

**INTEROBSERVER VARIATION OF
PROSTATE DELINEATION ON CT AND
MR BY RADIATION ONCOLOGISTS,
RADIOLOGISTS AND UROLOGISTS AT
THE UNIVERSITAS ANNEX ONCOLOGY
DEPARTMENT.**



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1. Abstract:

Introduction and aim: In recent years advances in delivery of radiation to clinically localised prostate volume has enabled dose escalation and greater sparing of organs at risk. At our department a significant proportion of prostate cancer patients are treated with curative radiation therapy and targets are defined through manual delineation. In this study we evaluate and quantify the variation of prostate contouring between radiation oncologists, radiologists and urologists respectively on CT and MR images and we determine the regions of significant concordance in segmented contours.

Materials and methods: CT and MR image sets of 5 prostate cancer patients were presented separately for prostate delineation in a blinded and independent fashion to each subgroup of specialists from various hospitals and included 7 radiation oncologists, 6 radiologists and 3 urologists. Variations were first analysed visually. In house tools and dedicated software was developed to automatically analyse various metrics in terms of volumes, volume centroids, maximum volume ratios (MVR), apex/base locations & diameters, ratio of scan encompassing volume (SEC), ratio of scan common volume (SCV), mean values & coefficient of variations and also to calculate the concordance index for each patient & each subgroup of specialists.

Results: Significant differences were observed between the subgroups of specialists. The volumes were significantly larger on CT than the corresponding MR image sets in all cases. The average prostate volumes were 28,3cm³ larger on CT than on MRI for oncologists with the MVR of 2.24; followed by radiologists with the average prostate volume of 18,1cm³ larger on CT than on MRI with the MVR of 1.57 and lastly the urologists had an average volume of 16,8cm³ larger on CT than on MRI with the MVR of 1.51. Furthermore the p-value was significant for oncologists vs radiologists (p=0.02) and for oncologists vs urologists (p=0.01) with regards to the maximum volume ratios (MVR). Variations in base positions were small and the base contours drawn were within 5mm of the defined base location on both CT and MRI where as for the apex position, the variations were significant and the apex contours drawn were mainly >5mm in relation to defined apex and varied more for CT than MRI. The inter-scan variation was similar (2.22) in both CT and MRI for radiologists demonstrating that they were more homogenous compared to other specialists. For the oncologists the variation on CT (1.72) was less than for MRI (1.82) whereas for the urologists the variation on CT (1.75) was larger than for the MRI (1.69). The conformity index (CI) for all the patients for combined images (CT and MR) were 0.45+/-0.04 for urologists; 0.56+/-0.08 for oncologists and 0.58+/-0.05 for radiologists which corresponds to poor concordance. Volume centroids provided useful interpretation of three dimensional spread of prostate volumes and uncovered larger CT derived prostate volumes delineated by radiologists and oncologists compared to urologists.

Conclusion: Major discordances were observed between radiation oncologists, urologists and radiologists delineations and areas of disagreements were identified indicating that this step needs to be improved. MRI images proved to be critical when delineating the prostate and thus making use of such an imaging technique provides a useful contribution in overcoming this difficult delineation. The urologists produced the most comparable delineations, followed by the radiologists and lastly the oncologists. The radiologists were more homogenous compared to other specialists. A better training of radiation oncologists in prostate imaging and the collaboration between radiation oncologists, radiologists and urologists should decrease this variability and ensure consistency in the delineation within the department.

2. Introduction:

In South Africa, Prostate cancer is the second most common cancer in all males after basal cell carcinoma according to latest statistics summary of cancers diagnosed histologically in 2009 by National Cancer Registry (1). External beam radiation therapy (EBRT) and radical prostatectomy are the mainstays of treatment of prostate cancer with curative intent (2).

Radiotherapy techniques and treatment modalities have rapidly improved and revolutionised over the years. Recent advances in the delivery of radiation therapy (RT) for clinically localised prostate cancer have enabled dose escalation and greater sparing of organs at risk (32,33). At Universitas Annex Oncology department, external beam radiation therapy (EBRT) remains one of the primary treatment modalities used for a significant proportion of patients with localized or locally advanced prostate cancer with curative intentions.

Successful radiotherapy depends on high geometric and dosimetric accuracy and precision. Special ways to deliver external beam radiation used in our department for prostate cancer treatment includes three dimensional conformal radiation therapy (3D-CRT) as well as Intensity modulated radiation therapy (IMRT).

With 3D-CRT, the radiation beam is shaped to include the 3-dimensional anatomical configuration of the prostate and any specified adjacent tissues including the seminal vesicles and peri-prostatic adventitial tissues, and utilizes high technology, as well as advanced computers and complex software's to enable accurate and more precise delivery of radiotherapy to the target volume while sparing surrounding normal tissues.

The IMRT modality achieves tight conformal dose distributions with the use of non-uniform radiation beams. This form of therapy creates highly conformal plan by treating the patient with either multiple static portals (so-called step-and-shoot IMRT) or dynamic fields. In dynamic IMRT, a series of arcs are administered to the area of interest. Multileaf collimators (MLCs) are reshaped many times as the machine performs a series of arc rotations around the target. Complex treatment-planning software algorithms allow exceedingly high doses of radiation to be delivered to the target while significantly smaller doses of radiation are delivered to the adjacent normal tissue. In contrast to the traditional method of radiation planning, inverse treatment planning is used for the calculation of doses during IMRT. IMRT establishes a treatment plan after the establishment of acceptable doses to regional (normal) anatomy. For instance, the maximum tolerable dose to be delivered to the involved segments of the bladder, small bowel, and rectum is specified. The desired

target dose is then prescribed to the planning target volume (PTV). The computer, through a series of complex iterations, designs a treatment that maximizes the dose delivered to the target and minimizes the dose delivered to adjacent normal tissue. Implicit in the name of this form of therapy is the concept that the intensity of the radiation beam changes throughout the course of therapy.

The target volume and organs at risk are defined through manual delineations by the Radiation Oncologists respectively on sequential axial CT and/or MRI images.(3)This information is essential to create a treatment plan with sufficient radiation dose to the tumour, without compromising the organs at risk. Delineation errors have a direct effect on the quality of the treatment. An excessive target volume entails unnecessary risk of complications, while an undersized target reduces the chance of cure.

Due to normal anatomical variations, physiological movement (internal motion) and inherent uncertainties in patient positioning (setup error), radiation to the prostate is subject to inter and intra-fraction variation. Planning target volumes (PTV) are thus generated to account for setup and internal motion error uncertainty. Contouring variability is a major source of error in radiation delivery having an impact on treatment accuracy similar to organ motion and setup variation (35). Therefore quality assurance of target volume delineation among radiation oncologists is essential to improve consistency.

Inaccurate contouring of the prostate will lead to imprecise dosimetry (8). The absence of a gold standard contouring technique makes it impossible to make conclusions about the absolute accuracy of contours .To minimise radiation induced toxicity to the rectum and bladder neck, co registration of magnetic resonance imaging with planned computer tomography data sets has been incorporated into clinical practice to improve soft tissue delineation (7,9,15).

Despite remarkable advances in treatment planning technology for prostate cancer, a critical unsolved problem is intra-observer and inter-observer variation and is well described not only in the prostate cancers, but also for breast, lung, as well as head and neck cancers (36,37,38).

Several factors that contribute to CT contour variation in prostate cancer patients includes (12,39):

- Lack of distinction of the prostate from critical adjacent structures on Computer Tomography (Radiographic)
- Wide variation in the anatomic position of the prostate relative to the pelvic bones and other structures identifiable on Computer Tomography (Anatomic)
- Variation in shape of prostate as benign prostate hypertrophy develops (developmental)

- Poor definition of interface between the posterior edge of the prostate and the anterior rectal wall
- Tendency to include portions of neurovascular bundle and difficulties in distinguishing the lower limit of the prostate apical region because of its close proximity to the pelvic floor muscles and poor contrast between these two structures.

In contrast, Magnetic resonance imaging (MRI) has improved resolution of soft tissues that allows more reproducible identification of prostate (34). A study done by R. Yueng et al in 2008 comparing dose volume differences for CT and MRI contouring showed significant differences between CT and MRI (24), Volumes for target treated were significantly different between the two imaging modalities: prostate volume and PTV volumes were smaller when MRI was used for delineation (11), presumably because of inclusion of neurovascular bundles and other soft tissue structures anteriorly and laterally on CT. For each individual patient there were minimal differences seen for normal tissues and large differences for prostate and PTV between CT and MRI.

It was hypothesised that the rectum-prostate interface was difficult to identify on CT, leading to inaccurate contouring of the prostate posteriorly, particularly at the apex. On the other hand, Magnetic resonance imaging (MRI) has improved resolution of soft tissues that allows more reproducible identification of the prostate. The Inter-observer contouring variation is also much lower with MRI compared to CT, as measured with the maximum volume ratio (MVR) (9).

Although the prostate can be seen more accurately on MRI, it is not possible to use it as the sole form of imaging in prostate radiation planning. CT serves as dual purpose because despite imaging it also provides electron density information to the planning system that is used for dose calculation. Dose calculation is therefore not possible with MR images because of the lack of electron density information (24).

