Optimization of clinical target volume delineation using magnetic resonance spectroscopic imaging (MRSI) in 3D conformal radiotherapy of prostate cancer

M. Robatjazi[1], S.R. Mahdavi[1*], A.R. Nikofar[2], B. Bolouri[1], H.R. Baghani[3]

[1]Department of Medical Physics, Tehran University of Medical sciences, Tehran, Iran
[2]Department of Radiation Oncology, Iran University of Medical sciences, Tehran, Iran
[3]Department of Medical Radiation Engineering, Shahid Beheshti University, Tehran, Iran

► ***Original article***

**** Corresponding author:***
Dr. S.R. Mahdavi,
Fax: *+98 21 88622647*
E-mail:
srmahdavi@hotmail.com

Revised: Dec. 2013
Accepted: March 2014

Int. J. Radiat. Res., October 2014; 12(4): 303-309

ABSTRACT

Background: For the purpose of individual clinical target volume assessment in radiotherapy of prostate cancer, MRSI was used as a molecular imaging modality with MRI and CT images. ***Materials and Methods***: The images of 20 prostate cancer patients were used in this study. The MR and MRSI images were registered with CT ones using non-rigid registration technique. The CT based planning (BP), CT/MRI BP and CT/MRSI BP was performed for each patient. For plan evaluation, Dose Volume Histograms (DVHs) data were used. A paired sample *T-test* was used for the analysis of the obtained data. ***Results***: The percentage of variation of CTV_{MRI} to CTV_{CT} and PTV_{MRI} to PTV_{CT} were 12.83% and 8.97%, respectively. CTV_{MRSI} and PTV_{MRSI} were 21% and 27.41% more than their corresponding values of CT volumes. The mean percentage of variation in rectum volume that received 60% of the prescribe dose (V60R) in MRSI/CT BP relative to CT BP was 14.66%. ***Conclusion***: The use of MRSI in detecting of prostate adenocarcinoma could provide some decisive information to determine optimum volume and safe margin for target definition to improve adaptive radiotherapy in prostate cancer.

Keywords: *MRSI, MRI, prostate cancer, 3D-CRT radiotherapy, target definition.*

INTRODUCTION

After lung cancer, prostate cancer, is the second most common type of cancer among men and has the second highest cause of mortality[1]. If it was treated by radiation therapy (RT), In order to have a successful result following this treatment method, every single tumor cell including those extended beyond gross, palpable or imaginable disease must be consider as the target of irradiation. The most significant task to maximize the advantages of RT is the specification of the target to be treated. For prostate cancer it is standard practice to apply a uniform margin around the gross tumor to account for microscopic invasion, regardless of individual considerations. In order to visualize the real tumor extent, imaging of microscopic spread of malignant cells is a remarkable point especially in the procedure of clinical target volume (CTV) determinations. Recently, application of Magnetic Resonance Spectroscopy (MRS), as a molecular imaging modality, has been considered by radiotherapist as a means of defining the target volumes in RT. Since MRS provides helpful information on the extra capsular extension (ECE) and real boundaries of tumor, it can be a powerful tool which is proved to be able of distinguishing between normal tissue and ECE in the case of prostate adenocarcinoma[2-3]. Many studies investigate the sensitivity & specificity of this technique for

the localization of prostate cancer. The sensitivity of MRS for this purpose is reported up to 100% [4-5].

There is a strong rationale for incorporating of MRS in the planning process, which may provide more specific information about the location of active tumor growth [4, 6].

MRS is done by single voxel or from a 2D or 3D array of voxels which are called Magnetic Resonance Spectroscopic Imaging (MRSI). One of the distinctive features of the adenocarcinoma of the prostate is its multifocal and ECE that is not detectable by MRI and CT scans accurately and MRSI has this potential in determining ECE and high cellular regions in prostate cancer. The main problem we face in routine clinical practice, concerns about the pattern of ECE. Some studies investigate the application of MRSI in Intensity Modulated Radiation Therapy (IMRT) and brachytherapy for dose escalation in prostate cancer [7-10]. In this study, we investigated the application of MRSI in ECE of prostate cancer, its impact on the determination of CTV for 3D-CRT, and eliminating, the adding uniform margin to prostate to going to individual radiotherapy.

