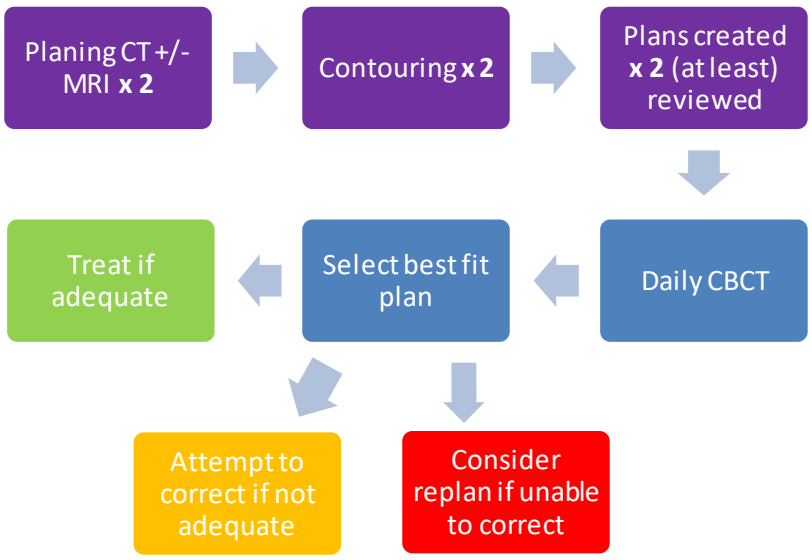

FIGURE 24 PLAN OF THE DAY PATHWAY

Plan of the day plus (offline)

This technique builds on the plan of the day, but additional plans are built up based on images obtained during treatment[173]. Using an offline approach, the patient is treated with the most appropriate plan available but if there is concern that the coverage is not good then an offline review can take place.

If required a further plan can be made without requiring a dedicated planning scan and added to the library for the next fraction. This means that it is possible to adapt the treatment to changes that are unrelated to bladder filling or occur during treatment, such as tumour shrinkage. It would also be possible for patients who start with a single radiotherapy plan, to build up a library of plans if required. As the number of plans increase, it may become difficult to select the best plan and automation or selection rules may be required.

There are currently no published examples of a plan of the day plus workflow in clinical practice for cervical cancer.

Radiotherapy could be delivered quickly, without the need for a doctor or contouring radiographer.
The criteria for offline review and adding another plan could be standardised for example using a traffic light or flow chart-based system. These rules could assess coverage of the CTV but also consider other factors such as if there has been tumour shrinkage, which could mean that the CTV could be reduced in size. This would need to be done carefully as there would potentially be the risk of undertreating microscopic disease. There is precedent in the brachytherapy setting where the high-risk CTV is adjusted for each fraction and can reduce in size between radiotherapy fractions.

FIGURE 25 PLAN OF THE DAY PATHWAY PLUS (OFFLINE REVIEW)

Plan of the day plus (online)

The plan of the day plus with the option of online adaption is similar to the previous option but will allow for a full online adaption if the plan is inadequate. This could be combined with offline adaption for plans that have adequate CTV coverage but could be optimised to reduce doses to organs at risk. The alternative would be to consider online adaption for all plans where it was felt that the plan could be improved. This could lead to uncertainty and therefore increase the time take to plan the treatment unless there were strict defined criteria.

The other benefit for a plan of the day plus approach would be that even if no plan was ideal, one plan is likely to be a better starting point than a standardised plan from the start of treatment. This could increase the speed of contouring/contour correction, aid auto contouring as well as plan optimisation.

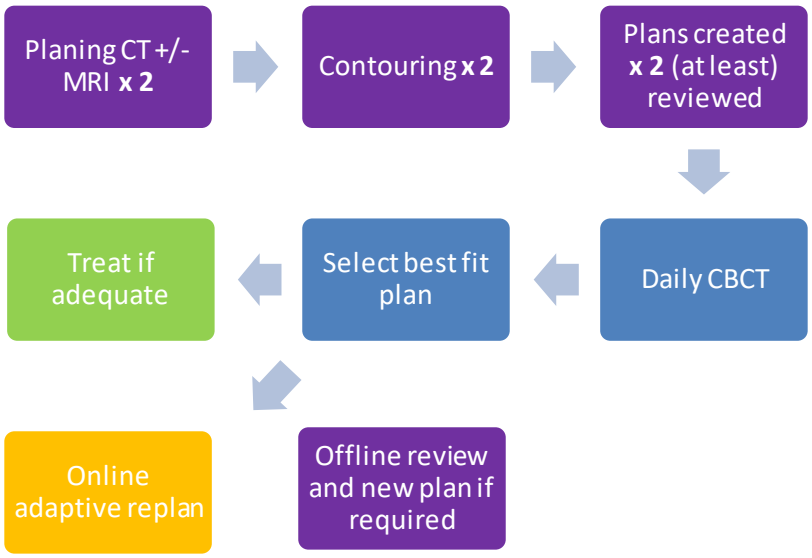

FIGURE 26 PLAN OF THE DAY PATHWAY (ONLINE REVIEW)

Full online adaption

There are now commercially available solution for both MR [232] and CBCT guided full online adaption [237]. The Elekta Unity linac has a fixed couch, but corrections can be made using an 'adapt to position' approach with a virtual couch shift but no adaption for soft tissue changes. The 'adapt to shape' allows for full re-optimisation based on updated contours of the CTV and organs at risk.

An initial plan is created and is re-optimised using an image obtained that day. The newly acquired scan is registered with the planning scan, the contours are propagated using deformable registration or auto contoured and then assessed or edited as required. The plan is re-optimised based on the new contours then checked. A further image is taken and then if CTV coverage is acceptable the treatment goes ahead. If the plan is no longer adequate than further changes could be made, possibly using the quicker 'adapt to position'

approach. A further scan may be performed following the completion of treatment to check that the position hasn't changed significantly.

A similar workflow is used for the CBCT guided online adaption, with OAR auto segmentation, contour propagation and checking, plan optimisation, repeat CBCT to check coverage then treatment[232].

This allows for the most accurate targeting of the CTV, with the potential to further decrease margin and spare organs at risk. It may be possible to develop patient specific margins by assessing motion over the initial fractions. Daily contouring will also reduce the volume of the CTV over time as most tumours shrink over the course of treatment, although this has the biggest impact on the GTV. There is uncertainty as to how the GTV changes with tumour shrinkage and whether there is residual microscopic disease. It would also facilitate biologically driven adaption if using a MR Linac. There is a benefit to doses to organs at risk in theoretical studies, compared to plan of the day, but these assume a margin of 3 – 5 mm from CTV to PTV [118,133,134]. There are no robust studies confirming that this margin is sufficient for the current workflow.

White et al, found that online adaption with a 3mm margin was the most effective strategy to reduce doses to the organs at risk. The reduction compared to a plan of the day approach was small, reducing median PTV volume from 1217 cm^3 to 952 cm^3. The rectal, bladder and bowel bag V40 were 45%, 58% and 670 cm^3 for the plan of the day approach and 34%, 34% and 517 cm^3 for full online adaption with a 3mm margin. This is unlikely to account for residual uncertainties, especial when treatment times remain long. Of note, the second smallest PTV volume, was not an adaptive technique but alteration of the CTV with exclusion of the uninvolved uterine fundus with a 1.5cm margin [234].

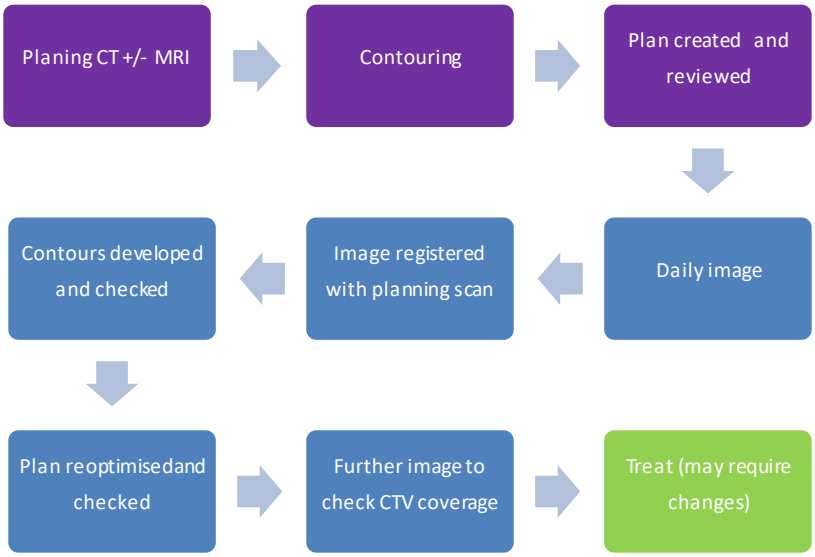

FIGURE 27 DAILY ONLINE ADAPTION

Technique	**Benefits**	**Disadvantages**	**Impact on dose to OARs/treated volume**	**Benefits for online MR imaging**
Standard/ITV approach	Standard practice, single plan, quick, can deliver VMAT plans	Large margins/volume treated, may need unplanned replans, risk of underdosing parts of CTV, delays assessing plans and	No reduction, ITV may increase dose to organs at risk	May be easier to see position of the CTV but unlikely to be of particular benefit
Plan of the day	Established technique, limited delay to treatment, can be done on the majority of linacs	Based on bladder filling only, increased pre-treatment requirements,	Improved coverage of CTV, variable impact on OAR doses	May be easier to select the correct plan but this is not confirmed