In modern radiation oncology centres CT and MR images of the prostate are fused by the medical physicists. Both sets of images are then available to the oncologist and radiographers during treatment planning. The advantages of both modalities can then be utilised in the planning process.

More conformal treatment requires optimal delineation of structures. With the increased use of these treatment modalities there is not much room for error concerning the delineation abilities of treating doctors.

Multiple randomized clinical trials have demonstrated improved biochemical control of prostate cancer with radiation doses in the vicinity of 78Gy compared with lower doses (70Gy) (40). However, this was achieved at the price of higher rectal toxicity in the trials hence the introduction of new

technologies to allow safe radiation dose escalation. The rectum in particular has dose limiting radiosensitivity, and the risk of toxicity increases when it is not contoured accurately (41).

Within our department, a study was conducted that determined the incidence and grading of side effects pertaining to prostate radiation between 2006 and 2009 (42). The results of the study were quite compelling as grade 2 or more incidences of rectal bleeding and proctitis were 26.51% and 22.89% respectively. Delivery of radiation in these patients was by 3D conformal radiotherapy with CT imaging above. This was prior to the IMRT use in the department. This prompted the introduction of IMRT and thus co-registration of MRI and CT datasets within the department. This has made it possible to shape the dose distribution to closely match the target volume.

Delineation of the prostate at Universitas Annex oncology department is currently performed by Radiation Oncologists as well as Registrars who sometimes have limited background and experience in radiology making it difficult to precisely identify the detailed anatomical structures on computed tomography images (CT).

On the other hand, the Radiologists, who are more skilled in radiological anatomy, do not always have detailed understanding of the natural history of the disease.

CT imaging has a limited role for Urologists in detecting prostate carcinoma however MRI is a useful tool for them. MRI is the most accurate imaging modality for localization of prostate cancer. MRI is recently used by Urologists in patients with elevated PSA without previous biopsy to detect cancer on imaging and to help guide further biopsy. They also use MRI for evaluating patients with persistently elevated PSA with two or more negative TRUS biopsies (13) as well as assessing possibility of anterior prostate tumours because MRI has a positive predictive value (PPV) for anterior tumours (14).

No literature was found of interobserver variation between Radiation oncologists, radiologists and/or urologists specifically for prostate delineation/segmentation, however studies gathered looked at delineation variation of other organs, for example Senan et al published an article in 2002 on delineation variations of gross tumour volume for lung cancer by radiologists and oncologists (21). In this study the Radiologists delineated on the CT scan more tightly than Radiation Oncologists, which suggested the essential role played by the choice of visualization parameters in the accuracy of delineation. The results also showed that the Radiologists were more homogeneous in 'difficult' cases, which confirmed their experience in Radiological analysis, based on stricter criteria than Radiation Oncologists.

The same results were observed by Leunens et al who compared delineations of brain tumours by radiologists, radiation oncologists and neurosurgeons (22). In this study the Radiologists delineated smaller volumes than what the radiation oncologists did and, interestingly the neurosurgeons delineated even smaller volumes than those of the other two specialities.

Differences of prostate delineation may therefore be anticipated between the Oncologists, Radiologists and Urologists, which could potentially be due to imprecise CT/MRI data or divergent assessments. The magnitude of these differences remains incompletely evaluated.

The objective of my study is therefore to compare prostate delineations on CT and MRI images as performed by radiologists, radiation oncologists and urologists.

This study is an extension/continuation of the study that was done in the department between 2013 and 2015 (43). The purpose of that study was to assess the Inter-observer variation of prostate delineation by in-house Radiation Oncologists and Registrars within the department. In that study, the researcher found that there was a large interobserver variation in prostate contouring and identified areas of poor concordance. The results of that study compelled the department to continue the study by involving the radiologists and urologists with the aim of determining and quantifying the interobserver variation among these respective specialists.

3 Treatment Planning Process

The following are proceedings in Steps during the treatment planning process within the department as per protocol for radical prostate radiation:

- The patient is first seen and discussed at the urology multidisciplinary clinic and is then scheduled for the placement of fiducial markers at the urology department.
- The fiducial markers used are stainless steel clips that are implanted in the prostate transrectally under ultrasound guidance by Urologist and these act as a radiologic landmarks to define the target lesion position within millimetre precision. These markers serve as identifiers visible on Computer tomography (CT) and on Magnetic Resonance imaging (MRI) which later helps for fusion of the two images as well as verifying the prostate location during daily treatment.
- MRI of the pelvis is subsequently done at Universitas Hospital and a copy of the MRI is burned to a compact disc that will be used at Radiation department.
- This is followed by the simulation process which provides the treatment team with the data to allow the construction of a highly individualised plan to treat prostate cancer
- The process relies on a non-contrasted CT planning scan done at Universitas Annex Oncology Department to obtain a detailed digital data set of the relevant pelvic anatomy. This dataset will later be used to create a three dimensional model for the treatment area of interest.
- The computer tomographic data is then imported on to the treatment planning system (TPS).
- Co-registration of MRI and CT datasets is performed.
- The Radiation Oncologist then contours the target volumes on MRI whilst the pelvic nodes and organs at risk are contoured on CT images.

4 Objectives of the study:

1. To quantify and compare the inter-observer delineation variability of the prostate on Computer tomography(CT) and magnetic resonance imaging(MRI) between Radiation oncologists, Radiologists and Urologists respectively.
2. To determine regions of significant discordance in the segmented contours.
3. To use the information from objective 1 and 2 to guide the department about future development and training regarding prostate contouring accuracy and consistency.

5 Methodology:

5.1 Study Design:

This is a cross sectional analytic study.

5.2 Study participants:

The participants included Seven(7) Radiation Oncologists from Universitas Annex hospital; six (6) Radiologists of which three(3) were from Universitas tertiary hospital and the other three(3) were from the private hospital; and furthermore there were three (3) Urologists from Universitas tertiary hospital included in the study. This made a total of 16 Specialists participating in the study.

5.3 Study sample:

The sets of CT and MR images of 5 randomly selected patients during the treatment planning process for prostate IMRT were used. Each participating doctor consequently contoured the prostate volume on 5 CT scans and 5 MRI scans of the 5 patients, making a total of 10 sets of images on which the prostate volumes were contoured.

These randomly selected patients had localised prostate cancer and their disease profile ranged from low risk to high risk group.

Various study samples from other pertinent studies were assessed and analysed and provided guidance to select appropriate sample size. Accredited

journals were screened for studies that performed similar measurements as in this project.

The proposed study sample came to be after literature review of diverse study populations from relevant articles which had variety of patient population ranging from larger patient population to approximately one to six patients. It was also recognised that there were lesser number of participants (Doctors) in certain studies compared to others.

As an illustration, Khoo et al published an article in 2012 on contouring variation. Imaging of 3 patients was used and 5 oncologists contoured the prostate. Another article published in 2012 by De Brabandere et al analysed imaging of 3 patients that was contoured by 8 physicians (25).

Facts provided above were all taken into consideration when the sample size was determined and therefore imaging of 5 patients ensured a fair amount of time for all study participants especially in light of their narrow time limitations.

5.4 Materials and methods:

5 patients with CT and MRI datasets, who had received radiation treatment at Universitas Annex Oncology department, were selected prospectively.

In accordance to treatment planning process protocol for IMRT of the prostate, Co-registration of MRI and CT datasets is done, matched on implanted intra-prostatic markers inserted by urologists two days prior to the MRI occurs.

The GE 1.5 Tesla Magnetic resonance imaging (MRI) scanner with 3 millimetres slices was used. Specifications of the scanner were as follows:

- ✓ Axial T2 weighted fast spin Echo: repetition time 3500 to 6000ms, echo time 90 to 120 ms and phase encoding right to left.
- ✓ Axial T1 Weighted fast spin echo: repetition time 600 to 700 ms, echo time 12 ms, and phase encoding anterior to posterior.

Magnetic resonance imaging (MRI) was subsequently followed by a non-contrast planning Computer tomography scans (CT) done at our department as per protocol and the scanner used was a Toshiba Aquilon LB with the slice thickness of 3 millimetres.

As mentioned above, co-registrations of CT and MRI datasets based on the prostate fiducial markers is a usual process in treatment planning done by the departments physicists but on the basis of this study, all the datasets were imported in separate individual folders into treatment planning system, Xio/focal software and this was achieved respectively with the help of the in-house physicist.

For economical and time constraints reasons, it was not feasible for the radiologists and urologists to come to the department for the study because they work at different institutions and have major time limitations hence we decided to take the software program to them in a portable manner and they were educated on the program and instructions were laid out effectively. The study participants were authorised to contour the prostate volume within a specified time frame and an agreement between the researcher and the participant was established and the code of conduct outlined and signed

Contouring

All 16 specialists were briefed on the instructions to contour the prostate. Neither the patient's name, demographic information nor disease profile were available during contouring session. Each set of images had a numerical form of identification only. The images of each patient appeared randomly to ensure that the CT and MR images of the same patient were not contoured sequentially.

