MMED RESEARCH PROJECT

Rectal and bladder radiation dose during curative radiotherapy for cervix cancer at Universitas Hospital Oncology.

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Abstract.

Introduction and aim. *Cervical carcinoma is a huge burden on the South African population and health care system. Treatment of this disease has improved dramatically with the advent of 3D imaging capabilities combined with brachytherapy to deliver dose to the tumor and limit dose to organs at risk specifically the bladder and rectum. Recent guidelines give recommendations for dose limitations of these organs at risk, specific for a volume of 0.1cc, 1cc and 2cc. Our departmental dose prescription method for brachytherapy is unique by dose limitation to the rectum for each brachytherapy. The aim of this study was to determine the total dose of combined external beam radiotherapy(EBRT) and brachytherapy to the rectum and bladder for 0.1cc,1cc and 2cc and compare the outcome to international findings.*

Methods. *57 patients that completed definitive radiotherapy for cervical cancer were retrospectively reviewed. All patients received EBRT 50Gy in 2Gy daily fractions with brachytherapy 4-5 doses. The dose normalised to the rectum point receiving the highest dose. The combined dose of EBRT and brachytherapy was converted to bio-equivalent dose in 2Gy fractions (EQD2) for each of the volumes of the rectum and bladder.*

Results. *Mean EQD2 dose to the rectum 0.1cc: 63.8(3.3); 1cc: 60.4(2.2); 2cc: 58.9(1.8). Mean doses to the rectum was lower than described in the literature with no patient receiving more than the dose cutoff for 2cc(70Gy). Mean doses to the bladder 0.1cc: 87.4(18.5); 1cc:75,5(11.9) and 2cc: 71,6(10.0). These doses are also lower as described in the literature however two patients received dose higher that the advised cutoff to 2cc of 90Gy. This could have been avoided for one of the patients if the correct method of dose determination was followed.*

Conclusion. *As expected the current dose prescription method yields safe doses to the rectum. The bladder dose is a concern even though only two patients exceeded the tolerance and it could have been avoided. High variation in the bladder dose among patients suggests an opportunity for dose optimisation techniques. These findings should be correlated with clinical outcomes of toxicity.*

1) Introduction

Epidemiology**:**

Cervical cancer affects one out of 41 south african women. It is estimated that the disease kills approximately 8 women in the country every day.[1] This incidence mortality ratio is higher in developing countries than in developed countries. In the USA new cases are estimated at 12 200 per year with mortality rate of 4200. Globally 500 000 women develop this disease and 233 000 die from it annually.[2] In South Africa the incidence is higher due to the infection rate of human immunodeficiency virus (HIV) and Human Papillomavirus (HPV). Women with HPV co-infection with HIV have a higher rate of persistent HPV infection. Persistent HPV infection translates into higher rates of premalignant lesions and cervical carcinoma compared to HIV negative patients.[3] There are many types of genetically distinct HPVs. The high risk types are 16 and 18 and are most prevalent. There are six other types that are also important: HPV 31, 33, 35, 45, 52 and 58. Of interest is that type 16 is mostly found in squamous cell carcinoma and 18 mostly in adeno and adenosquamous carcinoma.[4] Since HPV is a sexually transmitted disease, cervical carcinoma can also be viewed as a sexually transmitted disease. The mechanism of carcinogenesis is by viral DNA integration into the host genome. This leads to over-expression of oncoproteins E6 and E7. E7 has its carcinogenic effect via the RB (retinoblastoma) protein and enhances progression through the cell cycle. It also inhibits CDKIs(cyclin dependant kinases) p21 and p27 also having a positive effect on cell cycle progression. E6 has a complimentary effect by binding to p53 and BAX. p53 is a tumour suppressor gene encoding a protein that has been described as “the guardian of the genome”. BAX is a pro-apoptotic protein encoded by the BAX gene and is part of the BCL-2 family, in short E6 inhibits apoptosis.
Consistent condom use significantly reduces the transmission of HIV and HPV from male to female sexual partners.[6] But despite this finding the prevalence of cervical carcinoma in Southern Africa suggests that the method is not effective in preventing cervical carcinoma. Currently HPV vaccination programs are implemented around the world. Bivalent, quadrivalent and 9-valent vaccinations are available and all contain at least high risk types 16 and 18. These are non-infectious Virus Like Particle(VLP) vaccines and the aim is to achieve seroconversion.[7] Vaccination is recommended at 11-12 years of age but can be initiated at 9 years and given up to the age of 26 although it is approved for women up to 45 years . Three doses are given, the second dose is given one to two months after the first dose and the last dose 6 months after the first dose. The young age of initiation is due to the fact that the vaccines are effective as prophylaxis only and thus must be given prior to sexual activity and possible exposure to HPV. There is data suggesting that two doses given at month 0 and again at month 6 in ages 9-14 is immunological non inferior to the 3 dose schedule.[8] In South Africa the HPV vaccination program was initiated in April 2014 for all girls 9 years or older in public schools. These girls where offered the two dose schedule of the bi-valent vaccine. Cervical cancer is the number one cause of cancer deaths for women age 15-44 years of age so the effect of the vaccination program can take time for the effect to be seen in clinical practice and is estimated that it will be seen in 20 - 40 years from now. Although this is an exciting prospect at this moment cervical carcinoma causes significant morbidity and mortality for south african women.

Anatomy:
Anatomically the uterus is divided into a superior uterine corpus and inferiorly the uterine cervix. The cervix is approximately 3x3 cm and is divided in a supravaginal and vaginal portion. The vaginal portion projects into the vaginal vault and contains the external cervical os. The anterior aspect of the uterus is related to the bladder and laterally the

broad ligaments. The broad ligaments extend from the lateral walls of the uterus to the pelvic walls and is formed by two layers of peritoneum. The round ligaments extends from the anterolateral aspect of the uterus and crosses the pelvic brim and leaves the abdomen via the abdomen inguinal ring. Posterior of the uterus the peritoneum turns superiorly and covers the anterior part of the rectum forming the recto-uterine pouch. Lymphatic drainage of the cervix is initially to the para-cervical nodes and from there to external iliac nodes and also hypogastric nodes. The obturator nodes are also involved as the innermost station of the external iliac nodes. From there the pelvic lymph drain to internal and para-aortic nodes. The uterine fundus drain mostly to para-aortic nodes via the broad ligaments.[2] Organs in close proximity to the uterine cervix is the bladder and the rectum. The bladder is a muscular hollow organ and as noted above it is situated anterior to the uterus in the pelvis, the superior extent of the bladder can vary with degree of distention. It has a base posteriorly, inferolateral surfaces, an apex and superior surface. The superior surface of the bladder is covered by peritoneum. Posterior to the uterus is the rectum. Approximately 12 - 15 cm long the rectum extends from its junction with the sigmoid superior to the puborectalis ring inferior. The superior third of the rectum has a peritoneal covering anterior and lateral. As it extends inferiorly the middle third only has peritoneum on the anterior aspect forming the recto-uterine space as noted above. The inferior third of the rectum has no peritoneal covering.