		additional scans for any replan		
Plan of the day plus (offline)	Limited delay to treatment, can be done on the majority of linacs	May limit benefits of the approach, increased offline workload, with	Improved coverage of CTV, variable impact on OAR doses	High quality image to contour for plan if needed, not fully utilising machine benefits
Plan of the day plus (online)	Full online adaption not needed for every fraction, library of plans may allow for quicker contouring and plan optimisation	Special equipment required Requires a clinician or contouring radiographer present	Improved coverage of CTV, variable impact on OAR doses	May allow more accurate contouring
Fully adaptive approach	Most conformal technique	Special equipment required Requires a clinician or contouring radiographer present Slow Benefits may be negated by the impact of	Improved coverage of CTV, variable impact on OAR doses	May allow more accurate contouring, possibility of biologically adaptive radiotherapy

		intrafraction motion		

TABLE 25 SUMMARY OF PROS AND CONS OF DIFFERENT ADAPTIVE RADIOTHERAPY TECHNIQUES

Current clinical practice and challanges

As inter fraction motion is accounted for, the main areas of uncertainty are intrafraction motion and contouring errors. There is evidence that intrafraction motion increases over time for the majority of patients (Chapter 4).

Current MR guided strategies are slow, with a mean treatment time of 68 min (range 51-82min) for the first patient treated with full online adaption for locally advanced cervical cancer [232]. The median treatment time for patients receiving adjuvant treatment for cervical cancer was shorter with an abstract reporting treatment time for 6 patients, mean treatment time 32 mins (range 29-35 mins). It is not reported if the contours were adapted for every fraction[238]. Full breakdown of timings are not available but for patients with bladder cancer treated on the Elekta Unity, the median for each fraction was 39 minutes (range 33–48); recontouring time 7 minutes (range 4-11), plan reoptimisation 5 minutes (range 3-6) and on couch treatment time 9 minutes (range 8-12). The CTV for bladder cancer patients is smaller than for patients treated for cervical cancer, with a median CTV of 107 cm^3 (range 60 -243 cm^3)[239]. This means that the contouring time is likely to be lower.

Although there is limited experience of MR guided online adaptive radiotherapy for cervical cancer, evidence is accumulating for treatment of other pelvic cancers. Bladder and rectal cancers are most similar as they have a relatively large CTV volume compared to prostate cancer and intrafraction motion is likely to be important. Daily changes in patients with cervical cancer are likely to be larger and the variability of motion and deformation in different parts of the CTV means it is particularly challenging.

The first case series of patients treated with MR guided online adaption for rectal cancer showed broadly similar timings with a median overall treatment time of 49 minutes. Median recontouring time was 13 minutes, with oncologists being faster than trained radiographers.

The initial 25 patients were treated with standard margins, 10mm isotropically around the mesorectal CTV. This was reduced to 4mm in laterally and posteriorly and 6mm superiorly, inferiorly and anteriorly. The coverage of the CTV was maintained, apart from one fraction in which the passage of rectal gas changed the CTV. This suggests that for rectal cancer, the small margins were sufficient[240].

In patients with bladder cancer treated on the Elekta Unity, larger margins were required to account for intrafraction motion due to bladder filling, with anterior and superior margins CTV -PTV margins of 1.5cm, posterior margins of 1 cm, and lateral and inferior margins of 0.5 cm. The median on couch treatment time in this study was 39 mins but the authors noted that at another centre an on-couch treatment time of 15 and 27 min had been achieved [241].

Intrafraction motion for patients with cervical cancer is likely to be particularly important as bladder filling impacts motion of the CTV as shown in chapter 4 and CTV is large and subject to interfraction motion and deformation meaning contouring is time consuming. A theoretical study of CBCT online adaption had a median time of 13.1 minutes to contour the CTV for patients with cervical cancer. In the same study, contouring only took 2.7 minutes for patients with rectal cancer[237]. This is consistent with the case report of treatment of cervical cancer on the Elekta Unity, with contouring and optimisation taking between 11 and 14 mins [232]. The longer the contouring takes, the more likely there will be intrafraction motion.

The impact of online contouring uncertainty has not been formally assessed or quantified. Contouring under time pressure, without optimal imaging may lead to errors. This is particularly important when using tight margins.

Comparison of MR vs CBCT

The major impediment to treating patients with cervical cancer using an MR linac is the field length of the commercially available machines. A dual isocentre approach has been suggested to address this issue. This would use two isocentres to allow coverage of a longer

field length. An overlap region would be sited in the elective nodal CTV region, with initial treatment of the nodal volume with a simple 'adapt to position' approach, as there is less motion in the nodal CTV. This would be followed by an 'adapt to shape' treatment of the second isocentre primary CTV with a re-optimised plan. Initial research has shown that this approach would deliver an acceptable plan within adaptive workflow[242].

There is an example of clinical implementation of a dual isocentre approach for patients treated with an IMRT technique using the Varian Halycon linac accelerator [243]. Concerns have been raised including both the time that it would take to deliver treatment to the two isocentres as well as the risk of increasing dose to mobile organs at risk, specifically the small bowel [244]. This technique is still in development and is not available for clinical use for an MR linac.

MR scans benefit from improved soft tissue contrast compared to CBCT scans. Intuitively, it would therefore be easier to register the scans, check CTV coverage and contour using MR scans. This has not yet been confirmed and in a study assessing radiographers' ability to perform soft tissue matching comparing CBCT and MR, there was no improvement with accuracy using MR [245]. A study comparing CT vs MR based contouring for patients for cervical cancer showed improvements in contouring accuracy, but the impact was greatest for the GTV [77]. As there is no difference in dose between GTV and other areas of the CTV this is likely to be less helpful unless a boost is considered. An ability to image the tumour would also support the reduction in the CTV by excluding the uninvolved uterus.

CBCT scans are intrinsically susceptible to gas related artefacts but there have been incremental improvements in imaging quality [246]. This means that although the soft tissue contrast will not equal MR imaging, this may not translate into differences in plan of the day selection, contouring time or accuracy.

Currently, the commercially available MR linacs, deliver fixed beam IMRT, which is slower than rotational IMRT techniques, although it is likely that this will change in the future [247]. The treatment time only contributes a limited amount to the overall time but it is important as intrafraction motion during this time can't be corrected without the use of gating, which

extends treatment time further. As intrafraction motion is often dependant on bladder filling, we may be able to develop individual models to account for the change in the CTV over the treatment time. This is unlikely to be as effective as speeding up treatment delivery and wouldn't account for unexpected changes, such as passage of bowel gas. (Chapter 4.)

CBCT scans are also quicker to acquire, although there also quick MR sequences that are suitable for on line image guidance. There is also a potential to acquire additional sequences during the time for online adaption to develop standardised quantitative biomarkers [88]. This would support the development of biologically adaptive radiotherapy [248], which is a specific benefit for MR guidance. There is the potential for variable dose across the CTV, targeting areas of radio resistance and allowing for dose escalation or de-escalation depending on response.

Further areas for research

The only report of a patient with treated with online adaptive radiotherapy using the Elekta Unity used standard margins and therefore the impact of the treatment on doses to organs at risk likely to be small, as the main impact of adaptive strategies is allowing the reduction of margins. It does prove it is feasible [232]. There is evidence from other disease sites such as bladder cancer that centres treating high volumes of patients have managed to shorten the workflow by more than 10 min compared to other units. This would have a big impact on both intrafraction motion (and therefore CTV to PTV margins), as well as the practicality and cost effectiveness of the MR linac.

Comparison of MR vs CBCT

As MR guided radiotherapy is a limited resource, it is useful to confirm that the improved soft tissue definition translates into practical benefits. This would build on the work looking at soft tissue matching on MR and CBCT [245], to see if it easier to pick a 'gold standard' plan from a library of plans. Assessment of manual and automatic contouring should also be done as this may not be easier, quicker or more accurate on MR than CBCT.

Evaluation of different adaptive planning techniques

All aspects of the adaptive planning workflow need to be considered in analysis of different adaptive planning technique. As these techniques reduce interfraction changes, the impact of intrafraction changes will increase.

The impact of time both on movement of the CTV, organ at risk motion and set up changes needs to be quantified. This will help support optimal pathway development. It is also important to assess the accuracy of online contours as if only small CTV to PTV margins are used to maximise organ at risk sparing, the impact of CTV inaccuracies will increase.