At completion of each individual prostate contouring, the participants were instructed to immediately save the CT or MRI data and thus disabling them from referring back to the completed contour. This contouring sequence was repeated for all 5 patients by each participant in one session.

It was only possible to access/view one patient's scan at a time. For each image data, contouring was done on transverse slices only, although sagittal and coronal images were visible on the same screen as an anatomic guide and this was well instructed to the participants. Optimisation of window settings and image contrast was made possible on own participants discretion for better visualisation and optimal contouring. This is in accordance with standard practice at our institution.

After completion of contouring of a prostate for each patient, the contouring data was saved on the Xio software system in a numerical order allocated to that specific doctor and access to the saved contour data was made unavailable to the individual participant or colleagues.

5.5 Parameters acquired for analysis:

All measurements were done individually on each scan. A total of 160 scans were obtained for analysis (5 CT+ 5MRI X 16 doctors=160 scans)

Information of all the individual measurements of the various parameters was documented on a data sheet. Parameters of each scan acquired for further analysis were as follows:

1. Volume of the prostate in cm^3
2. Maximum superior-inferior diameter of prostate in millimetres (mm)
3. Maximum transverse diameter of prostate in millimetres (mm)
4. Maximum anterior-posterior of the prostate in diameter (mm)
5. Base slice location
6. Base Transverse diameter in millimetres (mm)
7. Base Anterior-posterior diameter in millimetres (mm)
8. Base Volume in cm^3
9. Mid-gland slice location
10. Mid-gland Transverse diameter in millimetres (mm)
11. Mid-gland Anterior-posterior diameter in millimetres (mm)
12. Mid-gland Volume in cm^3
13. Apex slice location
14. Apex Transverse diameter in millimetres (mm)
15. Apex Anterior-posterior diameter in millimetres (mm)
16. Apex Volume in cm^3

5.6 Software description:

A dedicated software program was written in IDL (Harris Geospatial©) to calculate various metrics for analysis of the contoured volumes. The metrics calculated are: Volume, Maximum volume ratio, Apex, midplane and base locations and diameters, Volume centroids, & Conformity Indices.

Volumes

Contours are read from the DICOM *Structure Set* file and packed into a 3D matrix. All voxels contained within the contour are then determined and given a value of 1. The volume is then calculated from the number of voxels that has a value of 1 multiplied by the volume of a voxel.

Maximum volume ratio (MVR)

The calculated volume of a given participant's CT contour is divided by the corresponding MRI contour, for the same patient.

$$\text{MVR} = \frac{\text{Volume on CTI}}{\text{Volume on MRI}}$$

Apex, Mid-plane, Base locations and diameters

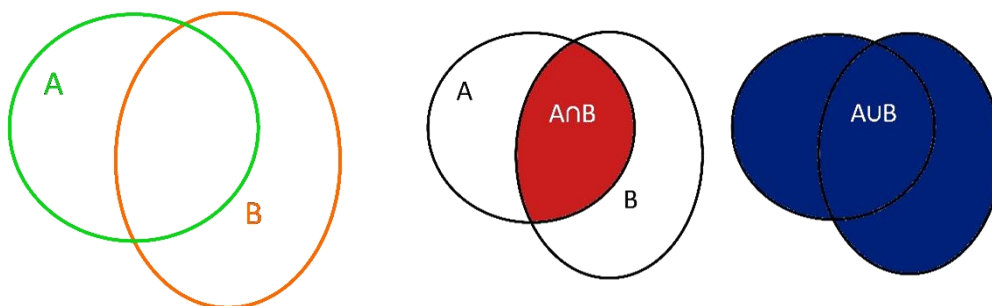
Using the 3D volume binary data created for the volume calculation, the slice location of the Apex and base are easily found (1st and last slice containing contour). The Mid-plane is calculated as the slice halfway between the Apex and Base.

The diameters are calculated on the determined slices, by searching for the maximum distance between voxels contained within the contour on that slice.

Volume centroids

The centroid of each volume is calculated from the 3D binary matrix, by determining the average x, y, and z location of all voxels contained in the volume.

Conformity Indices



The ratio of the overlapping and encompassing volumes gives the CI.

$$\text{CI} = \frac{\text{Overlapping volume}}{\text{Encompassing volume}} = \frac{A \cap B}{A \cup B}$$

For the overlapping volume, this is done mathematically by taking the 2 3D volumes and multiplying them with each other using the **OR** operator. The encompassing volume is determined using the **AND** operator. The conformity index can be reported as a fraction or if multiplied by 100, as a percentage. Conformity index is also referred to as concordance index or proximity index. CI of 1 represents two volumes coincides exactly. A CI of 0 means the volumes are disjoint. However, the CI does not give information on how contours may vary quantitatively in size, shape or location in absolute terms; it is a relative measure.

In this study, the CI_{pairs} are calculated since there are multiple participants, and the number of participants per groups are not equal. In order to do this, the CI is calculated for a participant (P1) by getting the average CI of this participant with each other participant's contour on the same image set, and then taking the average. In other words, for i different participants in the group,

$$CI_{P1} = \frac{\sum CI_{P1/Pi}}{i}$$

SEV/SCV

The ratio of the scan encompassing volume (SEV) to the scan common volume (SCV) is a measure of inter-observer variation in contouring and expresses the correlation between doctors when the same structure is contoured. For each scan, the scan common volume (the largest volume common to all observers in that scan) and scan encompassing volume (the smallest volume encompassing all of the volumes outlined by the observers in that scan) was obtained. The ratio between the scan encompassing and scan common volume is therefore indicative for the uncertainty in delineating the prostate in that particular scan. In other words if the ratio is large, the observer related uncertainty concerning the dimensions of the prostate in that scan is large and the variation is high; likewise the uncertainty is low when the ratio approaches unity.

Finally, all metrics were saved in a text file for further analysis

6 Statistical Analysis:

Submission of all the data of the measurements of the parameters obtained as outlined on the data-form to the Department of Biostatistics (University of the Free State) was done.

The mean, standard deviation and the coefficient of variation of the specific category of observers were calculated for each parameter of each patient. These values were summarised in terms of means, standard deviations and minima and maxima. Comparisons were achieved using paired t-tests, with $p < 0.05$ considered statistically significant.

Numerical variables:

Mean is the sum of the values of observations, divided by the number of observations.

Standard deviation is an indication of the average spread (variation) around the mean.

Coefficient of variation expresses the standard deviation of data as a percentage of their mean. It is a statistical measure of the dispersion of data points in a data series around the mean. The series of data for which the coefficient of variation is larger indicates that the group is more variable and it is less stable or less uniform. If the coefficient of variation is small, it indicates that the group is less variable and it is more stable and uniform.

The mean, standard deviation and coefficient of variation are used together as summary values for the data that is distributed symmetrically.

7 Ethical aspects:

This study was subject to approval by the health sciences research ethics committee at the University of the Free State and the reference number of the approval allocated was ECUFS 170/2015.

The research agreement established the basis of relationship between the researcher and participant. Each participating doctor signed a code of conduct and declared contouring of the prostate volumes independently and without assistance from colleagues or other participants and affirmed obeying of instructions as well as completion of the contours within the stipulated time frame.

All the participants were reassured that all the research activities and reports or publications arising from research would conform to the research principles and code of ethics outlined and that all the data obtained from the project shall be coded in a manner that guarantees the anonymity and confidentiality of the research participants, that is, data shall be coded in a way that does not allow for identification of individual research participants.

It was also highlighted that data from the study, including datasheet measurement results, will be stored in a secure location and upon completion of the study, data and records that are collected remains property of the Universitas Annex Oncology department.

The code of conduct also stipulated that data collected and stored may not be made accessible to other researchers and or used for research purposes other than those agreed upon without the department's knowledge and consent and without informed consent of participants

Permission to conduct the study was obtained from Dr A Sherriff, Head of the Oncology Department, as well as from Dr Motau who is the Head of Free state department of health.

The research was done in accordance with the declaration of Helsinki (1964) as amended in Tokyo (1975).

