Prostate cancer Volume on MRI: manual vs semi-quantitative

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**Word count:** (abstract) 212 ; (text) 2139

**Key Words (MeSH):** prostate neoplasms; MRI; Index Lesion, tumor Volume.

**Abstract 212**

**Objective:** The aim of the present study was to determine the accuracy of semi-automated and manual volume measurements of prostate cancer on multiparametric (MP) magnetic resonance imaging (MRI) compared with volumes derived from histopathology (Vh)

**Materials and Methods:** We evaluate 30 consecutive patients with a mean specific antigen of 8.5 ng/dl, who underwent MP-MRI before radical prostatectomy between March 2016 and September 2016 for localize prostate cancer. Index tumor was determined prospectively and independently by magnetic resonance imaging and histopathology. A single measurement of the largest dimension (MTD), a simplified ellipsoid volume formula (MREV) and ROI segmentation (MROV) using commercially available software (OsiriX; OsiriX Imaging) were used by two independent radiologists to determine MR tumor volume.

**Results:** Thirty index lesions were analysed with a mean histologic volume of 1.514 cm$^3$ (range from 0.05 to 3.780 cm$^3$). The MREV, MROV and Vh were significantly correlated with each other (Spearman’s correlation coefficients > 0.5). The agreement for inter-observer measurements was good for each method (Spearman’s correlation coefficients > 0.780). The MTD was the best predictor of maximum histologic diameter (p<0.0001) and had an excellent inter-variability correlation (p<0.0001)

**Conclusion** In clinical practice, one could use MTD on MRI for selecting and following patients for active surveillance and staging before surgery or focal treatment
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Purpose: (2139)

Accurately determining prostate cancer volume is clinically important. The aim of the present study was to determine the accuracy of semi-automated and manual volume measurements of prostate cancer on multiparametric magnetic resonance imaging (MP MRI) compared with volumes derived from histopathology.

Introduction (2096)

There is increasing interest in active surveillance and minimally invasive focal therapies in prostate cancer, especially image guided ablation to avoid the well-known morbidities associated with whole gland therapy. Tumor volume is a well-known prognostic factor of prostate cancer [1] and the definition of index lesion volume is important for appropriate decision making, especially for image guide focal treatment [2] or in case of active surveillance [3]. MP-MRI imaging is the modality of choice for detection and localization of prostate cancer foci [4, 5]. However, little has been published on MP MR imaging accuracy in determining prostate cancer volume, especially at 3 T. There is insufficient evidence and no consensus to determine which of the methods for measuring volume is optimal. Therefore, the purpose of our study was to determine the accuracy in assessing prostate tumor volume compare semi-automated and manual volumetric measurements of prostate cancer on mp-MRI using whole mount histopathology for validation.

Patients and Methods

Study population

This is a retrospective analysis of a prospective database. We evaluated 30 consecutive patients with a mean specific antigen of 8.5 ng/dl (with a range of 2.73-13 ng/dl) who underwent MP MR before radical prostatectomy between March 2016 and September 2016 for localize prostate cancer.

Index tumor volume was determined prospectively and independently by magnetic resonance imaging and histopathology. The current study was approved by the institutional review board and informed consent was obtained from all participants.
**Tesla multiparametric MRI**

All patients underwent preoperative MRI with a whole-body 3-T system (Magnetom Trio, Skyra, Siemens Healthcare) and anterior and posterior phased-array coils. Examinations included axial turbo-spin echo T2-weighted imaging (TR/TE, 4000–4960/105; slice thickness, 3 mm; FOV, 180 × 180; matrix, 256 × 256; parallel imaging factor, 2; number of signals averaged, 3) and axial fat-suppressed single-shot echoplanar DWI (TR/TE, 4100/86; slice thickness, 3 mm; FOV, 200 × 200 mm; matrix, 100 × 220; parallel imaging factor, 2; number of signals averaged, 10; b values, 50 and 1000 s/mm) from which the ADC map was constructed on a voxel-wide basis with a standard mono-exponential. All MRI examinations were obtained according to the same protocol. A dynamic-contrast-enhanced MRI was obtained using a fat-saturated T1-weighted fast-field echo sequence (FFE). Following acquisition of the T1 relaxation data, consecutive dynamic sequences were acquired after an intravenous bolus injection of 20 mL of gadoterate meglumine (Dotarem, Guerbet, Roissy CdG, France). Peristalsis was suppressed with intramuscular administration of 1 mg of glucagon (Glucagen: Nordisk, Gentofte, Denmark). This study was performed according to START consortium guidelines [6].