MATERIALS AND METHODS

Patients

Twenty patients (the median age of the patients was 57 years range: 51-67) with histopathology diagnosis of prostate adenocarcinoma (T2 and T3 stage) were chosen for the study. As we use the images of patients and did not interfere within treatment process, our study did not need to ethical considerations.

CT, MRI and MRS Imaging

The CT, MR and MRSI examinations were carried out on these patients. MRSI was done by 3D-CSI (3Dimensional Chemical Shift Imaging) spine echo sequence in a 1.5 T MRI system (Avanto/Siemens). TR, TE, NEX, FOV and matrix size were 1300 ms, 120 ms, 4, 11cm^2, and 25×25×3 (voxel sizes= 0.45 cm^3), respectively. Since MRSI is a low signal modality, endorectal coil was used to increase the signal to noise ratio. However, the main disadvantage of the endorectal coil is a slight deformation of the prostate which needs to be allowed for using the images in radiotherapy treatment planning. According to previous studies, application of rigid endorectal coils is less problematic than the usual balloon coils. Hence, we used rigid endorectal coils to decrease the deformation of prostate [11]. MRSI of prostate provides spectra dominated by three different metabolite peaks: Choline, Creatine and Citrate. Peak parameters were estimated by offline data processing for the specific metabolites within Volume of Interest (VOI). A [Choline + Creatine]/Citrate index was automatically calculated and displayed as different colors on the anatomical images of MRI. The VOI was selected manually to cover the whole prostate gland and seminal vesicle on T2 axial images and suspected regions. In prostate cancer, Choline is elevated and the normal production of Citrate is reduced [4, 12]. In accordance to previous studies, the ratio of [Choline + Creatine]/Citrate was found to differentiate cancer from the healthy peripheral zone tissue in all cases using a value of 0.86 (three standard deviations above the mean normal peripheral zone ratio) as the demarcation line. Figure 1 indicates the MRSI images and sample of spectrum from cancerous region in prostate [5].

T2-weighted imaging was performed by turbo spine echo sequence for which TR, TE and ETL were selected 4200, 108 and 23 ms respectively. For this pulse sequence, slice thickness, interval, matrix size FOV were 3mm, 0.3mm, 205×256 and 200 mm respectively.

The default protocol of pelvic RT which is stored in the CT system (Siemens/16 Somatom Sensation) was used for CT imaging. This protocol applied the effective mAs of 250, kV of 120 and slice thicknesses of about 3 mm.

Treatment planning

The CT and MR images in Digital Imaging and Communications in Medicine (DICOM) format were transferred into Treatment Planning System (TPS); then, MRSI images were converted into DICOM format and registered with the CT images. Non-rigid registration was used in