8 Results:

Mean values for specified measurements:

Table1

Parameters	Image	Mean values			Comparisons (p- values)		
		Oncologists	Radiologists	Urologists	O vs R	O vs U	R vs U
1.Prostate volume(cm3)	CT	58,7	60,7	55,9	0,08	0,57	0,3
	MRI	30,4	42,6	39,1	<0.01	0,05	0,41
2.Max sup-inf diameter(mm)	CT	47,1	45,9	41,7	0,48	0,06	0,19
	MR	39,5	38,7	38	0,57	0,13	0,65
3.Max transverse diameter(mm)	CT	57,9	57,9	61,2	0,96	0,26	0,16
	MRI	45,5	52,2	52,7	0,01	0,01	0,73
4.Max Ant-post diameter(mm)	CT	46,6	49,3	48,4	0,19	0,58	0,56
	MRI	35	42,7	42	<0.01	0,01	0,7
5.Base transverse diameter(mm)	CT	33,8	32	36,2	0,33	0,53	0,27
	MRI	21	28,7	32	0,04	0,06	0,44
6.Base Ant-post diameter(mm)	CT	22,1	26	27,9	0,02	0,02	0,33
	MRI	15,5	20,4	22,2	0,06	0,13	0,58
7.Base volume(cm3)	CT	1,2	1,3	1,6	0,47	0,13	0,26
	MRI	0,9	1,4	1,8	0,06	0,09	0,36
8.Midgland transv diameter(mm)	CT	48,5	48,9	50,9	0,45	0,34	0,33
	MRI	38,3	46	45,6	0,01	0,04	0,74
9.Midgland Ant-post diameter(mm)	CT	39,1	39,2	39,3	0,91	0,83	0,98
	MRI	29,2	36,6	35,2	0,01	0,01	0,32
10.Midgland volume(cm3)	CT	3,2	3,3	3,2	0,51	0,88	0,58
	MRI	3	4,2	4	0,01	0,01	0,46
11.Apex transverse diameter(mm)	CT	22	25,4	26,3	0,01	0,06	0,61
	MRI	14,6	20,7	21,9	0,02	0,02	0,26
12.Apex Ant-post diameter(mm)	CT	19,4	23,5	21,4	0,01	0,11	0,11
	MRI	13,3	19,4	17,8	<0.01	0,06	0,31
13.Apex volume(cm3)	CT	0,8	1	1	0,01	0,08	0,98
	MRI	0,5	1	1	0,01	0,01	0,74

Abbreviations: CT=computer tomography; MRI=magnetic resonance imaging; O=oncologists; U=urologists; R=radiologists

8.1 Mean values:

Mean values for inter-observer contouring obtained for the entire patient population with imaging performed on CT and MRI is summarized in table 1. Despite the similar mean prostate values in CT and MRI, there was significantly more variation in overall prostate values in MRI compared with CT between oncologists and Radiologists ($p < 0.01$). One also appreciates that there is a significant mean variation in maximum transverse diameter on MRI between Oncologists and Radiologists ($p = 0.01$) and between Oncologists and Urologists ($p = 0.01$) compared with prostate contoured on CT.

Overall the mean MRI volumes delineated by the specialists were smaller than the mean CT volumes. The mean prostate MRI volume for Oncologists was 30.4 cm^3 , for Urologists was 39.1 cm^3 and for Radiologists was 42.6 cm^3 . The CT mean prostate volume was 55.9 cm^3 by Urologists, then 58.7 cm^3 by Oncologists and by Radiologists 60.7 cm^3 .

Analysis of the different regions of prostate demonstrates significantly less contouring variation on MRI than on CT for prostate base anterior and posterior diameter among Oncologists and Radiologists as well as among Oncologists and Urologists. There is however a significant mean difference for transverse diameter of both base, mid-gland and apex on MRI image with significant p-values between Oncologists vs urologists and Oncologists vs Radiologists. The region with most significant mean variation is the apex in terms of the volume, transverse diameter and AP diameter for both CT and MRI amongst Oncologists vs Urologists. It is clearly evident that there were no significant variation between Radiologists and Urologists in all the specified mean parameters, there were also no significant variation in base volume between all the respective study participants.

Coefficient of variation for specified measurements:

Table 2

Parameters	Images	Coefficient of variation			Comparisons (p- values)		
		Oncologists	Radiologists	Urologists	O vs R	O vs U	R vs U
1.Prostate volume(cm3)	CT	13,1	13,8	11,8	0,77	0,79	0,65
	MRI	26	14,3	14,5	0,11	0,2	0,95
2.Max sup-inf diameter(mm)	CT	12,6	14,6	18,4	0,59	0,1	0,44
	MRI	11	17,4	14	0,1	0,08	0,94
3. Max transverse diameter(mm)	CT	7,1	5,7	8,8	0,39	0,61	0,46
	MRI	12	5,1	6,8	0,11	0,21	0,36
4.Max Ant-post diameter(mm)	CT	7,9	8,7	6,1	0,35	0,65	0,47
	MRI	14,4	8,1	9,2	<0.01	0,07	0,49
5.Base transverse diameter(mm)	CT	27,7	22,7	27,2	0,39	0,95	0,27
	MRI	33,6	26,2	26,2	0,37	0,44	1
6.Base Ant-post diameter(mm)	CT	29,3	29,1	25,9	0,98	0,73	0,42
	MRI	33,3	28,6	37,3	0,49	0,71	0,62
7.Base volume(cm3)	CT	49,4	42,9	38,8	0,62	0,4	0,41
	MRI	57,2	46,5	60,5	0,4	0,84	0,66
8.Midglad transv diameter(mm)	CT	11,3	15,6	5,3	0,56	0,21	0,31
	MRI	14	7,7	9,5	0,29	0,62	0,65
9.Midglad Ant-post diameter(mm)	CT	10,3	15,8	10,1	0,52	0,96	0,53
	MRI	14,8	9,5	13,8	0,11	0,86	0,5
10.Midglad volume(cm3)	CT	15,8	8,3	14,5	0,17	0,82	0,21
	MRI	25	12,2	20,3	0,08	0,69	0,35
11.Apex transverse diameter(mm)	CT	31,6	21,9	31,1	0,19	0,95	0,03
	MRI	49,2	29,9	41,2	0,04	0,34	0,26
12.Apex Ant-post diameter(mm)	CT	26,7	19,3	40,1	0,18	0,02	0,02
	MRI	40,9	29,5	41,2	0,2	0,97	0,12
13.Apex volume(cm3)	CT	54	33,8	64,1	0,08	0,17	0,01
	MRI	71,4	57,1	80,1	0,42	0,17	0,14

Abbreviations: CT=computer tomography; MRI=magnetic resonance imaging; O=oncologists; U=urologists; R=radiologists

8.2 Coefficient of variation:

Table 2 summarizes the coefficient variation of prostate contouring on CT and MRI for the entire patient population by respective participants. Analysis of prostate volume and maximum superior and inferior diameter as well as maximum transverse diameter demonstrates significantly less contouring variability on both MRI and CT for Oncologists, Urologists and radiologists and their values are more uniform across the specified parameters. There is however significant variation in maximum anterior posterior diameter on MRI between Oncologists and Radiologists. The coefficient values are high (14,4mm) compared to Radiologists (8.1mm) and this illustrates a large variation in maximum anterior-posterior diameter between Oncologists and Radiologists.

The table also demonstrates a significant contouring variation that occurred on the apex of the prostate on the following parameters: Apex CT volume between Radiologists vs Urologists ($p=0.01$); Apex transverse CT volume between Radiologists and Urologists ($p=0.03$); Apex transverse MRI diameter between Oncologists and Radiologists ($p=0.04$) and lastly apex anterior-posterior CT diameter between Oncologists and Urologists ($p=0.02$) and between Radiologists and Urologists ($p=0.02$).

8.3 Conformity index (CI)

Table 3

	CONFORMITY INDEX										MEAN CI & STD-DEVIATION (ALL PATIENTS)				MEAN CI & STD DEV (OVERALL)	
	Pt1		Pt2		Pt3		Pt4		Pt5		MEAN CT	CT STD-D	MEAN MRI	MRI STD-D	MEAN CI	STD-D (CI)
PARTICIPANTS:	CT	MR	CT	MR	CT	MR	CT	MR	CT	MR						
ONCOLOGISTS	0,57	0,52	0,58	0,45	0,50	0,59	0,55	0,46	0,69	0,70	0,58	0,07	0,55	0,10	0,56	0,08
UROLOGISTS	0,40	0,40	0,43	0,40	0,46	0,43	0,46	0,49	0,49	0,52	0,45	0,03	0,45	0,06	0,45	0,04
RADIOLOGISTS	0,59	0,57	0,53	0,57	0,53	0,54	0,54	0,57	0,65	0,67	0,57	0,05	0,59	0,05	0,58	0,05

Abbreviations: CT=Computer tomography; MRI=Magnetic resonance imaging; CI=Conformity index; STD-D=Standard deviation

Conformity: all data

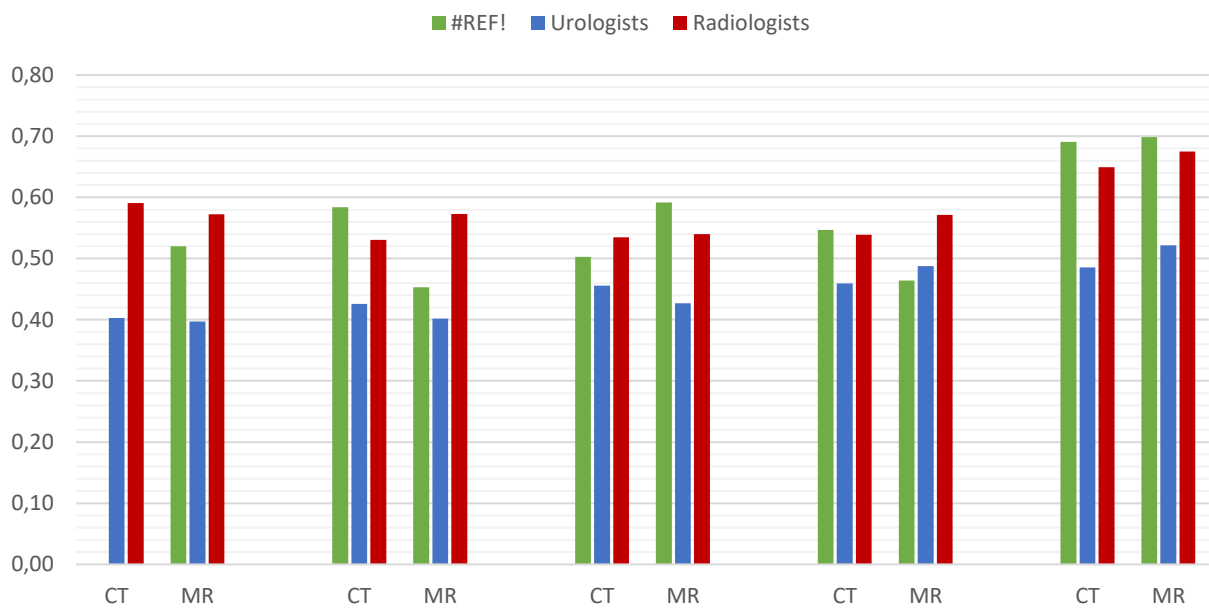


Figure1

Conformity of index:

Conformity indices for each patient obtained with different image modalities for prostate are listed in table 3 and figure1. CI data was analysed with respect to image modalities variations and inter patient variations. Overall mean CI for combined images (CT and MRI) for all patients ranged from 0.45 \pm 0.04 for Urologists to 0.56 \pm 0.08 for Oncologists and 0.58 \pm 0.05 for Radiologists.

For Oncologists the mean CI was 0.58 for CT and 0.55 for MRI; For Urologists the mean CI was 0.45 for CT and similarly 0.45 for MRI and for Radiologists the mean CI was 0.57 for CT and 0.59 for MRI. The inter modality analysis indicates that there was not much conformity index differences between CT and MRI modalities.

Inter- patient analysis of CI did not differ much except for patient 5 with slightly higher CI values compared to the other patients across all the varying participants with Oncologists having higher CI values in patient 5 for both CT and MRI compared to Urologists and radiologists

8.4 SEV/SCV:

Table 4

	SEV/SCV	
	Mean CT	Mean MRI
Oncologists	1.72	1.82
Radiologists	2.22	2.22
Urologists	1.75	1.69

The mean ratio between the scan encompassing and scan common volume for CT and MRI for the different specialists is outlined above respectively indicating the variation between the observers in each scan modality. Interestingly the inter-scan variation for the radiologists was similar between the CT and MRI image modalities. For the oncologists the variation on CT was less than for MRI and for the Urologists the variation on CT (1.75) was larger than the MRI (1.69).

8.5 Prostate base positions:

Table 5a

PARTICIPANTS	Pt1 Base position			Pt2 Base position			Pt3 Base position			Pt4 Base position			Pt5 Base position		
	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist
ONCOLOGISTS	48,86	55,79	6,93	17,71	20,39	2,67	53,14	54,92	1,78	40,86	41,06	0,20	2,29	6,19	3,90
RADIOLOGISTS	45,33	48,50	3,17	18,67	19,60	0,93	50,33	55,35	5,02	41,33	41,20	0,13	2,33	4,90	2,57
UROLOGISTS	46,67	51,50	4,83	17,33	19,10	1,77	49,33	54,35	5,02	40,67	41,20	0,53	2,00	5,90	3,90

CT-MR dist = Distance between the CT and MR base contoured by respective specialist

On average the observers contoured one to two base slices more on MRI compared to the CT across all the patients. The distance between the CT and MRI scans of the different patients contoured by the specialists ranged from 0.13 to 6.93 mm.

Defined base locations on CT and MRI in mm defined by calculating the average base location of the all the CT and MRI base locations of the specialists:

Table 5b

	Average CT base location	Average MR base location
Patient 1	-46.95	-51.93
Patient 2	-17.9	-19.7
Patient 3	-50.93	-54.9
Patient 4	-40.95	-41.15
Patient 5	-2.21	-5.66

Table 5c

PARTICIPANTS	Base distance difference between base contoured by specialist and defined base in mm as illustrated above									
	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	CT	MR	CT	MR	CT	MR	CT	MR	CT	MR
Oncologists	1.91	3.86	0.19	0.69	2.21	0.02	0.09	0.09	0.08	0.53
Radiologists	1.62	3.43	0.77	0.1	0.6	0.45	0.38	0.05	0.12	0.76
Urologists	0.28	0.43	0.57	0.6	1.6	0.55	0.28	0.05	0.21	0.24

Defined base=Base obtained by calculating average of all bases on a particular scan/image

The table above demonstrates the base distance difference between the base contoured by specialist and the defined base that was obtained by calculation the average of the overall bases contoured by specialists in light of the absence of gold standard for base contour location. Both the CT base

contours and the MRI base contours drawn by the observers were within 5 mm of the defined base location.

8.6 Prostate Apex positions:

Table 6a

PARTICIPANTS	Pt1 Apex position			Pt2 Apex position			Pt3 Apex position			Pt4 Apex position			Pt5 Apex position		
	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist	CT	MR	CT-MR dist
ONCOLOGISTS	96,86	90,93	5,93	59,43	51,24	8,19	81,43	82,78	1,35	77,71	72,34	5,37	70,57	62,76	7,81
RADIOLOGISTS	88,33	88,00	0,33	58,33	47,60	10,73	79,33	81,85	2,52	76,00	69,20	6,80	73,33	60,90	12,43
UROLOGISTS	87,33	86,50	0,83	54,67	49,10	5,57	80,67	82,35	1,68	72,00	68,20	3,80	59,33	58,90	0,43

CT-MR dist = Distance between the CT and MR apex contoured by respective specialist

On average the observers contoured one to three apex slices more on CT compared to the MRI across all the patients and this is contrary to the prostate base slices. The distance between the MRI and CT scans of the different patients contoured by the specialists ranged from 0.33mm to 12.43 mm.

Defined apex locations on CT and MRI in mm defined according to average apex location obtained by calculating the average of the total CT and MRI apex locations of the specialists:

Table 6b

	Average CT apex location	Average MR apex location
Patient 1	-90.84	-88.48
Patient 2	-57.48	-49.31
Patient 3	-80.48	-82.33
Patient 4	-75.24	-69.9
Patient 5	-67.74	-60.85

Table 6c

PARTICIPANTS	Apex distance difference between apex contoured by specialist and defined apex in mm									
	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	CT	MR	CT	MR	CT	MR	CT	MR	CT	MR
Oncologists	6.02	2.45	1.98	1.93	0.95	0.45	2.47	2.44	2.83	1.91
Radiologists	2.51	0.48	0.85	1.71	1.15	0.48	0.76	0.7	5.59	0.05
Urologists	3.51	1.98	2.81	0.21	0.19	0.02	3.24	1.7	8.41	1.95

Defined apex=Apex obtained by calculating average of all apex on a particular scan/image

The table above demonstrates the apex distance difference between the apex contoured by specialist and the defined apex that was obtained by calculation the average of the overall apexes contoured by specialists in light of the absence of gold standard for apex contour location. CT apex contours in certain patients were >5mm particularly for patient 1, the Oncologists CT apex distance difference was 6.02mm and for patient 5 the Radiologists CT apex distance difference was 5.59mm and for the Urologists was 8.41mm. The MRI apex contours drawn by the observers were however within 5 mm of the defined apex location.

8.7 Cranio-caudal/superior-inferior diameter of prostate volumes:

Table 7a

Average Cranio-caudal or Superior-inferior diameter of prostate volume of all specialists			
	CT	MRI	Difference
Patient 1	-43.89 mm	-36.55 mm	-7.34 mm
Patient 2	-39.58 mm	-29.61 mm	-9.97 mm
Patient 3	-29.55 mm	-27.43 mm	-2.12 mm
Patient 4	-34.29 mm	-28.75 mm	-5.54 mm
Patient 5	-65.53 mm	-55.19 mm	-10.34 mm

Table 7b

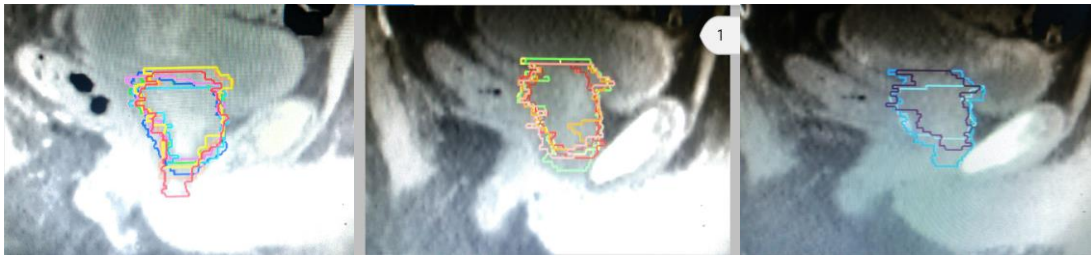
Avg Cranio-caudal or Superior-inferior diameter of prostate volume of individual specialists						
	Oncologists		Radiologists		Urologists	
	CT	MRI	CT	MRI	CT	MRI
Patient 1	-48.00 mm	-35.14 mm	-43.00 mm	-39.50 mm	-40.66 mm	-35.00 mm
Patient 2	-41.72 mm	-30.85 mm	-39.66 mm	-28.00 mm	-37.34 mm	-30.00 mm
Patient 3	-28.29 mm	-27.86 mm	-29.00mm	-26.50 mm	-29.00 mm	-28.00 mm
Patient 4	-36.85 mm	-31.28 mm	-34.67 mm	-28.00 mm	-31.33 mm	-27.00 mm
Patient 5	-68.28 mm	-56.57 mm	-71.00 mm	-56.00 mm	-57.33 mm	-53.00 mm

The table above demonstrates cranio-caudal diameters of prostate volumes. One can appreciate that the mean cranio-caudal diameters are smaller on MRI when compared with the CT in all specialists combined as well as in individual specialists.