Histology:

Squamous cell carcinoma of the cervix usually originates from the transformation zone in the endocervical canal and is by far the most common histological type >90%. Progression of normal cells to low and higher levels of dysplasia follow a step wise progression, the higher the level of dysplasia the higher the likelihood of progression to carcinoma. Adenocarcinoma makes up approximately 7-10% of tumors.

Staging:

Invasive cervical carcinoma is staged using the International Federation of Gynecology and Obstetrics (FIGO)[9]. It can be summarised as:

Stage IA: Invasive carcinoma diagnosed by microscopy. Stromal invasion with a maximum depth of 5mm and a horizontal spread of 7mm or less.
Stage IB: Invasive carcinoma clinically visible lesion confined to the cervix or microscopic lesion with more than 5mm invasion or horizontal spread more than 7mm.
Stage II Carcinoma invades beyond the uterus but not to the lower third of the vagina or the pelvic wall
Stage IIA1: Carcinoma with no parametrial invasion. Clinically visible lesion 4cm or less
Stage IIA2: Carcinoma with no parametrial invasion. Clinically visible > 4cm lesion
Stage IIB: Carcinoma with parametrial invasion.
Stage IIIA: Carcinoma infiltrating the lower third of the vagina without pelvic wall extension.
StageIIIB: Carcinoma with pelvic wall extension and or causes hydronephrosis or non-functioning kidney or regional lymph node metastasis.
Stage IVA: Carcinoma invades the mucosa of the bladder or rectum and or extends beyond the true pelvis.
Stage IVB: Distant mets.

Lymphatic or distant hematogenous metastasis may occur and usually increases with an increase in stage. Although this is not always the case as small primary tumors may

infiltrate the bladder or rectum or have disseminated metastasis. Parametrial node involvement in Stage IIB disease can be as high as 21.5% and if parametrial nodes are involved 81% of cases could also have pelvic node involvement.[10] This finding underlines the importance of lymphadenectomy during radical hysterectomy or inclusion of parametrial tissue and pelvic lymphnodes during radiotherapy.

Treatment:

The treatment of cervical carcinoma consists of either surgery or radiotherapy combined with chemotherapy. Surgical options include simple conization or radical trachelectomy for early stage disease or radical hysterectomy and pelvic node dissection for more advanced disease. External beam and brachytherapy radiation with concurrent chemotherapy are considered for patients with a radical or curative intent. Patients with locally advanced disease St IB2 - St IV A can be considered for curative radiotherapy with brachytherapy. This can be administered to patients who are not surgically resectable or patients who are inoperable due to medical reasons. External beam radiotherapy precedes brachytherapy and covers the primary tumor with any area of extension from uterosacral, parametrial and vaginal. It also addresses microscopic nodal disease in the pelvis. The term brachytherapy is derived from the Greek word “brachy” meaning over a short distance. This type of radiation makes use of radionuclide sources to deliver a high dose to the tumor near the source and less dose to surrounding tissue. This form of treatment is essential in the curative radiotherapy regime because cure cannot be achieved by external beam radiotherapy alone because of the small bowel being in such a close proximity to the uterus. It is the dose limiting organ for external beam radiotherapy. External beam radiotherapy dose range is in the order of 45-50Gy, above this dose the small bowel dose tolerance is exceeded.[11] Brachytherapy has the advantage of steep dose gradients to limit dose to organs at risk, (the bladder and the rectum). This is described by the Inverse Square Law where the dose at a certain point is inversely proportional to the square of the distance from that point to the source. These radionuclides can be inserted in the tumor either by interstitial implants or intracavitary brachytherapy and is achieved by manual or remote after loading. Intracavitary brachytherapy is used in our institution and is achieved by a central applicator and ring after loading system. The radionuclide source is $Iridium^{192}$, it decays by emitting beta particles and gamma radiation. It emits photons with average energy of 0.38MeV and has a half-life of 74 days.[12] The $Iridium^{192}$ delivers a high dose rate(HDR) defined as>12Gy/h. The radiation is prescribed to Point A which is defined by the American Brachytherapy Association as follows: a perpendicular line through the lateral most dwell positions in the ring. At the point of intersection of this line with the central applicator move superiorly the radius of the ring and another 2cm. From this point move lateral 2cm on each side of the applicator and this is Point A on both sides.[13] Point A is intended for use in a 2D imaging planning technique when using radiographs, with this technique target volume delineation is not possible. The International Commission on Radiation Units and Measurements(ICRU) report vol. 38 defined rectum and bladder points for organ at risk specification during the use of radiographic imaging. The report defined the bladder point as on the surface of a Foley catheter balloon filled with 7cc of iodinated radiographic contrast positioned at the trigone of the bladder. The rectal point is defined as 5mm posterior to the vaginal wall directly posterior to the centre of the ring. There is data to suggest that the bladder point and to a lesser extent the rectal points are not indicative of the highest dose received by these organs. These reference points have been compared with CT based volumetric minimal doses to $2cm^3$ (D2cc) of the bladder and rectum receiving the highest dose. The findings were that the ICRU rectal point is a reasonable surrogate for D2cc of the rectum but not for the bladder. The ICRU reference point of the bladder significantly underestimated the dose compared to the D2cc.[14]

Tumor volume (GTV) is regarded as a very important prognostic factor for local control, 3D imaging has the advantage of obtaining this volume as well as the clinical target volume (CTV). Complete coverage of these volumes with brachytherapy can be expected to yield better outcomes. Guidelines on GTV and CTV including High Risk (HR) CTV and Intermediate Risk (IR) CTV has been published. These guidelines by Gynaecological GEC-ESTRO Working Group uses MRI based delineation of the tumor volume at diagnosis and at each brachytherapy.[15] A comparison of CT and MRI contours has been done for tumor and organs at risk in a prospective trial. The contours and dose volume histograms (DVH) where compared for organs at risk (bladder, rectum and sigmoid) and HR and IR CTV as contoured on CT and MRI images using the GEC-ESTRO guidelines. The results showed that CTV was significantly over-estimated on CT images as compared to MRI. However the OAR DVH values for volumes 0.1cm^3, 1cm^3 and 2cm^3 where similar. Thus although MRI remains the standard for CTV delineation, CT imaging is acceptable for OAR contouring.[16] Contouring the external organ walls is technically less complex than contouring the organ wall itself. The obvious advantage when delineating the organ wall only as posed the external organ margin is that dose volume histograms are more specific to the organ tissue at risk because the dose delivered to the content of the bladder or rectum does not influence toxicity. This is however very time consuming especially if considered that each patient will have 4-5 brachytherapy treatments and each CT slice has to be contoured individually.