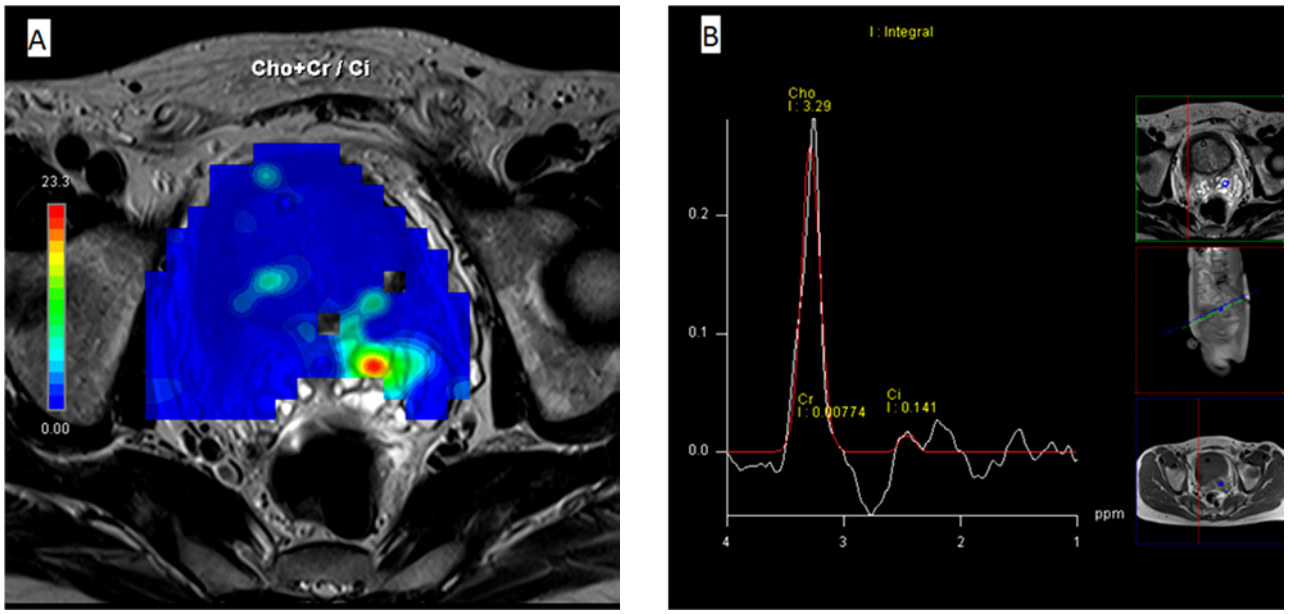

Figure 1. A) MRSI image that we can differentiate cancerous region in seminal vesicle by hot point in spectral map. B) Spectrum of hot point region in seminal vesicle that we can see elevation of Choline peak and decreasing of Citrate peak.

the registration of CT, MRI and MRSI images. For this propose, we used the automatic registration program prepared by Coreplan TPS. Three plans were done for each patient: CT-based, MRI/CT-based and MRSI/CT-based planning. Target delineation process was done by two radiologists whose expert in MRS and two radiation oncologist. According to the International Commission on Radiation Units and Measurements (ICRU) report No. 62 and 50, the whole prostate should be considered as gross tumor volume (GTV). In treatment planning based on CT and MRI images, the prostate gland plus 0.5 cm margin and seminal vesicles was considered as the CTV (CTV $_{CT\ or\ MRI}$). In the MRSI/CT-based planning the hot points in color map of MRSI images that were out of the CTV_{CT} were added to it as MRSI based CTV (CTV_{MRSI}). Planning Target Volume (PTV) was delineated that related to the margin that was added to CTV for setting up uncertainty and variation in patient position. It was equal to CTV plus 0.5 cm posterior margin to spare the rectum and an even margin of 0.8 cm for the other sides. In the RT treatment planning of prostate, the rectum, bladder and femoral heads were considered as the organs at risks (OARs) and delineated. A five-field planning technique was used with the incident angle of 0, 90, 120, 240 and 270 for 15 MV photon and a total prescribed dose of 7000 cGy in 35 fractions. Treatment plans were performed using Coreplan 3D TPS (Seoul C&J Co) engined by correction based (Equivalent Tissue Air Ratio, ETAR) dose calculation algorithm.

According to ICRU 50 and 62 reports the prescribed dose was normalized to 100% at the isocenter and 95% of the isodose surface covered the PTV as the minimum dose and 107% as the maximum dose. Volume and dose values of each plan were extracted from DVHs data.