Innovations

Further work is needed to support technical developments in auto contouring, fast replanning, and treatment techniques such as VMAT and dual isocentre techniques.
It is also important to investigate the impact of underdosage of the CTV, as well as the possibility of reducing the CTV volume to exclude the uninvolved uterus.

The clinical impact of adaptive techniques must be measured not only to assess the impact on toxicity but also to ensure that tumour control rates do not decrease.

Economic analysis and resource implications should be a central part of analysis [249], but research should also be aspirational to develop the treatments of the future.

The current optimal workflow

In the future, when fast and accurate auto contouring is available, alongside fast beam on treatment time and rapid replanning, full online adaption will be the best workflow. However, this is not currently the case. As a balance between the time taken to deliver a treatment, the doses to the organs at risk and CTV coverage, the use of a plan of the day plus approach with online adaptation should be investigated. A plan of the day plus approach with offline replanning, offers an attractive option for sites without access to online adaption.

Conclusion

All adaptive techniques are likely to improve coverage to the primary CTV and reduce dose to organs at risk by safely reducing margins to account for interfraction motion. There is increasing evidence that reducing dose to organs at risk does lead to meaningful reduction toxicity.

The impact of improving dose coverage to the primary CTV (outside the high-risk CTV) remains unclear. Improved image guidance and adaptive techniques could support excluding the CTV from the uninvolved uterus as part of a clinical trial as this may be as effective in reducing dose to the organs at risk as adaptive techniques.

It is likely that as technology advances, online adaptive radiotherapy will be automated. This will speed up the workflow and improve contouring inaccuracies to allow daily online adaption. In the meantime, plan of the day plus with online adaption represents the most efficient workflow. Currently, CBCT based approaches are most likely to be practical as the field size limitation on MR linacs limit its use.

However, MR guidance may not only allow the smallest margins but also facilitate biological adaptation, leading to a new era in radiotherapy.

Discussion

Over the last 20 years, knowledge of the impact of organ motion during external beam radiotherapy for cervical cancer has increased and motion management techniques have been developed to address this motion [97]. Bladder filling protocols have formed the basis of both the initial studies and the only motion management technique used in clinical practice, the plan of the day approach [152,166]. Bladder filling is easier to manipulate than other causes of motion such as rectal or small bowel filling. Although differences in motion at different parts of the uterus have been noted, the impact of this has not been fully addressed. This is an important consideration as the tumour is centred on the uterine cervix, which moves differently to the uterine fundus.

Changes across the duration of the PhD

The initial aim of the project, as outlined in the attached study protocol, was to assess the impact of different adaptive radiotherapy protocols on CTV coverage, including dosemetric analysis. As part of my PhD, I wrote the protocol, gained ethical approval, successfully recruited patients to the study as well as coordinating the timing of MR scans. Contouring of patient scans was carried out by me and a colleague, a visiting oncologist from Turkey, Dr Nesrin Atturk.

Whilst waiting for the data to become available, work commenced on the 'large cohort' of patients, as an available data source. This allowed for novel work to be undertaken whilst trial recruitment was carried out. During the project, other groups within the Elekta MR linac consortium, carried out research similar to the primary aim of the study [234]. I, therefore, focused on intrafraction motion, as this is an area where data is limited and is of particular importance in the era of adaptive radiotherapy. Work based on the secondary aims of the project has been carried out by members of the wider research group as discussed in the future work section. Again, this focused on novel areas, with potential clinical benefits, including auto contouring and a dual isocentre approach.

Since the completion of my PhD, a patient with locally advanced cervical cancer, has been successful treated on the MR Linac using daily online adaptive MR guided radiotherapy [232].

Summary

The aim of the thesis was to explore the causes and implications of motion of the uterine fundus and cervix to support the development of novel image guided radiotherapy. This has been successful in providing a potential rationale for the use of online adaption and palliative treatment as the first use for MR guided radiotherapy. However, there are still a number of challenges to develop this and ongoing work is being carried out as part of a larger project supported by the successful prospective imaging study.

The work presented in the initial 3 chapters uses a large cohort of patients treated with external beam radiotherapy for cervical cancer. A novel methodology using scans at three time-points was developed which accurately quantified motion at the uterine fundus, with the mean motion exceeding the CTV to PTV margin. Large motion at the uterine fundus was not associated with poor clinical outcomes including overall survival, progression free survival and toxicity. This raises an interesting hypothesis, suggesting that under-dosage at the uterine fundus does not impact on clinical outcomes and therefore part of the fundus could be excluded or the dose to the fundus reduced. Qualitative analysis highlighted the importance of rectal filling on motion at the cervix during the early stages of external beam radiotherapy and tumour shrinkage in the later stages. Even for motion at the uterine fundus, other factors (including bowel, rectum motion and tumour shrinkage) are still relevant even though bladder filling plays the most important role.

Intrafraction motion was assessed in 10 patients at 4 time-points and showed that the mean maximum distance to agreement was just over 0.5cm over 10 minutes but that the site of motion varied between fractions. Bladder filling was the most important cause of motion at both the uterine fundus and cervix. This was usually a gradual increase over time but the impact of bladder filling was variable between scans. Rectal changes were a less common cause of motion but they could lead to a sudden change in position of the cervix. Review of

motion in different planes suggests that anisotrophic margins, which are greater at the uterus than the cervix could be appropriate to compensate for intrafraction motion.

Palliative radiotherapy was assessed in a retrospective single site cohort and showed that the majority of patients benefited from treatment and rates of physician reported high grade toxicity was low. Given the smaller field size required, this makes this technique a good candidate for initial implementation on the MR-linac, although patient numbers are small. There is the potential to reduce toxicity by using adaptive techniques or to consider dose escalation, although the benefits of are unknown.

Novelty

This work adds to previous studies of pelvic organ motion in cervical cancer, complementing smaller studies with a detailed analysis of a small number of patients [97] by assessing a large cohort of unselected patients. Previous studies were often based on scans with specific bladder filling protocols, which highlighted the importance of bladder filling. Our qualiative analysis highlighted the various causes of interfraction motion, which has not previously been studied. The impact of organ motion in cervical cancer on clinical outcomes such as survival and toxicity has never been studied. As radiotherapy becomes more precise, delineation of the CTV becomes increasingly important, with interest focussed on whether the whole uterus should be included in patients without uterine fundal involvement. There is an ongoing retrospective cohort study of patients treated with a modified CTV [80] and a prospective trial to assess if reducing fundus dose is safe [81], however our method allows retrospective data analysis to evaluate the safety of fundus dose reduction in patients in whom the whole uterus has been included in the CTV and it would be very interesting to see this repeated in even larger cohorts.

In comparison to interfraction motion, intrafraction motion has rarely been studied with only three previous studies published. These show mean motion is usually small but maximum motion could be up to 1cm [105,211–213]. Our work was the most detailed analysis, with scans carried out at two minute intervals allowing assessment of changes over time. The use of a qualitative approach also provided additional information about the causes of motion.

The current work also represents the largest reported cohort of patients receiving palliative radiotherapy for gynaecological malignancy. The role of radiotherapy in patients with metastatic disease remains unclear and this work supports its use for palliation of common symptoms. The majority of patients experience some toxicity during treatment and refinement of radiotherapy techniques could improve this by using adaptive techniques and reducing margins. In the majority of cases the treatment field was small enough to allow treatment on the MR linac, however there were a relatively small number of patients.

The final chapter is a practical review of different workflows for adaptive radiotherapy for cervical cancer and combines both the work of presented in this thesis as well as the published literature.

Limitations

The study in the initial three chapters was based on assessment of motion in a single plane, allowing rapid assessment of patients. This may mean that causes of lateral motion are missed. However, lateral motion has been reported to be smaller than motion in other directions, and significant changes would be obvious on visible assessment of scans. Unfortunately, our method was not sufficiently accurate to assess motion at the uterine cervix, due to the difficulties accurately locating points in the lower portion of the uterus, especially on CBCTs. This methodology could be combined with implanted markers the cervix to assess motion in all parts of the uterus in a large number of patients.

Although this study was the largest study of motion in patients undergoing radiotherapy for cervical cancer, there was a limited number of events, causing the survival analysis to be underpowered. The methodology is quick and simple and therefore it could be easily scaled to a larger cohort.

The main limitation of the intrafraction motion study was that the examined time frame was only 10 minutes. It is likely that a fraction of MR guided adaptive radiotherapy will take at least 20-40 minutes to plan and deliver. However, the workflow will include a check image prior to radiotherapy delivery and adjustments can be made prior to the actual dose

delivery. The time between the check image and end of treatment would be well within the 10 minute time frame.

Prospective patient reported outcomes were not available for patients in either the retrospective or palliative cohort and therefore toxicity assessment was based on retrospective physician reported data. This means the results should be interpreted with caution as toxicity may be underreported.