Figure 1a:

Figure 1b:

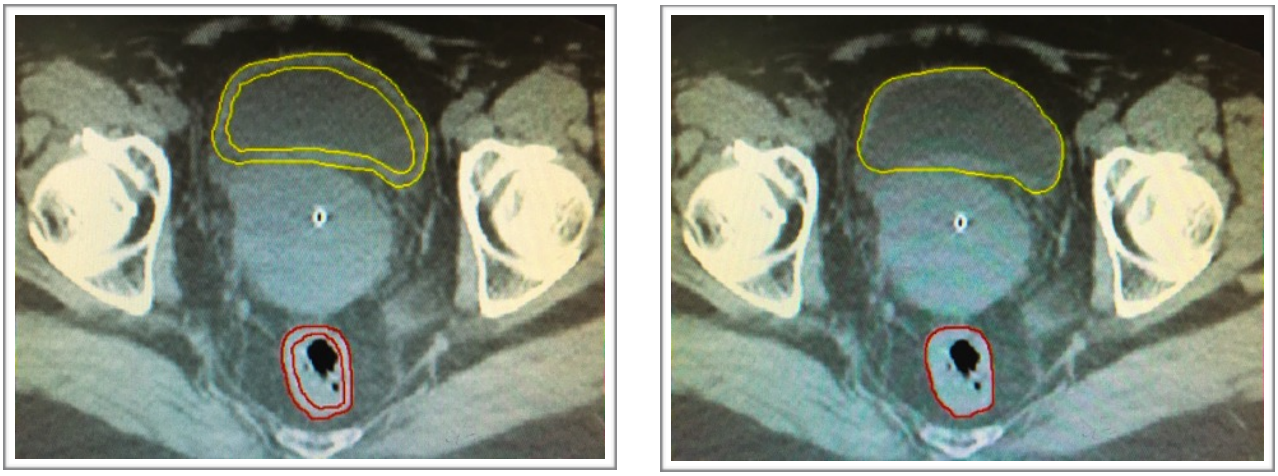


Figure 1: Transverse CT images showing central applicator in the uterus and rectum and bladder contours. Figure 1a shows organ wall contours, it can be seen that especially the rectum wall is not clearly visible on CT images and is time consuming to delineate. The bladder wall is easier to identify but it becomes more challenging when the bladder is empty. Figure 1b shows the external organ contour only. This approach is less time consuming and leaves less room for uncertainty regarding the extent of the organ.

The effect of external organ contours and organ wall contours on DVH was reviewed in a prospective study of 15 patients diagnosed with cervical carcinoma. These volumes were also compared to the ICRU reference points for the bladder and rectum. A good correlation between external organ contour and organ wall contour was observed for both the rectum and bladder for $2cm^3$ volumes. This correspondence was lost when larger volumes where used $5cm^3$ or $10cm^3$. In this study the rectum ICRU point also overestimated the dose for $2cm^3$ of the rectum wall. In contrast the bladder ICRU point underestimated the dose to $2cm^3$ of the bladder wall in case of inappropriate balloon placement.[17]

Now the question beckons why all the focus on $0.1cm^3$, $1cm^3$ and $2cm^3$ volumes of the OAR? These volumes have been found to correlate well with clinical outcomes. Clinical and endoscopic rectal side effects were compared to dose volume parameters for 35 patients receiving definitive radiotherapy for cervical carcinoma. Five of these patients had ulceration seen on endoscopy that correlated with the $0.1cm^3$. Also endoscopic findings were more pronounced in patients with higher dose to this volume.[18] Mean values in this study for the rectum was: 81Gy +- 13 to $0.1cm^3$, 70Gy +- 9 to $1cm^3$ and 66Gy +- 8 to $2cm^3$. Another study compared DVH parameters and late side effects in MRI guided adaptive brachytherapy. Grade 3-4 late rectal toxicity correlated well with D1cc and D2cc but not D0.1cc. 75Gy as a cutoff level for D2cc was recommended to predict morbidity, patients receiving more than 75Gy had a higher percentage of morbidity. For bladder toxicity all DVH parameters (D0.1cc, D1cc and D2cc) were predictive of toxicity. However the D0.1cc and D1cc did not add additional benefit in prediction and therefore the conclusion was that D2cc remains the strongest predictor and a cutoff level of 100Gy can be used for clinical morbidity.[19] Mean doses in this study for rectal D2cc where: 65Gy +-12 and bladder D2cc 95Gy +-22Gy. These volumes are also recommended for reporting by the GEC - ESTRO working group II.[20] Where 0.1, 1, and $2cm^3$ are recommended for reporting and 5 and $10cm^3$ are optional.

At this stage it is important to note that not all external beam and brachytherapy regimens are the same in terms of total dose or fractional dose. Common brachytherapy dose regimens in use are 7Gy x 4, 6Gy x 5, 5Gy x 6. Combined with a wide range of external beam radiotherapy prescriptions of 30.6-54 Gy in 1.8Gy fractions or 2Gy fractions.[21] To be able to compare all these regimens with each other the biological equivalent dose in 2Gy fractions needs to be calculated for both brachytherapy and external beam therapy and added together. This is done using the linear quadratic formula with α/β ratio of 3 for organs at risk.[22] The summation of the external beam and brachytherapy doses are done under the assumption that the full dose of external beam radiation covers the volume mentioned. A further assumption is that the brachytherapy applicator is in exactly the same position with every fraction. Although this is probably not the case because tumor volume changes during the course of radiation and the brachytherapy applicator changes the normal anatomy with each insertion. However it must be assumed that each brachytherapy fraction is given in the same location to be able to account for a worst case scenario.[20]

In a nutshell then the most important factor that causes late side effects is the total combined dose from external beam radiotherapy and intracavitary brachytherapy. Dose constraints suggested are D2cc < 75Gy (< 70Gy if possible) for the rectum and D2cc < 90Gy for the bladder.[22] The aim of this study was to compare the dose to these volumes of patients treated in our department to that of the above mentioned literature.

2 Aim:

The aim of this study was to do a retrospective analysis of the dosages received by the rectum and bladder during definitive external beam radiotherapy and intracavitary brachytherapy. This was done by collecting the data of 57 patients that were seen as new patients from Jan 2013 to Dec 2013 at Universitas Oncology department and subsequently received definitive radiotherapy.

3 Methodology:

Study design:

The study design was that of an observational descriptive study. A group of patients was described according to dosages they received.

Study population:

Patients seen in our department from January 2013 through December 2013 with newly diagnosed cervical cancer was eligible for the study if they received definitive radical radiotherapy. Patients from Lesotho or the Northern Cape treated at our department were not included in the selection because after completion of their radiotherapy they follow up at their respective facilities. Private patients treated in our facility was also not included due to the same reasons. A total of 62 patients met the above description and were screened. Of the 62 patients 3 did not complete brachytherapy due to either complications during applicator insertion or repeated uterine perforation. A further 2 patients received brachytherapy with a dose of 250cGy to the rectum per fraction and not 200cGy as with our routine prescription method and was also excluded. This meant a total of 57 patients were eligible for the study. On the outset the aim was to randomly select 50 patients from the group but in the end a amendment was made to the protocol and all 57 patients were included. Stage of the disease was not included in the study because it does not influence the external beam or brachytherapy dose prescription.

Measurements:

Placement of the brachytherapy applicator and ring was done with the patient in lithotomy position and under awake sedation. Before each brachytherapy patients were given a laxative and encouraged to empty their bowel just prior to the treatment. In our department we utilise the Elekta Nucletron® Ring CT/MR applicator set with remote afterloading. Two sets were available at the time: 45° and 60° with applicators of 40mm and 60mm and a ring diameter of both 26mm and 30mm with rectal retractor for both 45° and 60°.

Figure 2. Example of a ring and central applicator assembled with the rectal retractor. Nucletron®

After insertion of the applicator the patients were scanned using CT imaging with the patient in a supine position. The images where transferred to the planning system to confirm correct positioning of the applicator and to determine the dose of radiation that can safely be given using the Oncentra® planning software.