Graphic sagittal demonstration of prostate contours illustrating variation:

Patient 1:

CT images:



Oncologists

Radiologists

Urologists

MR images:



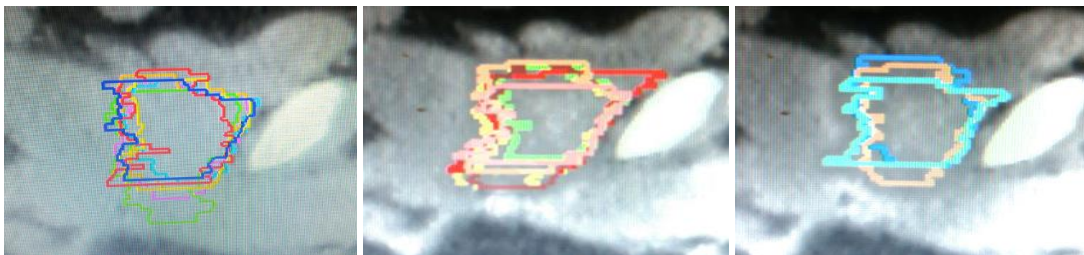
Oncologists

Radiologists

Urologists

Patient 2:

CT images:



Oncologists

Radiologists

Urologists

MR images:



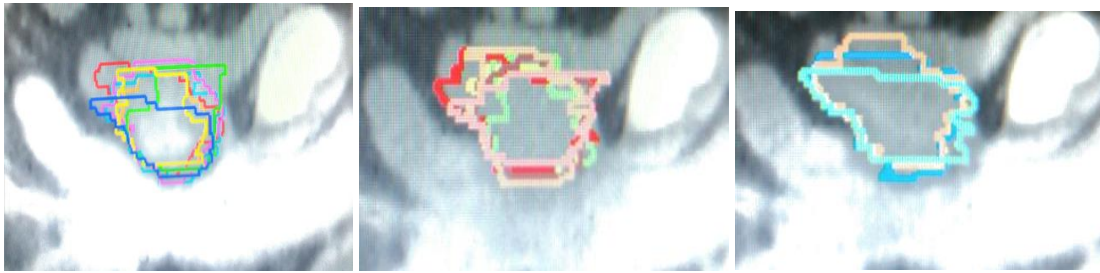
Oncologists

Radiologists

Urologists

Patient 3:

CT images:



Oncologists

Radiologists

Urologists

MR images:



Oncologists

Radiologists

Urologists

Patient 4:

CT images:



Oncologists

Radiologists

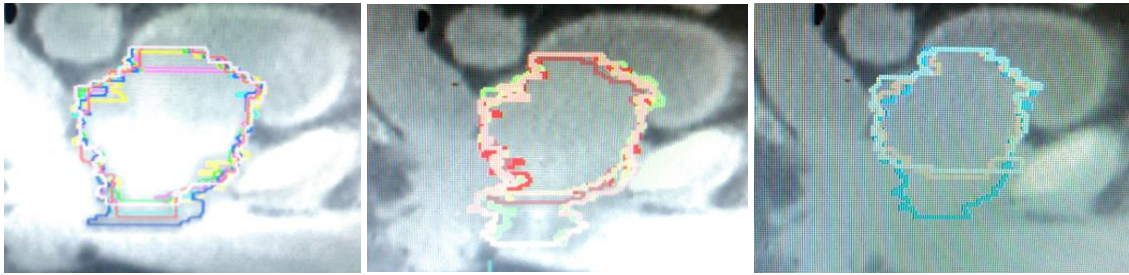
Urologists

MR images:



Patient 5:

CT images:



Oncologists

Radiologists

Urologists

MR images:



Oncologists

Radiologists

Urologists

8.8 Maximum Volume ratio (MVR):

Table 8

				p-values		
	Oncologists	Radiologists	Urologists	O vs R	O vs U	R vs U
Maximum volume ratios (MVR)	2.24	1.57	1.51	0.02	0.01	0.64

The average ratio of the CT volume and the volume outlined on axial MRI for Oncologists, Radiologists and Urologists is demonstrated above. On Average the CT derived volume was larger than the volume outlined on axial MRI. For Oncologists the MVR calculated was 2.24; for Radiologists MVR was 1.57 and for Urologists MVR was 1.51. P value was 0.02 between Oncologists and Radiologists and 0.01 between Oncologists and Urologists but was not significant between Radiologists and Urologists (p=0.64).

8.9 Centroids:

Table 9

Distance between centroids CT -> MR							
	Pt1	Pt2	Pt3	Pt4	Pt5	Average	Stdev
Directional deviations							
Oncologists	2,2	-3,3	2,5	-3,6	-0,3	-0,5	2,9
Urologists	3,2	-3,6	1,7	-3,2	2,2	0,1	3,2
Radiologists	2,2	-5,4	2,8	-3,2	-2,1	-1,1	3,5

Centroid of each volume is calculated from the 3D binary matrix, by determining the average x, y, and z location of all voxels contained in the volume.

The systemic modality difference between MRI and CT (i.e the average distance between the centre of the prostate and the edge of the prostate for each patient and observer in a given direction in MRI minus this distance in the CT scan is depicted above. A negative number indicating a larger CT derived prostate. The average Centroid value for Oncologists was -0.5mm and for radiologists -1.1mm whereas the average centroids for urologists was 0.1mm therefore this means that the CT derived prostate was larger for the Oncologists and the Radiologists compared to the Urologists.

9 Discussion:

Inter-observer contouring variability is well described not only in localised prostate, but also for other cancers such as lung, head and neck and breast cancers. Despite no widely accepted method of systematic contour comparison, volume-based metrics are the most frequently used assessment parameter (51).

The improved differentiation of soft tissues on MRI has led to general acceptance in the literature that it provides more accurate delineation of prostates compared with CT. Initial research conducted in patients treated with external beam radiotherapy suggested that CT based volumes were larger than MRI based volumes by 24% to 40%(15; 44), presumably because of inclusion of the neurovascular bundles and other soft tissue structures anteriorly and laterally. It was also hypothesized that the rectum-prostate interface was difficult to identify on CT, leading to inaccurate contouring of the prostate posteriorly, particularly at the apex.

Effect of scan modality on inter-observer contouring variation with regards to prostate volumes:

In my study the absolute prostate volumes (mean prostate CT volumes) were larger than the average MRI volumes as in the study by Roach et al where he compared the prostate volumes defined on MRI and non-contrast CT scans(7). In my study the average prostate volumes defined by CT (Table1) were 55,9cm³ by urologists, 58.7cm³ by Oncologists and 60.7cm³ by Radiologists whereas the average MRI prostate volumes were 30.4cm³ for the Oncologists, 39.1cm³ for the Urologists and 42.6cm³ by Radiologists and thus the average prostate volume was thus 28.3cm³ larger than MRI for Oncologists and 16.8cm³ larger than MRI for Urologists and 18.1cm³ larger for Radiologists. Similarly in study by Roach et al the average prostate volume defined by CT was 38.4cm³ while the average volume of MRI was 29.6cm³ and thus the average prostate volume was 32%(8.7cm³) larger when defined by CT compared to MRI (7). Also in a study by Anamaria et al titled dose volume differences for CT and MRI segmentation and planning for proton prostate cancer therapy, the volumes for the target treated were significantly different between the two imaging modalities, prostate volume was 24.5% smaller when MRI was used for delineation respectively(11)

One can appreciate that overall the average prostate volumes in my study were larger compared to the average prostate volumes in Roach et al. The

volume differences might be attributed to the differences in T-stage distribution and also might be explained by the hormonal treatment given prior to the scans in the study by Roach et al. In my study. One can also appreciate that the Oncologists average prostate volumes on CT were larger in comparison to Urologists or Radiologists. This might probably be explained by the fact that Oncologists in my study tended to overestimate the prostate volume on CT imaging in attempt to overcome tumour miss as a result of lack of more reproducible identification of the prostate due to diminished resolution of soft tissues on CT compared to MRI

It is also clear here that Radiologists delineated prostate volumes larger on CT (60.7cm^3) and MR (42.6cm^3) followed by the Oncologists (CT= 58.7cm^3 ; MR= 30.4) and then by the Urologists (CT= 55.9cm^3 ; MR= 39.1cm^3). This is contrary to a study by Giraud et al (20) who compared the delineation of the GTV of intra-thoracic tumours by Radiologists and Radiation oncologists with experience in the field in various centres and found that overall the Radiologists delineated smaller volumes compared to the radiation oncologists. In that study, the mean GTV volume was 97.9cm^3 for radiologists and 133.6cm^3 for radiation oncologists. The difference was therefore significant ($p=0.01$) and overall the radiologists experienced fewer difficulties to delineate “difficult” cases than the radiation oncologists.