Future work

As an initial step toward developing MR guided online adaptive radiotherapy, palliative radiotherapy is an attractive option, with chapter 5 showing that a moderately hypofractionated regimen is feasible. There is also potential to consider more significant hypofractionation as toxicity reduction may be possible due to higher accuracy. However, the greatest impact will be in the radical treatment.

The work presented in this thesis shows that clinically implemented plan of the day techniques based on bladder filling are not targeted at the most important causes of motion at the cervix: rectal changes and tumour shrinkage. Manipulation of rectal and bladder filling have been suggested to reduce motion, but this is very difficult to achieve in practice. Re-planning strategies have also been discussed, either ad hoc, which is relatively common in clinical practice, or at a defined time-point. Offline re-planning, however, usually requires acquiring additional planning scans and there is often a few days delay between decision to adapt and implementation of the new plan.

Our findings also raise the hypothesis that underdosage of the fundus does not impact survival, as motion at the uterine fundus greater than the CTV to PTV margin is not associated with either overall or progression free survival. This observation raises the possibility to alter the CTV to either exclude or reduce the dose delivered to the uninvolved fundus. This would reduce the CTV volume as well as excluding the most mobile part of the uterus, reducing margin requirements. In order to support this hypothesis, the study should be replicated in a larger cohort of patients to confirm the findings. Ultimately, the safety and benefit of such an adaptation would have to be demonstrated in a clinical trial.

Accurate MR based delineation and an adequate CTV margin would be required to ensure that tumour was not missed. Although daily MR guidance would not necessarily be required, it could potentially increase confidence as the importance of adequate CTV coverage increased.

Theoretical studies suggest that daily online MR guided external beam radiotherapy would provide the best CTV coverage and allow reduction of margins to reduce irradiated volumes and spare organs at risk. This has been successfully introduced for different disease sites but there are significant challenges to implementation for patients with cervical cancer. There are two case reports of patients receiving external beam radiotherapy for cervical cancer using an MR linac, however a standard plan was used with no online adaption. An international survey of 171 treatment centres suggested that 2% are currently delivering daily online adaption using both CT and MR but no further details are available [250]. Although it is intuitive that higher quality imaging with MR compared to cone beam CT will allow for more accurate on treatment image registration and easier plan of the day selection, such an assumption would have to be validated. A comparison of radiographer led soft tissue matching using CBCT and MR, showed, however, that registration accuracy was similar and MR guidance was not more accurate. An assessment of plan of the day selection, comparing the utility of CBCT and MR is ongoing.

A further challenge of introducing MR guidance for cervical cancer is that the field length is inadequate to cover the nodal CTV for at least 40% of patients [9]. Initial work as part of this project has shown that it is feasible in principle to use a dual isocentre approach, using an overlap based in the nodal region, the nodal field treated first and plan re-optimisation[10]. Further work will examine if this solution remains robust when combined with online adaption. Unfortunately, this technique is not currently possible in a clinical setting. Alternative uses include delivering the radiotherapy boost which is smaller on the MR-linac, with or without brachytherapy; and deliver the remaining fractions on a standard linac. There is evidence that external beam radiotherapy boost is less successful than [251]and interstitial techniques have reduced the number of patients with inadequate coverage. As mentioned before, there is also the potential to treat palliative patients with MR guided radiotherapy as in palliative patients, elective fields are not included.

Another consideration is the impact of the electron return effect, due to the deflection of electrons by the magnetic field which can lead to disruption in dose distribution around air

pockets. This is particularly relevant for treatments in the pelvis due to rectal gas. Work assessing rectal gas in the cervix MR study patients as well as bladder and prostate cancer patients suggests that gas patterns are sufficiently stable that their impact on dose could be important even in fractionated radiotherapy.

A further technical challenge for online adaption is the production of daily contours. The majority of clinical cases treated on the MR linac are for sites such as the prostate, pancreas and isolated lymph nodes. These are small targets, and limited re-contouring of organs at risk is required. As demonstrated there can be large intrafraction changes during external beam radiotherapy for cervical cancer and the PTV is large. Manual adjustment of contours is likely to be time consuming and may not be feasible. This is of particular concern as the magnitude of intrafraction motion is likely to increase over time.

Accurate rapid automatic contouring could facilitate this technique but although there are a number of commercial and research solutions, none have yet been proven in this setting. As part of this project, the use of patient specific atlas was trialled, using between 1 and 14 images from the MR imaging study to create contours for 6 patients. The accuracy of automated contours increased with the number images included in the atlas at the expense of increasing processing time and the number of contours required. A potential workflow solution could combine a MR planning scan with a bladder filling protocol as well as images from the initial fractions to build an appropriate atlas.

An alternative to full online adaption could use an evolving plan of the day approach, with a plan chosen on treatment each day unless all of the previous plans are felt to be suboptimal, either by clinician assessment or set criteria. In this case, a new plan could be created, either on- or off-line and added to the library. Although the online approach would allow for optimal accuracy, an offline approach provides more workflow flexibility and efficiency. This method could provide a feasible initial workflow whilst developing a full online approach.

As the volume of the PTV shrinks, contouring accuracy becomes increasingly important and care must be taken to ensure that microscopic disease is not missed. It will be important to evaluate the clinical benefits and risks of these approaches, either through a trial or using a robust prospective database. MR guidance could also facilitate the trial of a modified CTV excluding the uterine fundus, by ensuring the remaining parts of the CTV are always covered.

MR guided radiotherapy also raises the possibility of biological adaption based on imaging based biomarkers. This is of particular interest in patients with cervical cancer as hypoxia is recognised cause of radio-resistance. However, in order to deliver effective biological adaption, successful motion management is required, which was the aim of my study.

Conclusion

This work has added to our understanding of target motion during radiotherapy for cervical cancer, showing the importance of rectal changes and tumour shrinkage on interfraction changes at the cervix. The potential impact of intrafraction motion has also been highlighted. This work provides a rationale for the development of MR guided online adaptive radiotherapy. Despite the challenges, there is a strong clinical need for improved external beam radiotherapy to reduce toxicity for patients undergoing treatment for cervical cancer.

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Appendix 1

Study Protocol

A pilot study using Magnetic Resonance (MR) to assess cervix motion during radiotherapy treatment

Version 2.0
6th December 2017

SIGNATURES/PROTOCOL APPROVAL

A pilot study using MR to assess cervix motion during radiotherapy treatment

This document describes A pilot study using MR to assess cervix motion during radiotherapy treatment and provides information about procedures for entering patients into it. This protocol should not be used as a guide for the treatment of patients outside the study. Every care was taken in drafting this protocol; however corrections and/or amendments may be necessary. Care must be taken to use the most up to date and approved version. This study will adhere to the principles outlined in the ICH Good Clinical Practice guidelines. The study will be conducted in compliance with the protocol, the Data Protection Act (DPA Z6364106), The Declaration of Helsinki, Human Tissue Act (2004), the Research Governance Framework (2005) and other regulatory requirements as appropriate.

Chief Investigator
Dr Anthea Cree, Research Fellow & Clinical Oncologist, University of Manchester & The Christie NHS Foundation Trust.

Signed: …… Date: ……

I …… as Chief Investigator for 'A pilot study using MR to assess cervix motion during radiotherapy treatment' to be conducted at The Christie NHS Foundation Trust confirm that I will be responsible to ensure that all members of the local study team are appropriately trained on the study protocol and have the relevant qualifications and experience to carry out their role in accordance with the study protocol.

Table of contents

Research team & key contacts

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List of abbreviations

ADC	Apparent Diffusion Co-efficient
AE	Adverse Events
CBCT	Cone Beam Computed Tomography
CI	Chief Investigator
CRF	Case Report Form
CTCAE v3.0	Common Terminology Criteria for Averse Events Version 3.0
CT	Computed Tomography
CTV	Clinical Target Volume
DPA	Data Protection Act
DVH	Dose Volume Histogram
DWI	Diffusion Weighted Imaging
EMBRACE	International Study on **M**RI Guided **Br**achytherapy in Locally **A**dvanced **Ce**rvical Cancer
GCP	Good Clinical Practice
GP	General Practitioner
GTV	Gross Tumour Volume
HQ	High Quality
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IMRT	Intensity Modulated Radiotherapy
ITV	Internal Target Volume
kV	Kilovolt
MDT	Multi-Disciplinary Team
mg/m^2	Milligram per metre squared
ml	Millilitre
mm	Millimetre
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRL	MR Linac
MV	Megavolt
NHS	National Health Service
OARs	Organs at Risk
PIS	Participant / Patient Information Sheet
POTD	Plan of the Day
POTD+	Plan of the Day Plus
PTV	Planning Target Volume
R&D	Research & Development
REC	Research Ethics Committee

RRR	Radiotherapy Related Research
RT	Radiotherapy
RTP	Radiotherapy Planning
SAE	Serious Adverse Event
T	Tesla
T2	Transverse Relaxation Time
UK	United Kingdom
VMAT	Volumetric modulated Arc Radiotherapy
XVI	X-Ray Volume Imaging