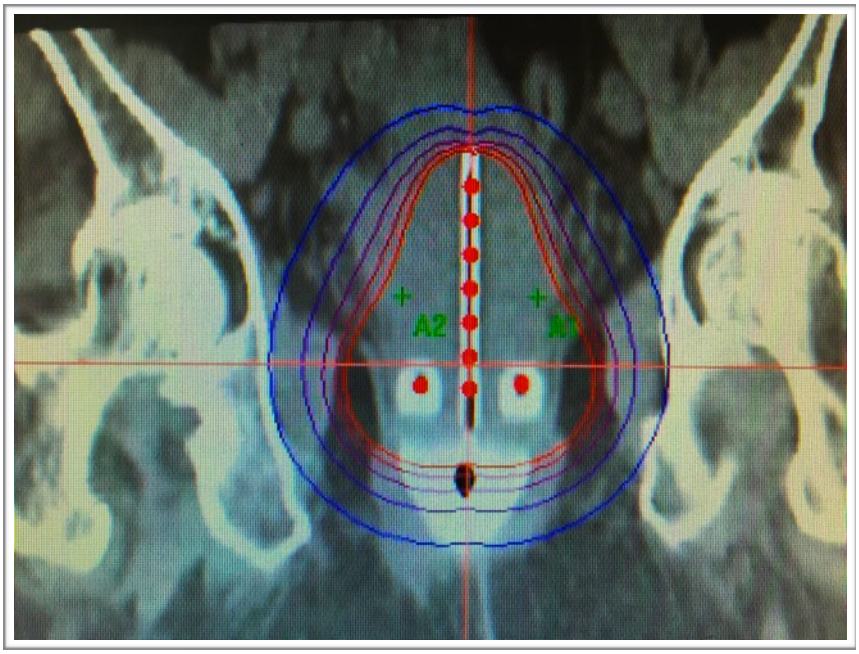
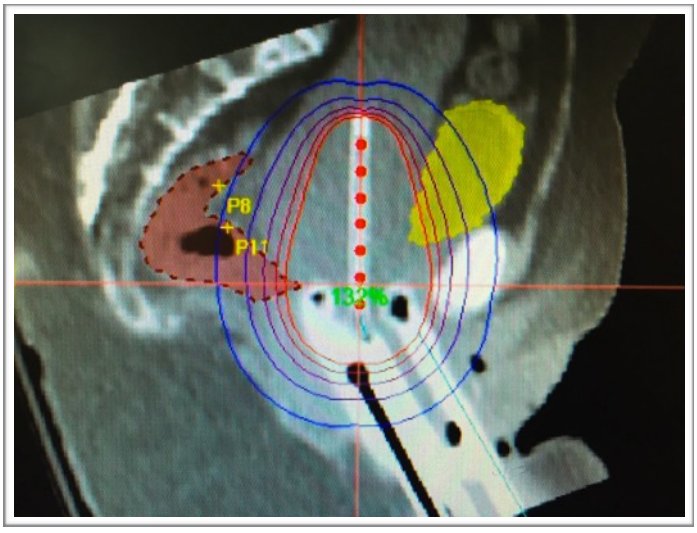


Figure 3. Coronal section CT image showing the central applicator and ring with surrounding dose distribution in a pear shape. Point A is marked in green. The red markers are the dwell positions of the Iridium^{192} source.

During each brachytherapy treatment the registrar doing brachytherapy on the particular day would have contoured the bladder and the rectum. These contours were retrospectively reviewed by the researcher and were only adjusted if deemed necessary according to available guidelines.[20] The rectum was contoured from the junction with the anal canal at the puborectalis muscle up to the junction with the sigmoid colon. The dose was prescribed to Point A and given in 4-5 fractions with total dose >1200cGy and rectal dose not exceeding 200cGy per fraction. This was achieved by placing rectal points in the anterior rectal wall closest to the applicator and ring on the images obtained from CT.

Figure 4. Sagittal CT images showing the applicator and dose distribution. The bladder is contoured in yellow and the rectum in brown. Rectal points are visible on the anterior border of the rectum. The point that would receive the highest dose would determine the dose prescribed.



The physicist then normalised the prescription dose for that particular brachytherapy to the rectum point that would have received the highest dose to limit the dose to 200cGy. The source used was Iridium^{192} with remote after loading. The dwell position of the source determined the dose and was given on the above constraint. After completion of treatment the doses to the organs at risk for the different volumes were recorded and entered into a Excel spreadsheet programmed by our physics department to convert the dose into EQD2. All patients received external beam radiotherapy to the pelvis with total dose of 50Gy in 2Gy daily fractions regardless of stage of the disease using a four field box technique without an midline shield. Patients received weekly concurrent Cisplat 25mg/m^2 at the discretion of the treating physician. Together the external beam and total brachytherapy dose was then converted to equivalent dose in 2Gy fractions(EQD2) for the bladder and rectum and included the volumes 0.1, 1, and 2cm^3.

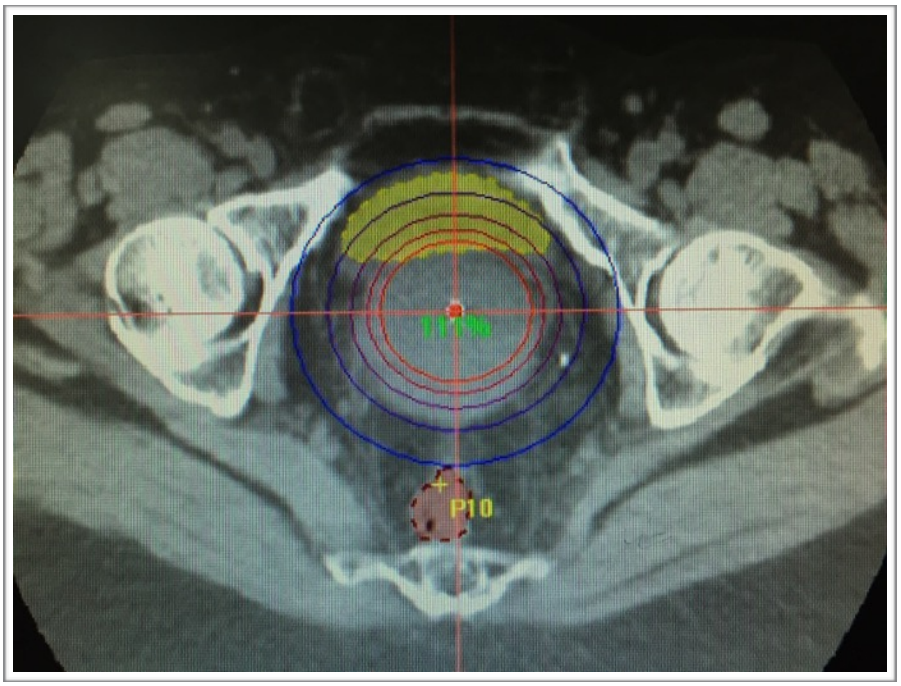


Figure 5. Transverse CT image showing the central applicator and bladder and rectum contoured in yellow and brown respectively. The circular dose distribution can be seen expanding outward from the source. The bladder would receive much higher dose due to the close proximity to the applicator.