**Image analysis.**

MP MR images were analysed independently by two uro-radiologists with 11 years (RRP, reader 2) and 3 years (ME, reader 1) of experience in prostate imaging at the start of the study. They knew that patients had undergone radical prostatectomy but were blinded to other data. Readers evaluated images obtained with the 3 pulse sequences concomitantly. First, they noted all prostate lesions of the peripheral zone that showed low signal intensity on T2-weighted images and/or apparent diffusion coefficient (ADC) maps and DCE imaging. Then, they noted all transition zone lesions that showed homogeneous low signal intensity on T2-weighted images, with ill-defined margins, no capsule, and no cyst [7].

All sequences were used for assessment of the Tumor Volume (TV) of the index lesion, whereas the actual measurements were performed on T2W images using 3 different techniques by the two readers: A single measurement of the largest dimension (Maximum Tumor Diameter MTD), Manual volumetric assessment:
Readers used a simplified ellipsoid volume formula using the longest perpendicular diameters: depth × width × length (in mm) x 0.52 (MREV) and *Semi-automated volumetric assessment using commercially available software* (OsiriX; OsiriX Imaging Software, Geneva, Switzerland) (MROV)

Abnormalities were graded using a PI-RADS score according to ESUR prostate MRI guidelines [7]. The PI-RADS score was as follows:

- Score 1 = Clinically significant disease is highly unlikely to be present
- Score 2 = Clinically significant cancer is unlikely to be present
- Score 3 = Clinically significant cancer is equivocal
- Score 4 = Clinically significant cancer is likely to be present
- Score 5 = Clinically significant cancer is highly likely to be present.

**Pathological findings**

Prostatectomy specimens were processed according to the Stanford protocol [8]. After a 24-hour fixation period in formaldehyde and conization of the apex and bladder neck, the prostate was cut from apex to base in an axial plane by using a specially designed machine that ensured that the blocks were evenly spaced (4 mm thick)(Pro-Cut slicing device, Milestone). The blocks were fixed for a further 24 hours, then processed, and paraffin embedded as whole-mount sections. Whole-mount sections were obtained every 4 mm, and their precise location within the blocks was monitored. One uropathologist (EC) with 10 years of experience at the start of the study and who was blinded to MR data, reviewed the whole-mount sections. Gleason score was assessed for all tumor foci according to the WHO 2016[9]. The tumor border was outlined on the coverslip of the slide using a marking pen. Individual tumor foci were delineated on the glass cover of each whole-mount section by the pathologist. The length (maximum histologic diameter), width and thickness of the largest single tumor focus was determined by marking both ends of the lesion with a pen and measuring this distance directly on the glass slide with a ruler. The histologic volume (Vh) was calculated with ellipsoid estimation described by Noguchi et al (* = k (π/6) length* width* thickness)[10].
**R Histologic Comparison**

The readers and the uro-pathologist reviewed the areas suspicious for cancer delineated on MP MR images by the readers. Then, the uro-pathologist decided which lesions matched histologic cancers and which did not, using side-by-side comparison with whole-mount sections. Matching lesions were considered true-positive lesions only if their largest diameter was within 50%–150% of the largest diameter of the corresponding histologic cancer on an image from at least one pulse sequence.

**Statistical Analysis**

Statistical analysis was performed by using MEDCALC software 17.1. Variables for the estimation of the volume according to investigators (R1 & R2) and 2 techniques (Osirix and ellipsoid) were compared together and to the estimation of the pathological tumor volume. We compare also the greatest diameter of the tumor on T2 sequences (investigator 1 & 2) and on the pathological specimens. We use to compare the variables Pearson correlation and the Passing & Bablok methods. Linear regression procedure regarding the distribution of the samples and the measurement errors were applied to visualize the goodness of fit of the linear model. Residuals may point to possible outliers (unusual values) in the data.

**Results**

**Volume study**

**Volume of tumors (table 1)**

Table 1 shows mean volumes and standard deviations of the 30 index lesions for each observer and each method. For the reference method, Vh, the mean volume was 1.514 cm³, range from 0.05 to 3.780 cm³. The mean volumes estimated by ROI
segmentation (0.712 and 0.614 cm$^3$) tended to yield slight underestimation of Vh as the ellipsoid volume by reader 2 (1.065).

**Correlation and agreement between the two methods for volume estimation (fig 1)**

The Spearman's correlation coefficients between ellipsoid and Vh were respectively 0.563 (R2) and 0.452 (R1). The Spearman’s correlation coefficients between ROI segmentation and Vh were 0.585 (R2) and 0.589 (R1)

**Inter-observer variability**

The spearman’s correlation coefficients between observers were respectively 0.781 for ellipsoid volume and 0.789 for ROI segmentation.

**Size study**

**Size of tumors (table 2)**

Table 2 shows mean size of the maximum tumor diameter (MTD) for each observer and the mean size of the maximum histologic diameter (MHD). The mean size of MTD was 16.7 range 7-29 mm for reader 1 and 14.734 range 8-26.69 mm for reader 2. The mean size of the MHD was 17.085 range 10-29 mm.