Study Summary

Title	A pilot study using MR to assess cervix motion during radiotherapy treatment
Brief introduction	The standard treatment for locally advanced cervical cancer is concurrent chemo-radiotherapy. This treatment is associated with long term side effects in around half of patients with up to 10% suffering from grade 3-4 toxicity. The development of intensity modulated radiotherapy (IMRT) allows for shaping of radiotherapy fields to reduce the doses delivered to organs at risk (OARs). This does appear to reduce the risk of long and short term toxicity (although there is little randomized evidence). However pelvic organ position varies both between and even during radiotherapy fractions; this means that radiotherapy margins must be generous to allow adequate coverage of the clinical target volume (CTV) but this also increases dose to OARs. There have been a number of studies evaluating pelvic organ motion in cervical cancer as well as assessing different adaptive radiotherapy strategies. These have included individualized margins, plan of the day and adaptive techniques. Most of these studies have been carried out using cone beam computed tomography (CBCT) imaging which is often poor quality with limited soft tissue contrast. MR offers better visualization of the tumour and OARs and is used for imaged guided brachytherapy treatment. This study will explore the role of MR imaging in adaptive radiotherapy for cervical cancer with development of a number of theoretical treatment strategies.
Design	Single site, non-randomised basic science study
Objectives	• To develop and test a MR imaging protocol suitable for soft tissue delineation, volumetric imaging over the duration of plan adaptation/delivery and diffusion weighted imaging (DWI). • To develop patient specific models of bladder filling; investigate intra-patient consistency and the feasibility of predicting the cervix position at the time of treatment.

	• To investigate different adaptive strategies; feasibility, scope for margin reduction and normal tissue toxicities. • To measure early changes in DWI imaging during radiotherapy.
Eligibility	Inclusion Criteria • Histologically confirmed diagnosis of cervical cancer • Treatment with primary curative intent • Undergoing external beam radiotherapy (+/-chemotherapy) followed by brachytherapy or an external beam boost • Age over 18 Exclusion Criteria • Any contraindications to MR identified after MR safety screening including completion of an MR Safety Screening Form (see appendix 1) • Previous hysterectomy • Unable to tolerate MR scans • Metastatic disease • Pregnancy
Study Methods	Patients will undergo standard treatment during the study with five weeks of external beam radiotherapy (25 fractions) followed by a MR guided brachytherapy boost or external beam boost (further 10 fractions.) They will be treated with weekly cisplatin 40mg/m^2 if clinically appropriate. As part of standard treatment patients have a staging MR scan at diagnosis, a radiotherapy planning CT and an MR scan in the 4^{th} week of treatment. Cone beam imaging will also be performed. Response will be assessed as standard with a MR scan at 3 months. As part of the study patients will undergo 3 additional MR scans. These will take place in the 1^{st}, 2^{nd}-3^{rd} and 4^{th}-5^{th} weeks of treatment. Extra sequences will be added to the clinical mid-point scan in the 5^{th} week of treatment. These MR scans will include anatomical images – with full and empty bladder as well as cine data (with a scan every minute for 10 minutes) to assess intra fraction motion. They will also include a DWI sequence, which will be used to assess if early prediction of response is possible. The frequency of cone beam imaging will be increased from approximately 10 scans as standard of care to 25 scans to allow for daily imaging. The 1^{st} MR scan will be contoured to outline clinical target volumes (CTVs) and OARs. A variety of planning strategies will be developed including standard planning target volume (PTV) margins, a plan of the day (POTD) approach, a POTD+ as well as an online adaptation model. These models will be used to assess coverage of CTV and PTV as well as dose to OARs using the scans obtained during the radiotherapy treatment. The

	practicality of each approach will also be assessed. Inter and intra fraction organ motion will also be analysed in order to develop patient specific models.
Study Duration	18 months
Sample Size	20 patients each undergoing 4 MR scans
Funding	Funding for additional scans and imaging will be from departmental funds.

Introduction

• Background

Over 3,000 patients are diagnosed in the UK with cervical cancer every year. For patients who present with locally advanced disease (stages IB-IVA) the standard treatment is chemoradiotherapy (with 25 radiotherapy sessions over 5 weeks) followed by brachytherapy. The five year survival following this treatment varies from 65-44% dependant on stage (Cancer research UK 2017).

Chemoradiotherapy is associated with long term toxicity affecting the bowel, bladder and vagina. Most studies report that up to half of patients develop some form of late toxicity which can impact on their quality of life. A significant number of patients (10% in a UK audit from 2010) (Vale C et al 2010) suffer from long term grade 3 to 4 toxicity including vaginal stricture, intestinal malabsorption, fistula formation or incontinence. Healthy tissue toxicity remains the single most important radiation-dose limiting factor and obstacle to cancer cure.

The introduction of IMRT/Volumetric Modulated Arc Radiotherapy (VMAT) has been shown to deliver less radiation dose to the bowel than conformal radiotherapy in dosimetric studies. There are a number of small studies which suggest that these theoretical gains are translated into clinical benefit in patients with cervical cancer (Ghandi et al., 2013). However the cervix/uterus is positioned posteriorly and above the bladder and therefore displays a large degree of positional uncertainty. This uncertainty arises from both inter-fraction variation due to different bladder states and intra-fraction variation due to bladder filling during treatment and to a minor degree due to bowel and rectum filling. These uncertainties show a large variation between patients, with some displaying a large degree of inter-fraction cervix motion and some displaying a small amount. The extent of these positional uncertainties makes margin reduction a challenge for cervix patients. This means that to ensure coverage of the cervix large margins are required, typically in the range of 15-21mm. Isotropic margins provide an amount of normal tissue sparing with ranges of 12mm – 32mm anterior-posterior, 8mm – 20mm superior –inferior, 7mm – 17.5mm left–right presented in the literature (Jadon, R et al., 2013).

Further reduction of normal tissue dose and toxicity is promised by using adaptive radiotherapy techniques, such as library plan of the day selection (Ahmad, R et al., 2013). Such techniques allow margins to be reduced further and an optimal plan to be delivered suited to the daily anatomical imaging. Careful image guidance and plan selection/optimisation is required to ensure that there are no geographical misses. Mean bladder volume has also been seen to reduce during treatment (Collen, C et. al.2010, Chan, P et. al. 2008). Tumour shrinkage may also occur towards the end of treatment leading to changes in anatomy (Beadle, BM et. al., 2009). This raises the additional question of the requirement to adapt plans at an appropriate time point during treatment.

Work on adaptive radiotherapy has been predominantly undertaken with kV imaging (cone beam CT) (Hoogeman MS et al., 2013) and MV imaging. This imaging may be performed with or without the use of fiducial markers to aid in assessing the position of the cervix. CT has

mostly been used to assess inter-fraction and intra-fraction organ motion, although some have used MR imaging (Chan, P et al., 2008, Taylor, A et al., 2008). MR imaging of the pelvis provides superior soft tissue delineation and these devices provide the possibility for improved adaptive radiotherapy pathways, allowing for local control to be maintained with a reduction in normal tissue toxicity.

The Christie NHS Foundation Trust is one of seven sites worldwide within the Atlantic consortium that is developing the MR-linac (MRL) prior to release at the end of 2017. The MRL allows MR images of patients to be acquired before, during and following radiotherapy (RT). This study will explore the role of MR imaging in adaptive radiotherapy for cervical cancer with development of a number of theoretical treatment strategies.

• Rationale for the proposed study

There is some evidence from dosimetric studies that adaptive radiotherapy techniques can be used to reduce margins and reduce doses to organs at risk. Most studies have been carried out using CT (some using cone beam imaging.) The development of a MR-linac offers the opportunity to utilise MR in a radiotherapy setting, prior to and during treatment, with benefits including better soft tissue delineation and no additional radiation dose for imaging.

• Preliminary Work

Previous work has been carried out to create a cervix MRI protocol with suitable image quality in healthy volunteers. This protocol includes anatomical images to allow radiotherapy planning and to assess inter fraction motion as well as a cine sequence to assess intra fraction motion. There is also significant institutional experience in the use of MR in image guided brachytherapy for cervical cancer.

• Study Hypotheses

- MR guided adaptive strategies for external beam radiotherapy on the MR-linac will facilitate margin reduction and reduced patient toxicity.
- Patient specific bladder filling can be modelled, predicting the position of the cervix at the point of treatment. This will allow reduction of margins, and for these to be personalised for each individual patient.
- Diffusion weighted MR imaging can be used to identify response early in treatment to allow for individualised plan adaption.

Study objectives

• Primary Objective

To develop a potential MR guided adaptive radiotherapy strategy which is practical and leads to adequate coverage of CTV and reduced dose to OARs.

- Secondary Objectives

To develop a patient specific model of bladder filling and pelvic organ motion to allow individualised margins and planning strategies.

To determine if DWI MR can be used to predict early response to treatment.