Statistical analysis:

The completed data for all 57 cases was analysed by the department of bio-statistics.

Results:

Rectum doses:

As expected the mean EQD2 decreases as the volume increases. This is consistent with the physical aspect of brachytherapy having a rapid dose drop inverse to the distance from

the applicator. The D0.1cc would be the closest to the applicator being the smallest volume. As the volume increased the Mean EQD2 decreases.

Table 1a. Rectum dose per volume

Rectum EQD2	Mean	Median	Standard Deviation	Min	Max
D0.1cc	63.8	63.1	3.3	57.2	73.9
D1cc	60.4	60.1	2.2	56.0	65.7
D2cc	58.9	58.9	1.8	55.3	63.4

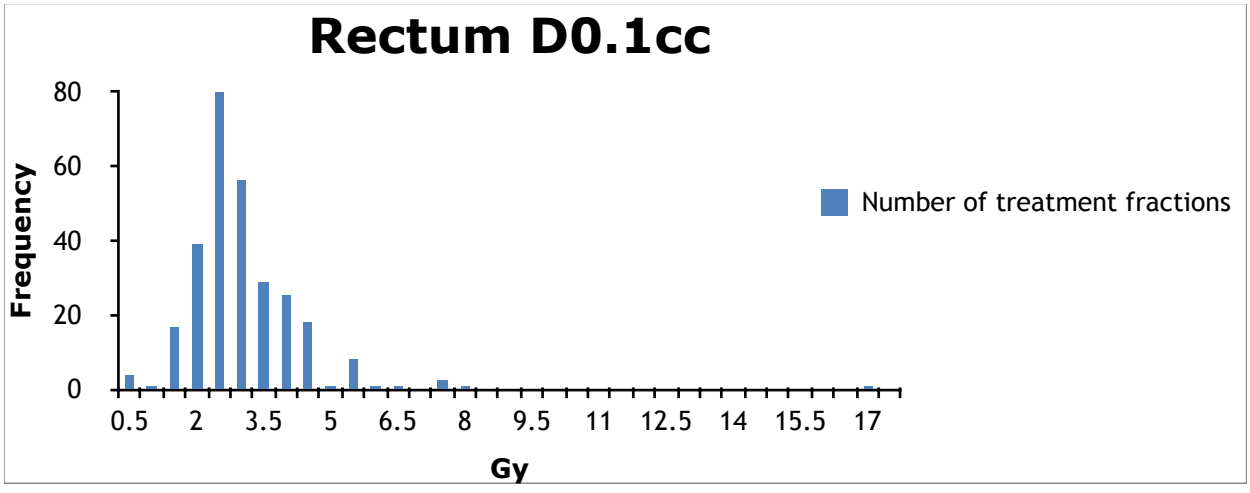
Table 1 shows the mean doses per volume in Gy. The maximum dose to D2cc was 63.4 and is lower than the prescribed dose cutoff of 75Gy.

Considering that the rectal point which is used during each brachytherapy fraction would get 50Gy from external beam radiotherapy and no more than 2Gy per brachytherapy fraction X5 a table giving the rectal prescription point total dose could be given as:
Table 1b

EQD2	mean	median	Std. dev.	Min	Max
Rectal point	60	60	0	60	60

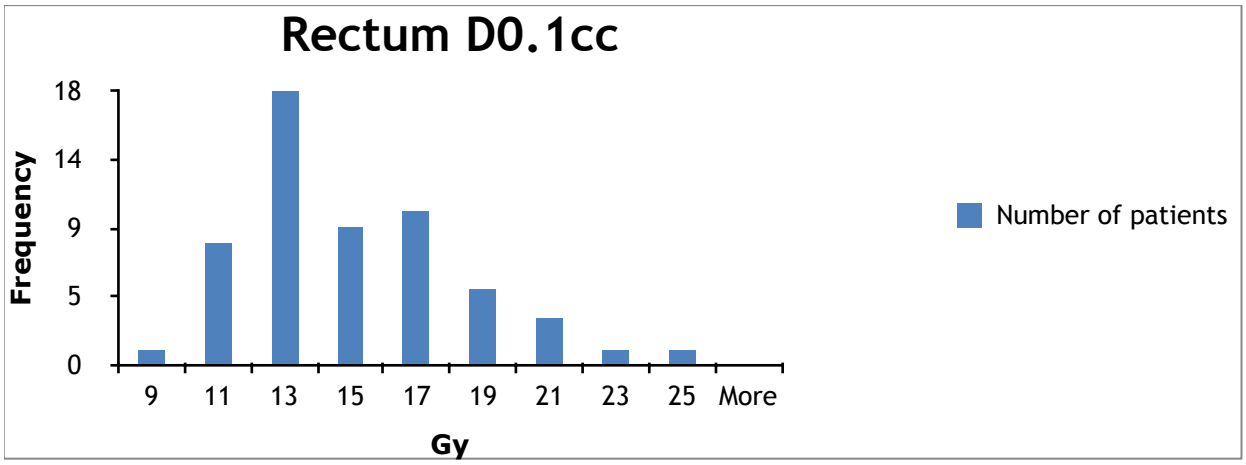
When comparing table 1a to 1b it would seem that the rectal point dose compares the best with the volume for D1cc. This is only of academical value because the rectal point would almost never be at exactly the same anatomical location for each brachytherapy fraction.

Graph 1a. Number of brachytherapy fractions and dose to D0.1cc per fraction



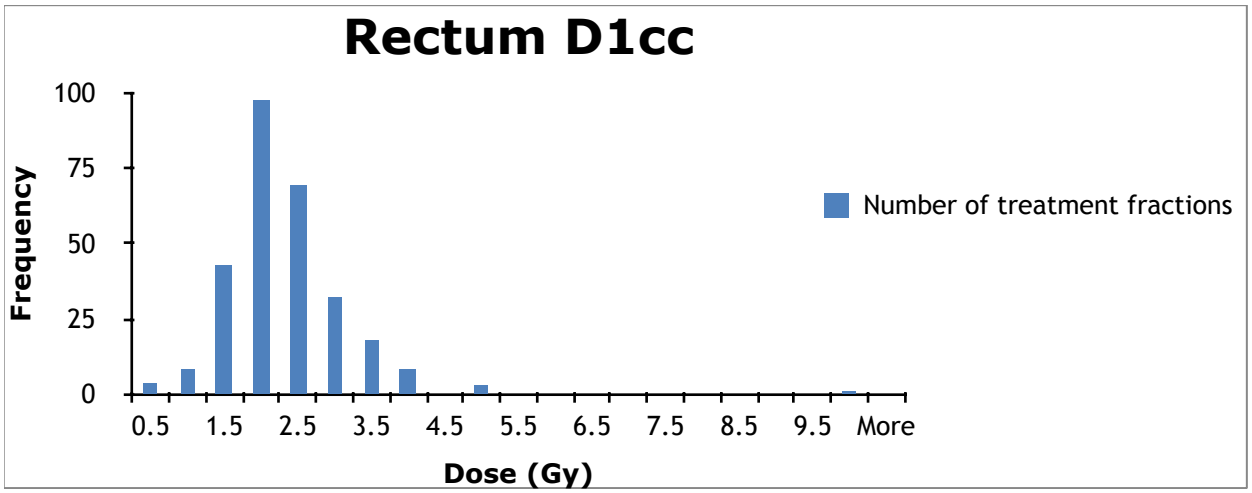
Graph 1a illustrates all of the individual fractions given to 0.1cc of the rectum. A total of 284 fractions were given. 62% (175) received between 2 and 3 Gy per fraction. One patient received a dose of 17Gy as seen to the far right of the graph, this was due to incorrect point placement as described below and could have been avoided.