There was a significant inter-observer variation with regards to average prostate volumes between Oncologists and Radiologists ($p<0.01$) specifically with regards to average MRI prostate volumes as illustrated in table 1. This significant difference might be attributed to radiological anatomical skill by Radiologists and thus these present findings emphasize the need to stick to very precise delineation protocols, jointly established by radiation oncologists and radiologists in order to homogenize the delineations performed by the different physicians.

Analysis of prostate contouring variations according to Maximum volume ratio (MVR):

The average ratio of the CT volume and the volume outlined on axial MRI (maximum volume ratio) for Oncologists, Radiologists and Urologists as shown in table 8 demonstrates that on Average the CT derived volume was larger than the volume outlined on axial MRI. For Oncologists the MVR calculated was 2.24; for Radiologists MVR was 1.57 and for Urologists MVR was 1.51. This means that on average the prostate was contoured 2.24 times larger on CT than on MR by Oncologists, and 1.57 times larger on CT than on MR by Radiologists and 1.51 times larger by Urologists. The study by Smith et al that evaluated the reproducibility and modality difference of prostate contouring reported the average ratio of measured prostate volume between

the modalities for all patients and observers of 1.16 ± 0.19 for CT/MR (12). Another study by Rasch et al who determined the difference between prostate delineation in MR and CT for radiotherapy treatment planning demonstrated the average ratio of 1.4 of the CT and MR volume respectively. Similar average ratio of 1.4 was also reported in a study by Steenbakkers et al whose purpose of the study was to determine the influence of MRI vs CT based prostate delineation using multiple observations the dose to the target and organs at risk (16). In my study, the P value was significant between Oncologists and Radiologists (0.02) as well as between Oncologists and Urologists (0.01) but was none significant between Radiologists and Urologists (0.64). This therefore suggests that more radiological anatomy knowledge is required by in-house Radiation oncologists to help overcome such a variation and overestimation of contours on CT scans as well as to allow appreciation of common contouring errors in CT based contouring.

Variation with regards to Sup-inferior, ant-posterior and transverse diameter of prostate contours by various specialists:

Analysis of maximum superior and inferior diameter demonstrated that the mean cranio-caudal diameters are smaller on MRI when compared with the CT for Oncologists, Urologists and radiologists as demonstrated in table 7. These results were similar to the results obtained in a study by Sedegin et al(55) where the mean cranio-caudal distance was smaller on MRI(base: 0.8 ± 1.6 mm; apex: 1.9 ± 2.7 mm) when compared with CT(base: 2.9 ± 2.1 mm; apex: 3.4 ± 2.6 mm).

More analysis of mean transverse diameter demonstrated significant contouring variability on MRI between Oncologists and Urologists (0.01) as well as Oncologists and Radiologists (0.01) and no significant variation between Radiologists and Urologists.

There was a significant variation in maximum anterior posterior diameter on MRI between Oncologists and Radiologists. The coefficient values were high for oncologists (14,4mm) compared to Radiologists (8.1mm) and this therefore illustrates a large variation in maximum anterior-posterior diameter between Oncologists and Radiologists.

Although coefficient of variation analysis of most of the different regions of prostate demonstrated significantly less contouring variability on CT and MRI, there was a significant contouring variation that occurred on the apex of the prostate. There was a significant variation of apex CT volume ($p=0.01$) and apex anterior-posterior CT diameter variation between Oncologists and Urologists ($p=0.02$) and between Radiologists and Urologists ($p=0.02$) as well as apex transverse CT volume between Radiologists and Urologists ($p=0.03$).

This is consistent with other reports that demonstrate significantly more contouring variability when CT scans is compared with MRI at the apex of the prostate (9). Another study by Mclaughlin et al also reported difficulty on reliably delineating the apex and base of the prostate on CT compared with MRI (30).

Inter-observer variation according to Apex and Base volumes and location of contoured prostate volumes:

The difficulty in outlining prostate is often in identifying the most cranial (i.e base) and caudal (i.e apex) extent of the prostate. This is consistent with the results of my study that demonstrated greatest inter-observer in identifying the apex on axial CT images with less variation with axial MR images. This is also supported by an inter-observer variation study by Segedin et al (55) which showed prostate contour variations most pronounced in apical region for both CT and MRI.

In our study as illustrated by the table 2 of coefficient of variation, there was a significant difference between Radiologists and Urologists in terms of CT apex overall volume ($p=0.01$) and CT Apex transverse volume ($p=0.03$). However the MRI imaging is a useful tool used by Urologists every now and then for localization of prostate cancer hence there was less variation in apex volumes on MRI imaging in comparison with other specialists.

The ideal and acceptable goal of CT contouring is to define the prostate within 0.5cm of the MRI defined prostate without underestimation. Table 6 demonstrates the apex distance difference between the apex contoured by specialist and the defined apex that was obtained by calculation the average of the overall apexes contoured by specialists in light of the absence of gold standard for apex contour location. CT apex contours in certain patients were >5mm particularly for patient 1, the Oncologists CT apex distance difference in relation to the defined apex was 6.02mm and for patient 5 the Radiologists CT apex distance difference was 5.59mm and for the Urologists was 8.41mm. The MRI apex contours drawn by the observers were however within 5 mm of the defined apex location. Improved apex definition allows for decreased doses to the external sphincter, rectum, and external sphincter, potentially

resulting in decrease treatment toxicity. In a study by McLaughlin et al aimed at accurate definition of prostate apex, three observers were able to define the apex on average within 3mm of MRI standard in all 15 cases (53).

With regards to the base location, both the CT base contours and the MRI base contours drawn by the observers were within 5 mm of the defined base location.

SEV/SCV:

The interscan distance is a systematic difference and thus the portals can be reduced with the use of MRI. As a result of this reduction, the amount of irradiated rectal wall is smaller and the rectal complication rate will decrease. As a result of smaller target volume, the risk of urological complications (i.e impotence) (49) might be reduced as well hence the use of MRI (i.e CT-MRI matching) for delineation of the prostate is recommended. It was also demonstrated by Steenbakker et al (11) that the dose delivered to the rectum and bulb of the penis was significantly reduced with the treatment plans based on MRI delineation of the prostate compared with CT delineation and this reduction allowed a dose escalation of 2-7Gy for same rectal wall dose.

In my study the ratio between the observer encompassing and common volume (indicative for the inter-scan variation) ranged from 1.69 to 2.22 for CT and MRI for the different specialists respectively indicating the variation between the observers in each scan modality. Interestingly the inter-scan variation for the radiologists was similar in both the image modalities, was 2.22 for both CT and MRI. This therefore demonstrates that the radiologists were more homogeneous compared to other specialists confirming their experience in radiological anatomy. For the oncologists the variation on CT(1.72) was less than for MRI(1.82) whereas for the Urologists the variation on CT (1.75) was larger than the MRI (1.69) which is similar to the study done by Parker et al who demonstrated the interobserver variation in prostate contouring being significantly less for MRI rather than CT. In that study the mean SEV/SCV ratio was 1.58(CI: 1.47-1.69) for CT scans and 1.37(CI:1.33-1.41) for MR scans(paired t-test; p=0.036). Debois et al(52) in a study of ten patients also analysed the difference between CT and MRI in terms of the contoured prostate volume found that the prostate volume on MR was significantly smaller than the CT prostate volume in nine of the ten cases.

Spatial differences:

Three dimensional presentation of the difference between the prostate outlined on CT and MRI (table 9) reveals that the average Centroid value for Oncologists was -0.5mm and for radiologists -1.1mm whereas the average centroids for urologists was 0.1mm therefore this means that the CT derived prostate was larger for the Radiologists and Oncologists compared to the Urologists which might be explained by the rare use of CT imaging by urologists in clinical practice. These results were consistent with a study by Segedin et al (55) who showed that the radial inter-contour distances were smaller on MRI than on CT. Another study by Rasch et al (19) demonstrated that the overall observer variation was similarly distributed for all the scans but was in general smaller in the axial MRI compared to the CT

Correlation of the delineated volumes:

The mean and standard deviation of Conformity indices as presented in table 3 and figure 1 demonstrates that the ratio between the total intersection (total common volume) and the total union (the largest volume common for combined images (CT and MRI) for all patients were 0.45 ± 0.04 for Urologists, 0.56 ± 0.08 for Oncologists and 0.58 ± 0.05 for Radiologists. This means that on average the intersection of the volume delineated by the three respective specialists is more or less about half the union, which corresponds to a poor concordance and demonstrates large discrepancies in the volume delineation strategy. A study by Moeckli et al (17) who compared the delineations and interpretations of the target volumes by physicians in different radio-oncology centres similarly showed large discrepancies between all delineated target volumes and reported a proximity/conformity index of 0.50 ± 0.13 for the CTV contoured in a prostate plan and thus meant that on average, the intersection of the volume delineated by respective centres was about half the union, which corresponded to a poor concordance.