- Study Design

This is a Basic Science Study which does not include an investigational medicinal product or other treatment. The aim of the study is to develop a practical MR adaptive radiotherapy strategy. Patients will undergo additional MR scans (in radiotherapy planning position with a flat top scanner and bridging coil.). These scans will not be used for medical decision making.

The first study MR scan will be used as a planning scan (with full and empty bladder) and will be contoured to develop CTV and OARs . These will be used to develop a number of planning strategies including a standard clinical plan with fixed PTV, individualised Internal Target Volume (ITV) based plans and also a variety of plan of the day strategies (including a plan of the day plus where information from further MRs will be used to develop further plans if required.) These plans will be assessed using the MR scans obtained during treatment. Coverage of the CTV of the as well as the doses to OARs will be calculated for each adaptive strategy. The use of daily cone beam CT scans will allow for assessment of organ motion each day and ensure that the images from the MR scans at 4 time points are representative of actual organ motion.

A patient specific model of bladder filling (and therefore cervix position) will be created using volumetric imaging over a number of fractions and used to develop a personalised margin recipe. An attempt will be made to stratify patients into groups with a large range of cervix movement and those where the cervix shows little positional changes.

The final part of the study will use DWI gradients to assess if it is possible to predict early response to treatment.

The study begins with the consent of the first participant and will be complete when the final participant has had their post treatment MR scan (3 months following completion of radiotherapy) and all data processing has been completed.

Selection of Study Participants

- Inclusion Criteria
  - Histologically confirmed diagnosis of cervical cancer
  - Treatment with primary curative intent
  - Undergoing external beam radiotherapy (+/-chemotherapy) followed by brachytherapy or an external beam boost
  - Age over 18 years

- Exclusion Criteria
  - Any contraindications to MR identified after MR safety screening including completion of an MR Safety Screening Form (see appendix 1)
  - Previous hysterectomy
  - Unable to tolerate MR scans
  - Metastatic disease

- Pregnancy

• Concomitant Medications

No specific recommendations or exclusions for this study.

• Expected Toxicity

No additional toxicity is expected as part of this study as treatment will be standard of care. MRI (including DWI) is carried out in routine clinical practice without any known adverse events. No contrast agents will be used.
The expected toxicity from radiotherapy treatment doses of radiation are listed below. These adverse events **are not to be reported** for this study, since they are incurred by the standard of care.
Radiotherapy/chemotherapy for Cervical Cancer:

Acute chemotherapy/radiotherapy toxicity: CTCAE v3.0 grades 0-5
Fatigue / Lethargy
Radiation dermatitis
Cystitis
Proctitis
Diarrhoea
Nausea/vomiting
Fistula formation
Neutropaenia (+/-fever)
Anaemia
Thrombocytopaenia
Hearing impairment
Renal dysfunction

Late chemotherapy/radiotherapy morbidity: CTCAE v3.0 grades 0-5
Bowel urgency/ diarrhoea
Urinary urgency/cystitis
Fistula formation
Vaginal stenosis
Small bowel dysfunction (malabsorption/obstruction)

Safety Reporting

The study does not involve any new treatments. Anatomical and diffusion weighted imaging (DWI) is routinely used in clinical MR imaging protocols. We therefore do not anticipate any adverse or serious adverse events directly relating to the scanning protocol. In the unlikely event a serious adverse event should occur which is considered to be directly related to the scanning protocol, the CI will be contacted to assess the causality and expectedness of the event.

Definitions

The following definitions apply in this protocol:

An Adverse Event (AE) for this study includes any untoward medical occurrences in a participant which **have a causal relationship** with the study related procedures. (see table 1 for causal relationships)

A Serious Adverse Event (SAE) for this study is any untoward medical occurrence in a participant that:

- requires inpatient hospitalisation or prolongation of existing hospitalisation **(due to additional MRI scans)**.
- results in persistent or significant disability/incapacity **(due to additional MRI scans)**
- results in a congenital anomaly/birth defect **(due to additional MRI scans)**
- is life threatening **(due to additional MRI scans)**
- results in death **(within 90 days of last MRI scan and is due to additional MRI scans)**

Serious Adverse Events that are both **serious and unexpected** are subject to expedited reporting to the sponsor and the Research Ethics Committee (REC). The following list details all adverse events that should be recorded throughout the study.

- The study team are not expecting there to be any serious adverse events which specifically relate to the study procedures.
- Serious adverse events relating to radiotherapy treatment are not required to be reported for this study.

Reporting

Relevant AE's and SAE's for all patients should be captured from the moment a patient is registered onto the study for the duration of the study only. Should any AEs occur they will be recorded in the Case Report Form (CRF). Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning AE reporting should be directed to the Chief Investigator (CI) in the first instance.

Serious adverse events

All events meeting the criteria for seriousness as defined above must be reported immediately (within 24 hours of knowledge) by the study team to the CI using the Study SAE form. Any new information collected after sending the initial report should also be forwarded to the CI when available. The CI should assign the causality and expectedness of the event. Additional information should be sent to the CI if the reaction has not resolved at the time of reporting.

Study specific exceptions to expedited SAE notification and reporting

Radiotherapy treatment related toxicities, disease progression or events related to disease progression are **not** considered to be SAEs and should **not** be reported as SAEs. Adverse events relating to other anti-cancer treatments, that the patient may be receiving are **not** to be reported. Any events related to chemotherapy are not considered to be SAEs and should **not** be reported on the CRF. Due to the seriousness of the disease in this study, the following

situations that fulfil the standard definition of an SAE **are excluded** from expedited notification on an SAE form.

- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by study treatment
- Hospital admission related to disease progression
- Hospital admission related to radiotherapy and/or chemotherapy (delivery of treatment or toxicity)

Causality

Most adverse events and reactions that occur in this study, whether they are serious or not, will be expected treatment related toxicities due to the RT treatment, previous chemotherapy or due to expected disease progression NOT due to the study related procedures. The assessment of causality should be made using the definitions in table 1 below.

Relationship	**Description**	**Response**
Unrelated	There is no evidence of any causal relationship	Yes or No
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Yes or No
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	Yes or No
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes or No
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes or No
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.	Yes or No

Table 1. List of factors used to determine causality of AE from this study.

Reporting SAEs

All serious adverse events occurring during the study should be faxed to the Chief Investigator on 0161 446 8111, within 24 hours of the study team becoming aware of them.

Expedited reporting by the CI

The CI will notify the Sponsor and the REC of all events that are unexpected and related to the study treatments occurring in the study procedures within 15 days of notification.

Recruitment of Study Participants

Participant recruitment will only commence when the study has:

- Documented REC, and other regulatory approvals
- Confirmation of capability and capacity to run the study from the local R&D department
- A signed site agreement and all other essential documents are in place
- Final approval from the sponsor

• Identifying Participants

Potential participants will be identified via the multi-disciplinary team (MDT)/referral letters by members of the clinical team. They will be approached and given written information during their first oncology appointment. When they attend for their radiotherapy planning scan, they will be consented and screened for the study.

• Consenting Participants

Patients who are suitable for the study will be invited to take part and will be provided with a Patient Information Sheet (PIS) and Informed Consent Form (ICF), and will have the opportunity to discuss the study in detail with a clinician before deciding whether to participate.

The person taking consent will be Good Clinical Practice (GCP) trained, suitably qualified and experienced and will either be the CI or have been delegated this duty by the CI on the delegation log. The person taking consent will either be a consultant clinical oncologist, clinical fellow, registrar or nurse clinician who has had suitable training to do so.

After being given verbal and written information about the study, patients will be given sufficient time to consider participation (there is no minimum waiting period for this study) and the opportunity to raise any questions they may have. Three copies of the consent forms will be completed (one copy will be given to the patient), one copy will be retained in the hospital notes and a further copy will be stored in the Investigator Site File.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, would be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study.

• Screening for Eligibility

- Medical history and physical examination

- Assessment of performance status
- Satisfactory completion of MR safety screening form
- Pregnancy test where appropriate

• Randomisation

Randomisation is not applicable for this study.

• Registration

Once a patient is deemed eligible for the study and has consented to participate, they will be registered and given sequential ID numbers. These ID numbers will be used to identify all collected anonymised imaged data.

• Discontinuation/Withdrawal of Participants

Patients will be taken off the study for the following reasons:

- Patients withdraw their consent to the study.
- Patients cannot tolerate the MRI scan because they are claustrophobic or for any other reason.
- Image artefacts which are the result of *technical issues* render scans useless.

Patients can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. After withdrawal, no further data will be collected on or in relation to the participant.

The CI will be contacted as soon as a decision has been made to withdraw a patient from the study.

If a participant withdraws from the study prior to completion of the 3rd study MR scan then a new participant will be recruited onto the study until all of the funding is depleted.