Graph 1b. Brachytherapy total dose to D0.1cc



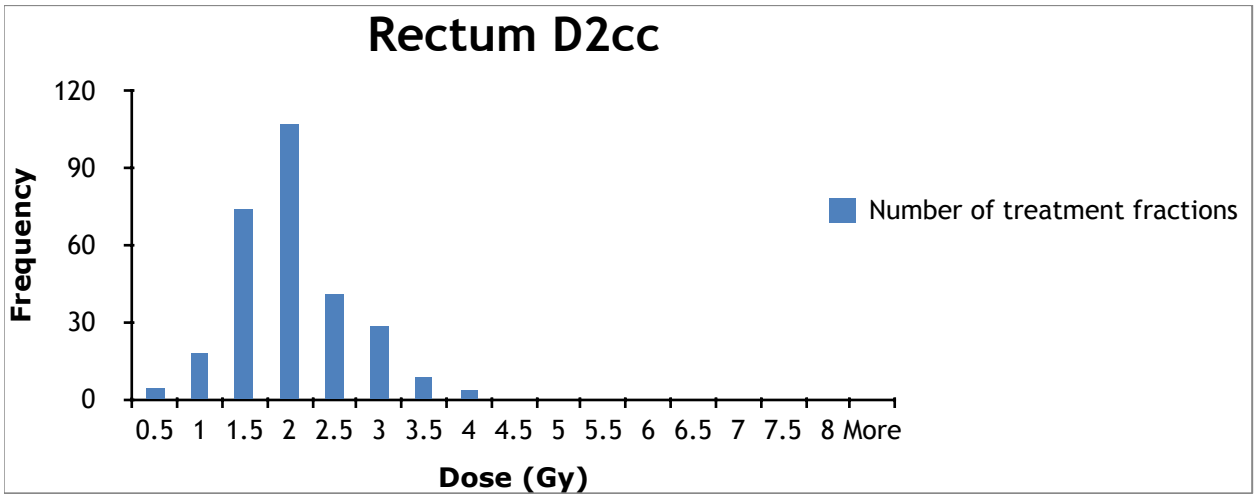
Graph1b shows total brachytherapy dose per patient to 0.1cc of the rectum

Graph 2a. Number of brachytherapy fractions and dose to D1cc per fraction



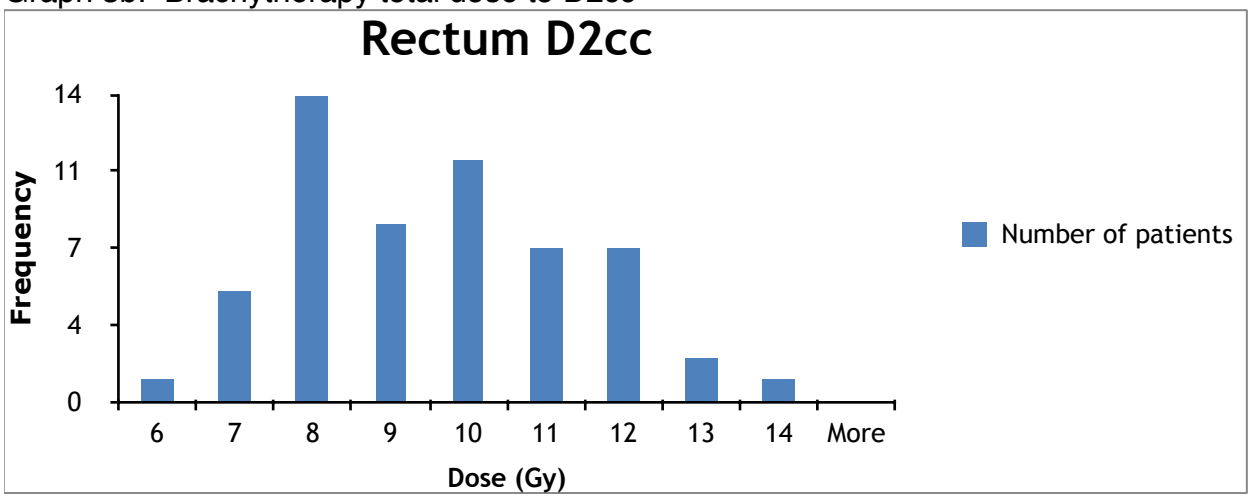
Graph 2a illustrates the frequency of doses for individual fractions to D1cc. As expected the doses would be lower for this volume but also more consistent with 74% (210 fractions) receiving dose of between 1.5 - 2.5 Gy to D1cc per fraction.

Graph 3a. Number of brachytherapy fractions and dose to D2cc per fraction



Graph 3a illustrates the frequency of doses for individual fractions to D2cc. More consistent doses was achieved for this volume with 78% (222 fractions) receiving between 1.5 and 2.5Gy to D2cc.

Graph 3b. Brachytherapy total dose to D2cc



Despite the fact that the rectum is used as a point to determine dose prescription there is still large variation in the total brachytherapy dose per patient to D2cc. As seen above the the minimum dose was 5.3Gy and maximum 13.4Gy.

Bladder:

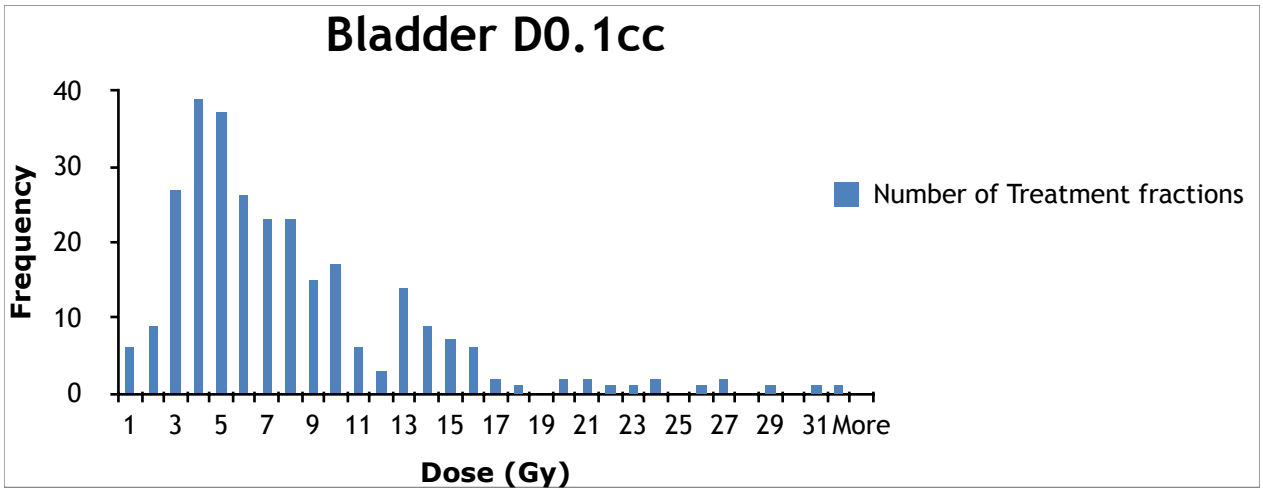
The bladder dose showed the same trend with decrease in mean EQD2 as the volume increased.