**Correlation and agreement between the size estimation (fig 2, fig 3)**

The Spearman’s correlation coefficients between MTD-R1, MTD-R2 and MHD were 0.980 and 0.79

**Inter-observer variability**

The spearman’s correlation coefficient between MTD-R1 and MTD-R2 was 0.757

**Discussion**

Accurate non-invasive measurement of prostate cancer tumor volume could substantially improve the determination of tumor prognosis and assist in the selection of appropriate treatment especially in case of focal therapy and active surveillance [2, 3]. Tumor volume is by far the most frequent and most important criterion defining the index tumor. The PI-RADS Steering Committee [11] believes that standardization of measurements will facilitate MR-pathological correlation and research and recommends that some rules must be used for measurements. The minimum
requirement is to report a single measurement of the largest dimension (the maximum diameter) of a suspicious finding on an axial image. Alternatively, three dimensions of lesions could be measured so that lesion volume may be calculated (maximum AP diameter _ maximum transverse diameter _ maximum cranio-caudal diameter *0.52). Finally, lesion volume may be determined using appropriate software. However, there is insufficient evidence and no consensus to determine which of the methods for measuring size is optimal for distinguishing between natural fluctuation in tumour volume, measurement errors over time, or true disease progression [3].

In this study we wanted to compare 3 different methods for measuring prostate cancer volume: single measurement of the largest dimension (MDT), manual volumetric measurement of prostate cancer (ellipsoid method) and ROI segmentation using software (Osirix).

Our study shows a good correlation between semi-automated and manual volume measurements of prostate cancer index lesion on MRI with Coefficient correlations respectively of 0.589R1 and 0.585 R2 for semi-automated and 0.563 R2 for manual volume.

We found that measurement of prostate cancer tumor volume led to a light underestimation of the histologic volume regardless of technique used to measure (fig 1). However, those results are in agreement with data in previous studies [12-14]. Some underestimation may be inevitable due to tumor heterogeneity and blending with healthy tissue [15].

However with found that MDT may provide a more precise estimation of histologic volume. MDT is an objective method evaluating prostate cancer on the basis of size instead of the tumor volume. In our study, the MDT was significantly correlated with the maximal histological diameter with an excellent coefficient correlations (0.980 R1 and 0.791 R2). These results are concordant with two previous studies. Mizuno et al, found the MTD was the more significant pathological feature associated with the local extent of disease [14]. Nakashima et al, found that the MTD was correlated with histologic examination for index lesion measuring more than 1.0 cm in diameter in histology [13].

Inter-observer variability is a crucial issue in assessing tumour volume and subsequently tumour changes especially in case of active surveillance. In our study, inter-observer variability was very low regardless of the method used. Moreover MDT had the lowest inter-observer variability (p > 0.0001).
To our knowledge, comparison of semi-automated and manual assessment of prostate cancer volume has not been performed. Our study shows a good correlation between semi-automated and manual volume measurements of prostate cancer with a low inter observer variability. ROI segmentation volume using software could be an accurate method but it may be too time consuming for routine use, and for small lesions best seen on functional images, a single diameter may be more accurate than a volume, with the lowest inter observer variability, and an excellent correlation with the largest histologic diameter.

Limitations in studies assessing accuracy of MRI with histopathology arise from free-hand slicing of the specimens (deformation and variable slice thickness) and non-uniform shrinkage during fixation (distortion). We did not apply any correction factor for tissue shrinkage because these correction factors remain difficult to evaluate and are within the wide range of 1–1.5 in existing literature [16, 17]. As others, we tried to minimize chance detection of prostate cancers by including a location match and a reasonable concordance in size with the corresponding histologic tumor in the definition of MP MR imaging true-positive lesions [18]. Histologic volume measurement remains challenging. The ISUP 2016 Consensus Conference recommended reporting on the three longest diameters in addition to the longest diameter out of all possible planes [19]. We tried to measure it as precisely as we could by standardizing the thickness of the histologic blocks (4 mm), and monitoring the position of the whole mount sections within the blocks.

In conclusion, prostate cancer histologic volume can be assessed by using manual simplified ellipsoid volume or ROI segmentation with a good accuracy and low inter-observer variability. However MTD, simple, easy, and inexpensive parameter, had the lowest inter-observer variability and provide the more precise correlation with the maximal histological diameter. In clinical practice, one could use MTD on MRI for selecting and following patients for active surveillance and staging before surgery or focal treatment.
Tables and figures.

Table 1 Mean volume (Cm$^3$) of index lesion by method and by observer.

Fig 1 Passing H, Bablok W regression line including confidence interval for the regression line (dashed lines). Correlation between MRI and histologic Volumes by observers.

Table 2: MRI and histologic size estimation (mm) of index lesion

Fig 2: Passing H, Bablok W regression line including confidence interval for the regression line (dashed lines). Correlation between MRI and histologic size by observers.