For Oncologists the mean CI was 0.58 for CT and 0.55 for MRI; For Urologists the mean CI was 0.45 for CT and similarly 0.45 for MRI; and for Radiologists the mean CI was 0.57 for CT and 0.59 for MRI. The inter modality analysis indicates that there was not much conformity index differences between CT and MRI modalities. This is contrary to the study done by Segedin et al (55) whose aim was to quantify feasibility of delineation and degree of inter-observer variation in MRI and CT based contouring for prostate brachytherapy and in his study the ratio between common and encompassing volume of reference and test contours was higher for MRI than CT (0.83 ± 0.04 vs 0.69 ± 0.05).

Inter-patient analysis of CI did not differ much except for patient 5 the conformity index was higher compared to the other patients across all the varying participants with Oncologists having higher CI values in patient 5 for both CT (0.69) and MRI (0.70) compared to Urologists (0.49 and 0.52) and radiologists (0.65 and 0.67) for both CT and MRI and this possibly indicates that patient 5 was an easy case to contour compared to other patients.

10 Limitations of the study:

- A major criticism of the study is the lack of a gold standard. Unfortunately there is no gold standard to which all contours can be compared in this analysis. The absence of a gold standard makes it impossible to make conclusions about the absolute accuracy of contours. One study has compared the contouring variability of the 6 radiation oncologists on CT with photographic anatomical images of a single cadaver (45). The group identified systematic errors by physicians in underestimating the prostate posteriorly and overestimating the prostate anteriorly on CT compared with the anatomical images, similar to observations made by our group and others when comparing CT or MRI.

There are suggestions in the literature that MRI may correlate closely with the true anatomy. A study by Sosna et al demonstrated that MRI-based prostate volumes are similar to pathologic specimen volumes of the prostate, at both 1.5 T (46) and 3.0 T (47). However there are no studies that compare contouring variability on MRI with anatomical images or specimens to determine the correlation between this imaging modality and “true” anatomy.

- Non contrast planning CT was used which may contribute more towards tendency to overestimate the prostate volume compared to MRI.
- Inconsistent levels of imaging expertise and lack of metrics for assessing the influence of such inconsistencies on contouring.
- Lack of prior studies on inter-observer variation on contouring of the prostate between oncologists, radiologists and urologists.
- Since the sample sizes are typically smaller in qualitative research, it was thus acceptable to use the sample size chosen, however larger sample size would have provided more credibility to the results.
- The population of one of the experimental subgroup (urologists) was smaller compared to other subgroup of specialists and might not represent the majority of urologists and might have yielded statistical results that are less widely generalizable to other groups and in light of this, the findings were approached with caution.

- The study was dependent on the integrity and trust of participants as it was impossible for the researcher to be present during the contouring process.

- Lack of standardized metrics in evaluation of segmentation and lack of shape based statistic tools to provide morphometric information for the evaluation of contour algorithms to provide detailed insight into any systematic errors in the algorithms as well as to eliminate large degree of uncertainty over the apparent edge of the target, makes comparison of developed methodologies difficult.

- The study did not evaluate how the differences in prostate volume definition affect the normal tissue complication probability (NTCP) and tumour control probability (TCP) (56).

- This study was carefully designed to try and limit the many inherent biases that can confound the results of an analysis on contouring variability including the creation of anonymous images that did not contain patient demographic details and scan information.

11 Recommendations:

- A structured interactive educational intervention program to reduce inter-observer variation as well as to maximise knowledge retention over time may lead to further gains in contouring quality assurance.

There is little literature on how to teach prostate and rectal contouring; nor is there a consensus as to the best teaching method. An assessment survey that was conducted among 21 Canadian radiation oncology centres identified the need for education in prostate and rectum contouring for planning of 3D-CRT for prostate cancer (31). According to the survey, the majority of radiation oncologists and radiation therapists who delineate the prostate and rectal volumes on planning CT scan acquire these skills by practice, without any formal training. Thus there is undoubtedly a need for research of methods to optimize such training.

A study by Khoo et al (4) also showed that a systematic education program for radiation oncologists reduced such variations and it was feasible to implement such a program in a busy radiation oncology department. The well-structured education program reduced both inter and intra-observer prostate contouring variations and had a greater impact on MRI than on CT.

Recently a follow up study to that reported by Khoo et al was done by Nicholis et al (54) with the aim of assessing variation in prostate contouring 12 months following a structured interactive educational intervention (EI) and to test the hypothesis that EIs positively impact on prostate contouring accuracy and consistency long term. The study concluded that good retention of applied knowledge 12 months following an EI on prostate contouring was demonstrated and advocates for EI to be included as part of contouring medical education to reduce contour variation among radiation oncologists and to improve knowledge retention long term.

- Increasing awareness by the Radiation oncologists of the overestimation of contours on CT is crucial and in light of this, more recent studies have suggested modifying contouring practices to create volumes that are similar to MRI-based volumes (9). In a study by Kagawa et al (44), it was concluded that prostate delineation on MRI was superior to CT delineation and Steenbakkers et al (16) deduced that organ at risk sparing was also increased for treatment plans with

MRI delineated prostate cases. Thus MR imaging remains a vital part of prostate IMRT planning despite the added cost.

- Incorporating a Radiologist in a Radiation oncology department would be of vital importance within the department. A study by Dimigen et al (22) which was the first study aimed at assessing whether the availability of an in-house radiologist would be beneficial in enhancing the interpretation of oncological imaging and accuracy of contouring showed that an on-site radiologist with an understanding of radiation oncology contours had a significant outcome on patient management and patient audit contours. This therefore reflects importance of good interpersonal and interdepartmental relationships. Also a study by Horan et al (50) showed that collaboration between radiologists and oncologists reduces systematic errors in GTV.

- The American society for Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) both have established contouring programmes across multiple tumour streams. ASTRO have recently incorporated online contouring programmes in its annual meeting and have now presented an e-Contouring programme for radiation oncology trainees.

- Periodic peer review of contoured volumes is fundamental to ensure consistency and for good quality assurance.

- Manual contouring is still standard of practice. There is currently little literature on the application of atlas based segmentation of the prostate volume on MRI. A study by Klein et al (48) focused on the use of 3 dimensional MRI to delineate prostate volume for treatment planning purposes. For this study, deformable registration of a set of pre-labeled atlas images (a multi-atlas method) was used to delineate prostate and seminal vesicles on MR images. They concluded that the contours provided by human observers were superior to automated contours in most regions of interest with a median DSC of 0.85 achieved for the prostate. Klein et al concluded that improvements were needed for future applications of automated atlas based segmentation methods.

- A study that investigates a morphometric (shape based) statistic tool for evaluation of radiotherapy treatment planning contours as well as a

study that investigates the dosimetric implications of contouring variation is strongly advised.

12 Conclusion:

Inter-observer variation was shown to exist in prostate contouring between radiation oncologists, urologists and radiologists and areas of disagreements were identified indicating that this step needs to be improved and measures to minimize these variation should be taken.

The absence of a gold standard contour makes it impossible to make conclusions about absolute accuracy of contours hence education programs for target contouring should be incorporated as part of the continuing medical education of radiation oncologists and with the ongoing incorporation of new technologies into routine practice the future looks bright.

The study demonstrates that MRI allows decreased contouring variability of prostate compared with CT. The volumes were significantly larger on CT than the corresponding MR image sets in all cases. The variations at apex position were significant and varied more for CT than MRI.

In the study, the urologists produced the most comparable delineations, followed by the radiologists and lastly the oncologists. The radiologists were more homogenous compared to other specialists.

Delineation errors have a direct effect on the quality of treatment and thus the quantitative assessment of target volume contouring in radiotherapy treatment planning is an important aspect of quality assessment and educational exercise.

Incorporating an in-house radiologist in the radiation oncology department would be of vital importance as it may lead to reduction of systematic errors in the gross tumour volume (GTV) and may yield great benefits for our patient's in-terms of ensuring a good quality assurance in the treatment planning process. Otherwise inclusion of a radiology rotation would be useful during registrar training for radiation oncology, however this would implicate an extension in the training duration since the curriculum is already constrained.

13 Acknowledgements:

I am grateful to my supervisor, Dr Alicia Sherriff, whose expertise, understanding, generous guidance and support made it possible for me to work on such an incredible topic that was of great interest to me. I would like to express my gratitude to her for putting her faith in me and for urging me to do better. It was a pleasure working with her.

I am highly indebted and thoroughly grateful to Mr Lourens Strauss for immense technical support, for creating a dedicated software program to assist with the research and for providing me with materials and tools that I could not possibly have discovered on my own. I do not think I can ever repay the debt I owe him.

I am grateful to Prof Gina Joubert from the department of biostatistics for her kind advice and for assisting with regards to analysis of data.

I am hugely indebted to the study participants which includes, the radiation oncologists, urologists and radiologists both from state and from private for finding time to partake in the study, words can never be enough to thank their kindness. I am humbled.

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