Table 2. Bladder dose per volume

Bladder EQD2	Mean	Median	Standard deviation	Min	Max
D0.1cc	87.4	82.45	18.5	61.7	145.5
D1cc	75.5	71.18	11.9	59.1	113.0
D2cc	71.6	68.24	10.0	58.2	104.0

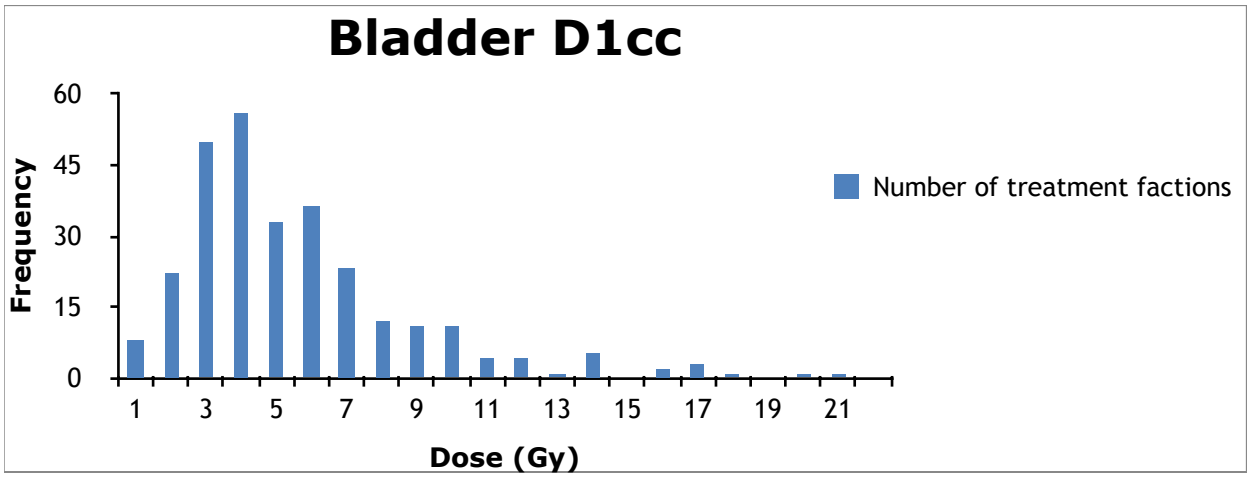
Table 2 shows the bladder mean dose per volume. Maximum dose to D2cc was 104Gy and above the 90Gy cutoff.

Graph 4a. Number of brachytherapy fractions and dose to D0.1cc per fraction



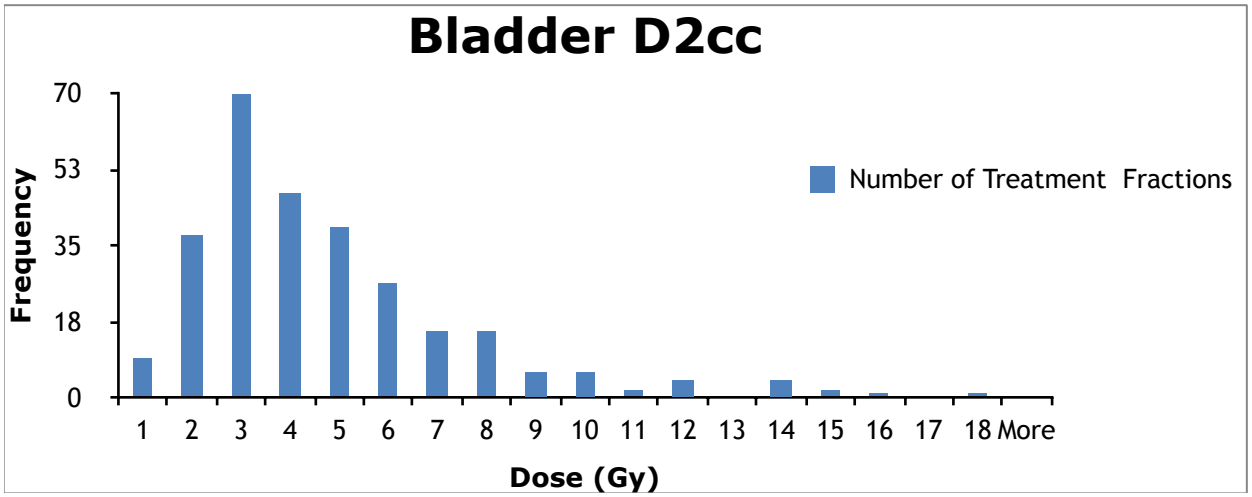
Looking at graph 4a there seems to be relative consistency of dose delivered to D0.1CC of the bladder per fraction at lower doses between 3 and 9 Gy. But there are many single fraction doses between 20 and 30Gy. The mean is 7,4Gy but the median 5,9Gy with a maximum dose of 31,1Gy to D0.1cc. The patient that received 31,1Gy was one of the two patients that had an incorrectly placed rectal points. However there is still reason for concern regarding the high frequency of high doses delivered to the bladder.

Graph 5a. Number of brachytherapy fractions and dose to D1cc per fraction



The uneven distribution of dose per fraction continues as the volume increases but is less pronounced with maximum dose 20Gy and mean dose 5,1Gy and median 4,2Gy

Graph 6a. Number of brachytherapy fractions and dose to D2cc per fraction



The trend continues for D2cc with maximum dose 17,79Gy. Median 3,59Gy and mean 4,3Gy.

The mean combined external beam and brachytherapy dose for D2cc was well within the prescribed dose cutoff of 95Gy. Only two patients received more than 90Gy to D2cc(104Gy and 94Gy).These figures were also lower than that found in the literature and is below the clinical cutoff level. Further, one of these could have been avoided if the correct method of dose determination was used. (See below).

6 Discussion:

Cervical brachytherapy has come a long way from 2D orthogonal treatment planning to 3D image guided techniques. As is the case in our department. Our dose prescription process is unique and hence the need to have a better understanding of dose to the organs at risk compared to international literature. The long term goal would be to optimise our cervical cancer brachytherapy technique. Since implementation of our CT image guided brachytherapy unit many studies have shown correlation of dose to organs at risk and clinical side effects. Clear guidelines are now available for treatment planning and dose constraints. Comparison of different regimes are also now possible due to a common denominator the EQD2. Regimes that give higher brachytherapy doses because the external beam doses are lower, for instance a regime of 45Gy given in 1.8Gy fractions has a EQD2 of 43,2Gy. This allows larger brachytherapy doses to be given.

Both mean and median were determined due to the concern of a skewed data set with a few outliers. For the rectum the mean and the median were similar but not for the bladder, this could be explained by the the fact that the dose is determined using the rectal point and thus should be more consistent. The standard deviation for the bladder was much bigger than the rectum for the same reason.