Statistical analysis was performed by means of SPSS software (version 18) and "Paired sample T-Test" was employed. In this analysis, the MRSI/CT and MRI/CT based planning data was compared with CT based planning data as a reference plan. For all parameters with significant deference, percentage of variation (PV) is calculated by equation 1.

$$PV = \frac{CT_{Volume\ or\ Dose} - MRS\ or\ MRI_{Volume\ or\ Dose}}{CT_{Volume\ or\ Dose}} \times 100 \quad (1)$$

RESULTS

Target and OARs volumes

Delineated targets and OAR volumes were extracted from each plan. The mean values of these volumes were derived and have been presented in figure 2.

The results of statistical analysis showed significant difference between the PTVs ($P<0.001$) and CTVs ($P<0.001$). In the other results, associated with GTV_{MRI}/GTV_{CT} ($P=0.937$), GTV_{MRSI}/GTV_{CT} ($P=0.391$), $bladder_{MRI-}/bladder_{CT}$ ($P=0.086$), $bladder_{MRSI-}/bladder_{CT}$ ($P=0.330$), $rectum_{MRI}/rectum_{CT}$ ($P=0.629$), $rectum_{MRSI}/rectum_{CT}$ ($P=0.331$), and the femoral $heads_{MRI}$/ femoral $heads_{CT}$ ($P=0.164$), femoral $heads_{MRSI}$/ femoral $heads_{CT}$ ($P=0.741$), there is no significant differences. PV for MRI and MRSI relative to CT was obtained by Eq-1. CTV and PTV in MRI have 12.38% and 8.97% reduction comparing to those obtained based on CT images. These values in MRSI, respectively, showed 21% and 27.41% increase relative to obtained volumes by CT.

Dose values in target volumes and OARs

DVHs of CTV, PTV, rectum, bladder and femoral heads were computed for each plan and patient. Received doses of 60% of rectum volume (V60R), 50% of bladder volume (V50B), and 50% of the femoral heads volume (V50F) were reported. The relevant values are provided in table 1.

In comparison of this data, there is significant deference between $V60R_{MRSI}/V60R_{CT}$ ($P=0.024$). V60R in MRSI has 14.66% increases relative to CT.

There is no significant difference in other data. $V60R_{MRI}/V60R_{CT}$ ($P=0.318$), $V50B_{MRI}/V50B_{CT}$ ($P=0.133$), $V50B_{MRSI}/V50B_{CT}$ ($P=0.792$), $V50F_{MRI}/V50F_{CT}$ ($F= 0.520$), and $V50F_{MRSI}/V50F_{CT}$ ($P=0.504$).

Table 1. Indication of quantitative dose values (percent of prescribed dose) that received by OARs.

OARs dose	*MRSI/CT*		*MRI/CT*		*CT*	
	Mean	SD	Mean	SD	Mean	SD
V60R	52.70	9.18	45.03	11.92	47.66	10.65
V50B	42.11	13.79	46.86	14.40	41.31	14.04
V50F	39.60	8.56	39.52	7.14	46.13	4.31