Methodology

• Data Acquisition

Patients will undergo CT planning scans as per standard of care. Cone beam imaging will be performed on a daily basis (increasing the number of scans from an average of 10 to an average of 25), using the Christie HQ pelvic M20 setting to allow adequate imaging quality. The first study MR (MR-1) scan will take place on the first day of radiotherapy treatment; the second study MR (MR-2) scan will take place in the second week or third week. The third MR scan (MR-3) will be in the second or third week of treatment. The fourth MR scan (MR-4) will be the clinical scan with additional sequences and will take place in the fifth week of treatment. There will be at least one week between scans. These scans will be fitted around radiotherapy treatments which will allow us to minimise patient travel and time at the hospital.

- Image contouring

The initial MR scan (MR-1) will be used as a simulated planning scan to develop theoretical radiotherapy planning strategies. Gross Tumour Volume (GTV), CTV and OARs will be contoured on axial T2 sequences by the clinical fellow for both full and empty bladder scans (following the EMBRACE protocol). The daily cone beam CTs will also be contoured to ensure that the MRI scans represent an accurate representation of daily organ motion.

MR-2, MR-3 and MR-4 will be used to evaluate potential planning strategies. GTV, CTV and OARs will be contoured and used to assess coverage of CTV and used to estimate doses that would be given to OARs depending on the simulated treatment protocols. The 'cine' sequences will also be contoured and will be used to develop patient specific models of pelvic organ motion.

- Adaptive radiotherapy strategies

Radiotherapy strategies assessed will include a standard PTV with uniform 15mm expansion (current clinical standard of care). A further approach will be to create an ITV with individualised margins using information gathered from MR-1.

The first adaptive strategy developed will be a library plan of the day (POTD) involves creating a series of plans, typically three, that aim to encompass the likely cervix positions that will be encountered. These will be developed using MR-1 to create plans dependant on bladder filling - the most appropriate plan will be assessed for coverage for each MR-2, MR-3 and MR-4. If none of the plans are satisfactory, 'a robust plan' with large margins will be used.

The final adaptive strategy will be a library plan of the day plus (POTD+). For this strategy the images from MR-2 and MR-3 will be used to create at least one additional plan for the library based on full and empty bladder scans. The plan will be available for assessment for the next MR scan. This opens the possibility of starting from a smaller number of plans and building the library as required for each patient.

Full on-line re-optimisation will also be assessed.

Additional analyses may be performed using the anonymized images at discretion of the investigators.

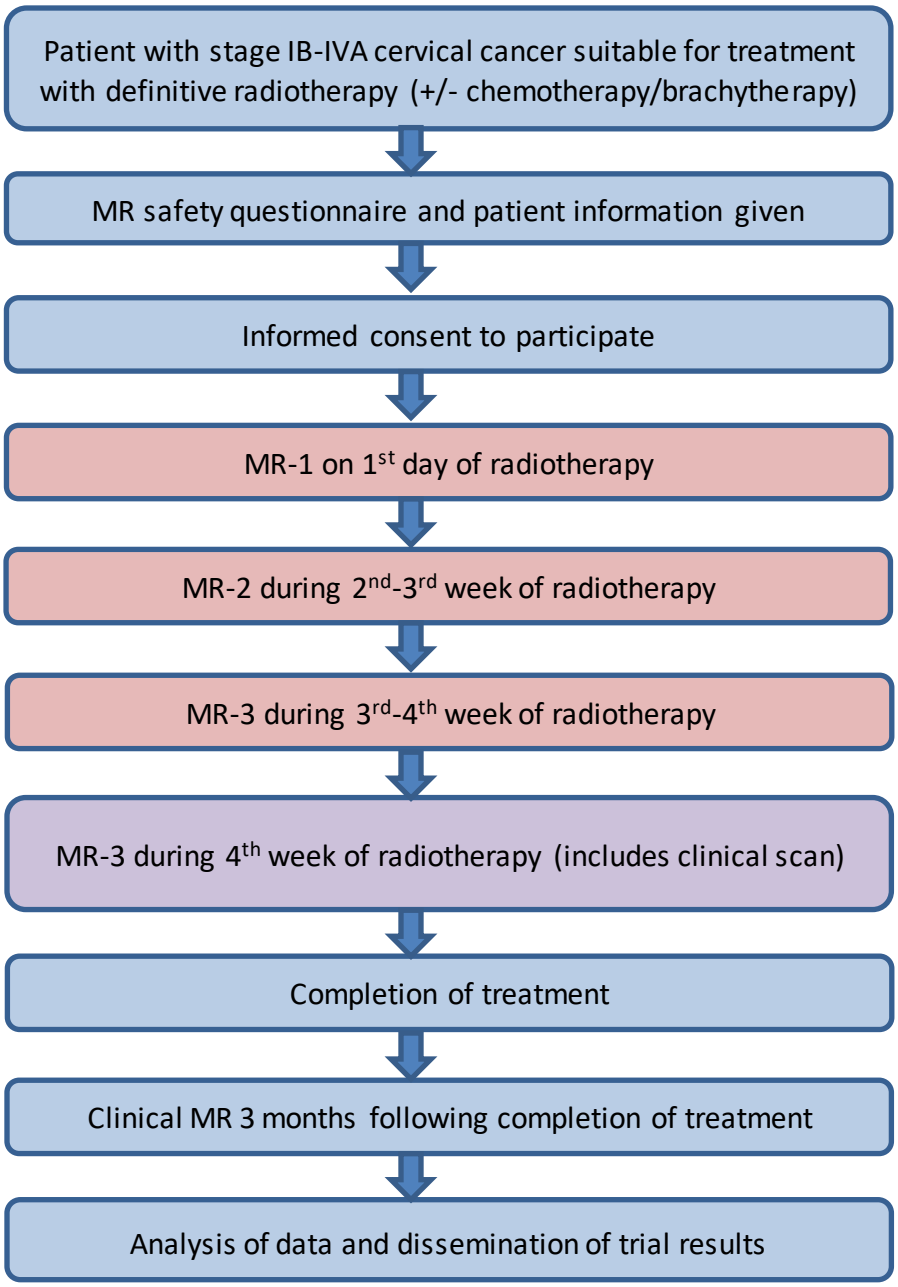
- Other methodology

Sequences from MR-1 (empty/full bladder and ‘cine’) will be used to create a patient specific model of bladder filling, and therefore cervix position, and therefore to create a personalised margin recipe. If insufficient information is available from the initial MR scan, sequences from further MR images will be used. These models will be used to assess if it is possible to stratify patients into groups with a large range of cervix movement and those where the cervix shows little positional changes.

To assess DWI imaging an Apparent Diffusion Coefficient (ADC) map will be created using 4 gradient values on each of the available MR. A region of interest will be determined with

maximum tumour volume (standardised for each patient over each scan) A variety of ADC parameters will be assessed.

Study Flow Chart



Summary of Examinations

Each patient will have three additional MR scan sessions. Patients will be scanned on a Siemens 1.5 T Aera wide bore scanner on a flat table top with a coil bridge. Patients will be scanned in radiotherapy planning position. Patients will be asked to empty their bladder and drink between 300ml -500ml water immediately prior to the scan.

The scan protocol will include an initial high resolution anatomical sequence to provide visualisation of OARs and tumour (with empty bladder). Other sequences will include a cine sequence with imaging every minute for 10 minutes (to assess intra-fraction motion) and a DWI sequence. These will be followed by a further high resolution anatomical sequence to represent pelvic organ position with a full bladder.

Each MR scan is expected to last approximately 45 minutes per patient. Each scan slot will last for 1 hour which includes time to position the patient correctly and a patient safety screening check to determine whether the patient is suitable for MR scanning.

Cone beam images will be performed using the Christie HQ pelvic M20 protocol and will take place on a daily basis during external beam radiotherapy.

	Baseline	Week -2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6-7	Week 20
Standard of care	Clinical review	RTP scan Consent	External beam radiotherapy (+/- chemotherapy)					Brachytherapy or external beam boost	Post treatment imaging
Written consent		X							
XVI			Daily Cone beam CT imaging (including 10 clinical scans)						
MRI scan	MR (Clinical)		MR-1	MR-2		MR-3 Scans at least 1 week apart	MR-4 (Clinical/research)		MR (Clinical)

Outcome measures

- Primary Outcome Measure

Assessment of different adaptive radiotherapy strategies with regard to coverage of CTV and dose to OARs. To identify the best approach, with regards to coverage and practicality, as a starting point for further studies.

- Secondary Outcome Measure

Correlation between DWI imaging on MR prior to and during treatment and clinical response to treatment on post treatment MR scan.

Assessment of individual bladder filling model – number of MR sequences required and ability to stratify patients into large or small cervix motion

Confidentiality and Data Protection

- ### Confidentiality

All identifiable records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC.

The Investigator and trial site staff involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any confidential information to other parties.

- ### Data Protection

All investigators and site staff involved with the study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

All images will be anonymised, i.e. all identifiable information will be removed. Sharing of anonymised images will be at the discretion of the Chief Investigator. Anonymised images may also be shared with Elekta and members of the MR-linac consortium to allow for software and workflow development.