The results from the rectum doses show that they are well below the tolerance dose advised for D2cc. This was expected because we use the rectum as a way to determine dose per fraction of brachytherapy. Standard deviations are low for all the rectum volumes and that indicates that there is less variation across the dose received between the fractions, this was also expected, again because the rectum is the determining factor in the prescribed dose. Comparing our findings with that of other published literature we see that in this study the doses are lower across all the volumes. For the D0.1cc no patients received more than 90Gy. Although this is not a clear guideline it was found that rectal ulceration did correspond to the volume of 0,1cc receiving more 90Gy.[18]

Comparing our findings with results from other publications:

Table 3. Mean rectal dose during **MRI** based brachytherapy compared to our data.

Rectum	Mean(our data)	Mean	Standard deviation
D0.1cc	63.8	81	13
D1cc	60.8	70	9
D2cc	58.9	66	8

Correlation of dose–volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. P.Georg et al.[18]

Table 4. Mean rectal dose during **adaptive** brachytherapy.

Rectum	Mean(our data)	Mean	Standard deviation
D0.1cc	63.8	86	27
D1cc	60.4	69	14
D2cc	58.9	65	12

Dose–Volume Histogram Parameters and Late Side Effects in Magnetic Resonance Image–Guided Adaptive Cervical Cancer Brachytherapy. P.Georg et al.[19]

Table 5. Mean rectal dose during CT based treatment planning.

Rectum	Mean(our data)	Mean	Standard deviation
D2cc	58.9	65.9	3.8

Adaptive brachytherapy of cervical cancer, comparison of conventional point A and CT based individual treatment planning. A.D. Wanderås et al.[23]

In table 3, 4 and 5 it can be seen that our study found consistently lower mean dose to all three volumes for the rectum.

Bladder:

Larger variation was seen in the bladder doses. This could be because the bladder does not influence the current dose prescription method. Higher doses for the bladder is consistent with existing data. Although two patients received more than the prescribed cutoff dose, the mean doses of all the volumes are below what is found in the literature. Due to normal anatomical anteversion of the uterus as is seen in figure 4. the bladder could be closer to the applicator than the rectum and receive a higher dose. Fortunately the bladder has a higher tolerance dose than the rectum.

Comparing our findings with results from other publications:

Table 6. Bladder mean dose during image guided adaptive radiotherapy.

Bladder	Mean(our data)	Mean	Standard deviation
D0.1cc	87.4	162	75
D1cc	75.5	108	31
D2cc	72.6	95	22

Dose–Volume Histogram Parameters and Late Side Effects in Magnetic Resonance Image–Guided Adaptive Cervical Cancer Brachytherapy. P.Georg et al.[19]

Table 7. Mean bladder dose during CT based treatment planning.

Bladder	Mean(our data)	Mean	Standard deviation
D2cc	72.6	85.2	3.4

Adaptive brachytherapy of cervical cancer, comparison of conventional point A and CT based individual treatment planning. A.D. Wanderås et al.[23]

The results of this study is not unexpected. Although it has not been confirmed in a clinical trial, the impression in our follow up clinic is that very few patients complain about severe late toxicity from the bladder and rectum. This together with the observation that our brachytherapy doses are usually lower than 5-7Gy per fraction as described in the literature started the curiosity to determine the dose to organs at risk in our department. As noted above the most used volumes are D2cc to predict clinical outcomes and this volume has clear guidelines for dose. limitations. We included D0.1cc, D1cc and D2cc to have a complete set of data for comparison.

Possible limitations of this study are the relatively small amount of cases included for evaluation. The wide variety of doctors that were involved in the initial contouring of the organs at risks leeds to a lack of consistency as inter-observer variation is a natural phenomenon although the volumes were reviewed by a second party. That being said only the researcher reviewed the organ volumes which could lead to bias.

A reason for concern however is the couple of patients that had higher than advised dose to the bladder. Although this was not the aim of this study, further investigation of these two cases where done to look for irregularities. For both of the patients the rectal point used to determine the dose did not correspond to the contoured volume for one of their five fractions.

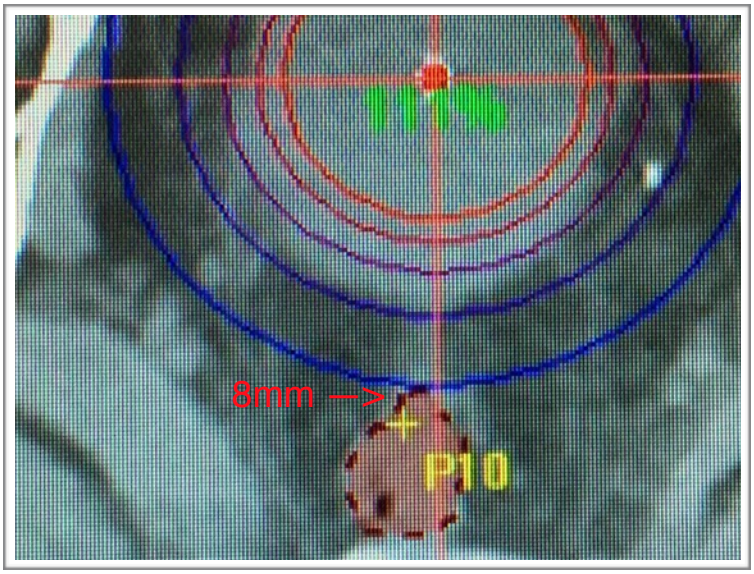


Figure 6.

As an example in the above image it is demonstrated that the point (yellow cross) is not placed on the anterior rectal wall. The point was 8.6mm posterior to the anterior edge of the rectum. The dose for this case was recalculated to determine what the dose would have been if the point was correctly placed. For this specific case the dose given to D2cc of the bladder was 94Gy, it would have been 85.3Gy if the correct point was used and thus within the dose tolerance. For the second case the dose would have been significantly lower but still above the advised cutoff of 90Gy.

Conclusion:

Going forward it seems safe to say from this retrospective analysis that our current method of brachytherapy should not exceed dose tolerances for the rectum but the bladder might be at risk of exceeding the tolerance if the method is not correctly applied. Since the initiation of this study more comprehensive training is given to new registrars before they can proceed with brachytherapy unsupervised. Bladder dose restriction by determining the bladder dose during the course of brachytherapy could further prevent exceeding the tolerance. High variation in the bladder dose suggest that more can be done to optimise the dose prescription to have a better consistency between the trade of to limit toxicity to the organ at risk but optimise dose to the tumor.

These numerical results would ideally have to be confirmed with clinical findings to determine if our patient population has the same clinical cutoff for prediction of toxicity as the international literature suggests before any practice changing could be advised. Since 2012 all patients from the Free State that received definitive radiotherapy for cervical carcinoma is being followed up and side effects are noted with each clinical visit. The 57 patient cases involved in this study is part of that follow up group and to do a cross reference of the findings in this study with their actual toxicity profile would be very insightful. Another aspect not included in this study is the Total dose to Point A or to Clinical Target Volume. This could also be a future project to compare recurrence rate to the dose at Point A with the current method of prescription.

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