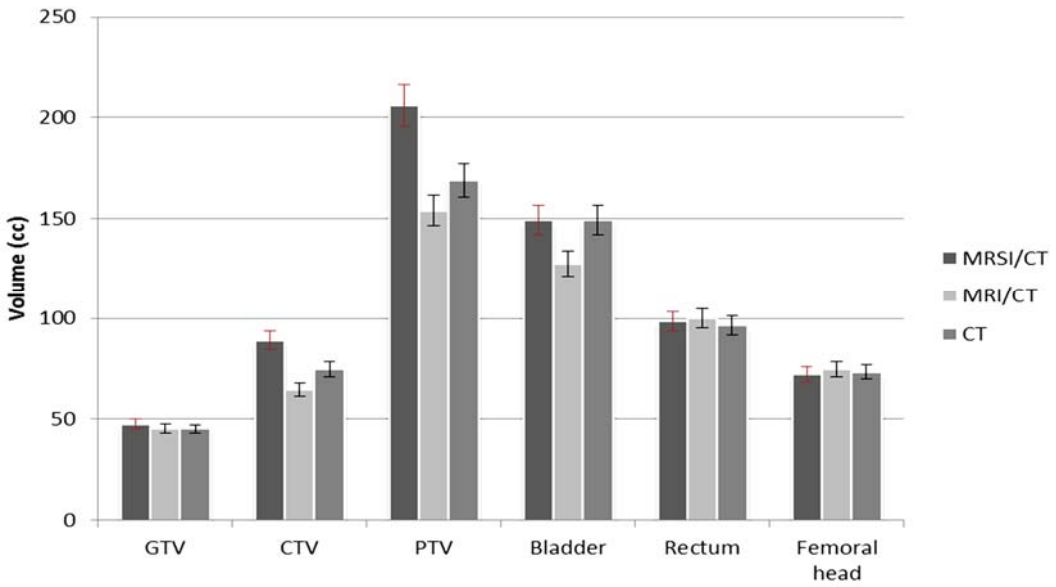

Figure 2. Comparison diagram of mean delineated target and OARs volumes (cc) based on application of 3 imaging modalities.

DISCUSSION

Delineation of target volumes is an obligatory step in the planning process. Basically, the CT images are used in treatment planning for the purpose of dose calculation and delineation of target and OARs, however, it has limitations in prostate treatment planning for target delineation [13]. These limitations include; low contrast resolution and lack of differentiation between prostate and surrounding soft tissues. In particular, these limitations are noticeable in the apex of prostate due to the same X-ray attenuation of soft tissues [14]. On the other hand, MR images have higher ability in representing the contrast of soft tissue than other anatomical images. So, MRI can help the oncologists to determine treatment volume and OARs more accurately, but it has some limitations, such as dose calculation in RT treatment planning, too. MRSI is a non-invasive molecular imaging technique which has a great potential to be used for the definition of biological target volume for the purpose of radiation therapy[5]. Some studies showed that using MRSI would lead to an accurate detection of ECE in prostate cancer. Prando and colleagues tried to estimate the accuracy of MRSI in tumor staging for patients with prostate cancer in T1c stage; In their study, pathologic findings were compared with MRSI findings and the accuracy of MRSI was reported about 80%[15]. Studies of Scheidler and Cerhange indicated that MRSI is a useful technique for determining the tumor position, volume and stage. Cerhange reported that use of MRSI in determination and distinction of ECE of prostate cancer decreased interobserver variations [16-17].

The results of our study demonstrated quantitative differences between the target volumes defined by MRI, CT and MRSI. Both CTVs and PTVs delineated using MRSI data were significantly larger than those obtained using anatomical images (CT & MRI). Teh and colleagues quantify the ECE in the prostatectomy specimens and differences between the pathologic prostate volume, CT-based GTV, and PTV. In the comparison of this study the GTV and PTV to the pathologic prostate volume, the average GTV was 2 times larger than the pathologic prostate volume. The average PTV was 4.1 times larger than the pathologic prostate volume [18]. Sannazzari evaluated effect of application of MRI in treatment planning in patients undergoing 3D-CRT for localized prostate cancer. The result of this study showed a mean overestimation of CTV of 34% with CT compared with MRI. The DVHs resulting from CT and MRI comparison showed that it is possible to spare a mean 10% of rectal volume and approximately 5% of bladder and femoral heads, respectively. The study of Steenbekkers and colleague in using MR images for prostate radiotherapy showed that average ratio of the CT and MRI prostate volume was 1.4 [19]. Jackson and colleagues investigated the role of MR images in radiotherapy target definition of prostate. They indicated a significant difference in target volume relative to CT based targets; Mean determined volume of prostate based on CT slices was about 38±14 cc and based on MRI images was 33±13 cc[20].

In agreement with these studies, the use of MRI for prostate treatment planning in our study led to reduction of CTV and PTV in the amount of 12.83% and 8.97%, respectively, but we don't have significant deference in received dose in OARs in application of MRI. This decrease in volume due to the ability of MRI images in the visualization and differentiation of soft tissue around the prostate.