- ### Publication Policy

The results of this study will be submitted to peer review journals for publication and will also be presented at national / international conferences.

Participants will be provided with a contact address and email from which to obtain results from the study and copies of publications.

- ### Statement of Indemnity

The University of Manchester will arrange insurance for research involving human subjects that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of The University of Manchester, subject to policy terms and conditions. In addition the study will be covered by the NHS insurance and indemnity scheme.

Trial Conduct

- ### Protocol Amendments

Any changes in research activity (except those necessary to remove an apparent, immediate hazard to the participant) will be reviewed and approved by the CI and submitted in writing to the University of Manchester, and to the appropriate REC, Regulatory Authority and local R&D for approval prior to enrolment into an amended protocol.

- ### Protocol Violations/ Deviations/ Serious Breaches

Investigators will not implement any deviation from the protocol without agreement from the CI, the University of Manchester and appropriate REC, Regulatory Authority and R&D department except where necessary to eliminate an immediate hazard to trial participants.

- ### Trial Record Retention

All trial documentation will be retained and archived in accordance with the existing regulations and the University of Manchester/The Christie's standard operating procedures. All trial documentation will be held by the investigator in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 5 years) for possible audit or inspection. Documents should be securely stored and access restricted to authorised personnel.

- ### End of Trial

The Chief Investigator and the trial team have the right at any time to terminate the trial for clinical or administrative reasons. The end of the trial will be reported to the University of Manchester and the REC within the required timeframe if the trial is terminated prematurely. Investigators will inform participants of any premature termination of the trial and ensure that the appropriate follow up is arranged for all involved. A summary report of the trial will be provided to the University of Manchester and the REC within the required timeframe.

Ethical and Regulatory Requirements

The study will be conducted in full conformance with principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and within the laws and regulations of the UK.

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by a main research ethics committee and R & D department, prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical approval prior to implementation.

The CI and sponsor will ensure that the main REC is notified that the trial has finished (either as expected or prematurely) within required timeframes with summary reports to be provided as required.

Statistical considerations

- Statistical Analysis

Dose volume histogram (DVH) parameters will be calculated for CTV coverage as well as dose to organs at risk (including bladder and rectum) for each strategy. The V95 (volume receiving at least 95% of total dose) will be used for both CTV and OARs. The volume of PTV and OARs will also be calculated. The averages per patient of the DVH parameters and PTV/OAR volumes obtained by each strategy will be compared using the student paired T test.

For assessment of DWI, average ADC maps will be created for a variety of parameters. Correlation between imaging metrics and baseline clinical features will be evaluated using the Mann Whitney test and confirmed using multivariate analysis if correlation is found.

- Sample Size

Funding is available for 20 patients to have 4 MR scans each (one added to the standard of care scan.) Each scan will include imaging with a full and empty bladder. Therefore there will be patient 80 MR data sets in total. As this is a pilot study a formal sample size calculation has not been performed. This study is hypothesis generating but the sample size of 20 patients with 4 scans should allow us to collect sufficient data to assess change in CTV (clinical target volume) to PTV (planning target volume) with mean and standard deviation. A similar study (Bondar et al 2012) used a sample of 14 patients with scan data from two time points and demonstrated a CTV-to-PTV volume by 48% +/- 6%.

If a participant withdraws from the study before completion of all 4 MR scan then a new participant will be recruited onto the study until all of the funding is depleted. Additionally, if the patient cannot tolerate the entire scan, e.g. because they are uncomfortable, then the data for those scans obtained will still be used for analysis.

Funding

Funding for additional imaging (to take place at The Christie NHS Foundation Trust) will come from within the academic supervisor's University of Manchester departmental budget.

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Appendices

Appendix 1 – MRI Patient Safety Screening Guidelines

Patient screening form: MRI Scan

It is important that you complete this questionnaire accurately so the scan can be carried out safely. Please tick yes or no to each question.

Office Use..

Patient Name…… Date of birth…….. Weight……..(kg)

- Have you ever had a cardiac pacemaker/Implanted defibrillator? Yes No
- Have you ever had an aneurysm clip? Yes No
- Have you ever had surgery to your heart? Yes No
- Have you ever had surgery to your head, brain or eyes? Yes No
- Have you **EVER** worked with metal for example using a high speed lathe, or had metal fragments in your eye? Yes No
- Have you ever had metal fragments such as shrapnel, in any part of your body? Yes No
- Have you ever had any operations involving the use of implants, metal plates, clips or breast tissue expanders? Yes No
- Have you ever had any type of electronic, mechanical or magnetic implant? Yes No
- Do you have any prosthetic limbs? Yes No
- Have you had surgery within the last 6 weeks? Yes No
- Do you have any kidney or liver disorders? Yes No
- Do you wear any of the following?

  Dentures Hearing aid Wig Drug/Skin patches
- Do you have any of these conditions?

Epilepsy Diabetes Heart disorders/Angina Allergies

- You may have an injection of **BUSCOPAN** when you attend for your scan. Buscopan may cause a dry mouth and blurred vision for up to 1 hour. Please do not drive while your vision is affected.

Do you have the eye condition Glaucoma?	Yes	No
Do you have the muscle condition Myasthenia Gravis?	Yes	No
Are you taking anticoagulants?	Yes	No

- **LADIES ONLY**

Could you be pregnant?	Yes	No
Are you breast feeding?	Yes	No
Do you have an IUD or sterilisation clip?	Yes	No

If you answered yes to any of the above questions, please give details below
……
……
……
I confirm that the information above is correct to the best of my knowledge and I agree to the scan.

Patient's signature…….. Date…….

Verified by…… (MRI staff signature)

For office use only

Coil used
Image sequences

Final check completed by……..

Radiologist…….. Scanning
Radiographer……..

Was a moving and handling assessment applicable?.....

IV contrast Cannulated by……..

Volume…….. Lot no. ……. Expiry …… Injected by……

Serum Creatinine…… Date sample taken…….. eGfr……..

Buscopan

Volume…… Lot No. …….. Expiry ……Injected by……

Saline

Volume…… Lot No. …….. Expiry ……Injected by……

Extravasation Details:

Date……. Time……..

Site of extravasation……

Contrast given……

Approximate volume of extravasation……..

Patient's signs and symptoms:

Burning ☐	Stinging ☐	Pain ☐	Discomfort ☐	Inflammation ☐	Swelling ☐

Other:

Extravasation recorded on CRIS…….. Datix form completed…….

Green Card completed…… ? ring patient following day…….

Appendix 2

List of publications and poster presentations
The following relate to the work presented in this thesis.

Publications

The Potential Value of MRI in External-Beam Radiotherapy for Cervical Cancer. Cree, A, Livsey J, Barraclough L, Dubec M, Hambrock T, Van Herk M, Choudhury A, McWilliam A. Clinical Oncology 30: 11: 737

Comparison of radiographer interobserver image registration variability using cone beam CT and MR for cervix radiotherapy. Rodgers J, Hales R, Whiteside L, Parker J, McHugh L, Cree A, van Herk M, Choudhury A, Hoskin P, McWilliam A, Eccles C.
The British Journal of Radiology 93:1112

Poster presentations

What are the main causes of interfraction motion of the uterine fundus and cervix? Cree A, Vasquez Osorio E, Dubec M, Mistry H, Hoskin P, Choudhury A, McWilliam A. ESTRO 2020 (Poster Highlight)

Can a dual isocentre technique enable cervix treatments on the MR-Linac? Chuter R, Cree A, Whitehurst P, Hales R, McWilliam A. ESTRO 2020 (Poster Highlight)

Quantitative analysis of mean ADC in cervix cancer patients during chemoradiotherapy Datta A, Dubec M, Cree A, Mistry H, West C, Choudhury A, Hoskin P. ESTRO 2020 (E-Poster)

Simulation of Automatic Contour Propagation using Previous Imaging on an MR-linac Jackson S, Cree A, Chuter R, McWilliam A. MR in the Radiotherapy Pathway 2019 (Oral Presentation)

Is Intra-fraction Motion an Important Consideration in MR Guided External Beam Radiotherapy for Cervical Cancer? Cree A, Dubec M, Mistry H, Hoskin P, Choudhury A, McWilliam A. ASTRO 2019 (E-poster)

Palliative radiotherapy to the pelvis for gynaecological cancer Cree A, Atturk N, Livsey J, Barraclough L, Haslett K, McWilliam A, Kennedy J, Choudhury A, Hoskin P. BGCS 2019 (E-poster)

A comparison of cone beam CT and different MR sequences for use in image guided radiotherapy for cervical cancer Cree A, Thiruthaneeswaran N, Dubec M, McWilliam A, Choudhury A. MR in RT 2018 (E-poster)

Motion of the uterine tip during radiotherapy is not correlated with survival. Cree A, Price G, Morrison S, Livsey J, Barraclough L, Choudhury A, McWilliam A. ESTRO 2018 (E-Poster)