For the first time, we use MRSI images in 3D-CRT to determine the target volume of prostate. The purpose of this study was to eliminate the adding uniformly margin to the GTV for CTV definition and adding the active regions outside the CTV_{CT} and definition of actual CTV based on this molecular imaging modality. By application of this method, the regions that out of CTV_{CT} and were not fully exposed in treatment field, which would increase the likelihood of recurrence, were treated. As can be seen, this method led to increasing of the CTV to 21% relative to CTV_{CT}. Basically, variation of irradiation volume affects the received dose of OARs. In treatment planning based on MRSI images increasing in CTV and PTV led to increasing of received dose by rectum.

CONCLSIONS

Incorporation of MRSI into RT treatment planning may help to target the active tumor more effectively and thus to prevent early recurrences due to the inadequate radiation dose delivery.

The main limitation of the present MRSI technique is the voxel sizes that topically 4-8 mm^3 that required achieving an adequate signal-to-noise ratio and this low spatial resolution can be affected the target volume determination by MRSI. This large voxel size leads to relative partial volume effect that can be affecting the result of our study. Future studies should acquire MRSI data at field strength of 3T or more to enhance the signal to noise ratio of the data and optimize the voxel size in order to recognize tumor boundary more accurately. Although, application of MRSI for treatment planning of prostate cancer would lead to considerable changes in determining target volumes relative to CT based planning, we confess that the partial volume effect and large voxel size is one of the causes that led to increasing the target volume that delineated by MRSI.

Finally, the use of MRSI in detecting of prostate adenocarcinoma could provide some decisive information to determine optimum volume and individual safe margin for target definition to improve adaptive radiotherapy in prostate cancer.

REFERENCES

1. Parkin DM Bray, Ferlay F, Pisani JP(2005) Global cancer statistics, 2002. CA: *a cancer journal for clinicians,* ***55 (2):****74.*
2. Coakley F, Kurhanewicz J Lu, Jones Y, Swanson K, Chang M, Carroll S, Hricak PH (2002) Prostate Cancer Tumor Volume: Measurement with Endorectal MR and MR Spectroscopic Imaging 1. *Radiology,* ***223(1):****91.*
3. Yu K, Scheidler J, Hricak H, Vigneron D, Zaloudek C, Males R, Nelson S, Carroll P, Kurhanewicz J (1999) Prostate cancer: prediction of extracapsular extension with endorectal MR imaging and three-dimensional proton MR spectroscopic imaging. *Radiology,* ***213(2):****481.*
4. Payne G and Leach M (2006) Applications of magnetic resonance spectroscopy in radiotherapy treatment planning. *British Journal of Radiology,* ***79(Special Issue 1):****S16.*
5. Yuen J, CH T, Khin PH, Phee LW, Xiao SJL, Lau D, Ng WKO, Cheng WS (2004) Endorectal magnetic resonance imaging and spectroscopy for the detection of tumor foci in men with prior negative transrectal ultrasound prostate biopsy. *The Journal of urology,* ***171(4):****1482-6.*
6. Nelson S Graves, Pirzkall E, Li A, Antiniw Chan X, Vigneron A, McKnight DT (2002) *In-vivo* molecular imaging for planning radiation therapy of gliomas: an application of 1H MRSI. *Journal of Magnetic Resonance Imaging,* ***16(4):****464-76.*
7. Pouliot JH, Kurhanewicz I, Noworelski JS (2005) Targeting MRS-Defined Dominant Intraprostatic Lesions with Inverse -Planned High Dose Rate Brachytherapy: DTIC Document 2005.
8. Pouliot J Kim, Lessard Y, Hsu E, Vigneron I, Kurhanewicz DJ (2004) Inverse planning for HDR prostate brachytherapy used to boost dominant intraprostatic lesions defined by magnetic resonance spectroscopy imaging. *International Journal of Radiation Oncology Biology Physics,* ***59(4):****1196-207.*
9. van Lin, Futterer EN, Heijmink JJ, van der Vight SW, Hoffmann LP, van Kollenburg AL, Huisman P, Scheenen HJ, Witjes TW, Leer JA, Barentsz JW, Visser JO, AG. (2006) IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. *International Journal of Radiation Oncology Biology Physics,* ***65(1):****291-303.*
10. ZaiderM, Zelefsky M, Lee EK, Zakian K, Amols H, Dyke J, Cohen G, Hu Y, Endi AK, Chui C (2000) Treatment planning for prostate implants using magnetic-resonance spectroscopy imaging1. *International Journal of Radiation Oncology Biology Physics,* ***47(4):****1085-96.*
11. Kim Y, Noworolski S, Pouliot J, Hsu IC, Kurhanewicz J (2004) Analysis of prostate deformation due to different MRI/ MRS endorectal coils for image fusion and brachytherapy treatment planning. *Medical Physics,* ***31:*** *1728.*
12. John SS, Zietman AL, Shipley WU, Harisinghani MG (2008) Newer imaging modalities to assist with target localization in the radiation treatment of prostate cancer and possible lymph node metastases. *International Journal of Radiation Oncology Biology Physics,* ***71(1 Suppl):****S43-7.*
13. Khoo VS, Padhani AR, Tanner SF, Finnigan DJ, Leach MO, Dearnaley DP(1999) Comparison of MRI with CT for the radiotherapy planning of prostate cancer: a feasibility study. *British Journal of Radiology,* ***72(858):****590-7.*
14. Mack R, Pamela F, Christine M, John H, Hedvi H (1996) Prostate volumes defined by magnetic resonance imaging and computerized tomographic scans for three-dimensional conformal radiotherapy. *International Journal of Radiation Oncology Biology Physics,* ***35(5):****1011-8.*
15. Prando A (2010) Clinical stage T1c prostate cancer: evaluation with endorectal MR imaging and MR spectroscopic imaging. *International Brazilian jouranl of urology,* ***36:*** *100-1.*
16. Scheidler J, Hricak H, Vigneron D, Yu K, Sokolov D, Huang L, Zaloudek C, Nelson S, Carroll P, Kurhanewicz J (1999) Pros-

tate cancer: localization with three-dimensional proton MR spectroscopic imaging-clinicopathologic study. *Radiology,* ***213(2):****473.*

17. Crehange G, Parfait S, Liegard M, Maingon P, Ben Salem, Cochet D, Al Funes de la Vega, Cormier M, Bonnetain L, Mirjolet F, Brunotte C, Walker FP (2010) Tumor Volume and Metabolism of Prostate Cancer Determined by Proton Magnetic Resonance Spectroscopic Imaging at 3T Without Endorectal Coil Reveal Potential Clinical Implications in the Context of Radiation Oncology. *International Journal of Radiation Oncology Biology Physics, [doi: DOI: 10.1016/j.ijrobp.2010.03.007].In Press*
18. Teh B, Bastasch M, Mai W, Butler E, Brian W, Thomas M (2003) Predictors of Extracapsular Extension and Its Radial Distance in Prostate Cancer: Implications for Prostate IMRT, Brachytherapy, and Surgery. *The Cancer Journal,* ***9 (6):*** *p. 454-460.*
19. Steenbakkers R, Deurloo K, Nowak P, Lebesque J, Marcel R, Coen R (2003) Reduction of dose delivered to the rectum and bulb of the penis using MRI delineation for radiotherapy of the prostate. *International Journal of Radiation Oncology Biology Physics,* ***57(5):****1269-79.*
20. Jackson A, Reinsberg S, Sohaib S, Charles-Edwards, Mangar E, South S, C.Leach M, Dearnaley D (2007) Distortion-corrected T2 weighted MRI: a novel approach to prostate radiotherapy planning. *British Journal of Radiology,* ***80 (959):*** *926.*