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Clinical Investigation: Genitourinary Cancer

Locally Advanced Prostate Cancer: Three-Dimensional Magnetic Resonance Spectroscopy to Monitor Prostate Response to Therapy

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Summary

The aim of this study is to correlate 3D magnetic resonance spectroscopy results with prostate-specific antigen (PSA) levels and with time since external-beam irradiation (EBRT) to verify successful treatment by assessing the achievement of metabolic atrophy (MA). According to our results, MA detection increases with decreasing PSA levels and with increasing time on adjuvant hormone therapy after EBRT, which supports long-term treatment with hormonal therapy in advanced prostate cancer.

Purpose: To correlate results of three-dimensional magnetic resonance spectroscopic imaging (MRSI) with prostate-specific antigen (PSA) levels and time since external beam irradiation (EBRT) in patients treated with long-term hormone therapy (HT) and EBRT for locally advanced disease to verify successful treatment by documenting the achievement of metabolic atrophy (MA).

Methods and Materials: Between 2006 and 2008, 109 patients were consecutively enrolled. MA was assessed by choline and citrate peak area-to-noise-ratio <5:1. Cancerous metabolism (CM) was defined by choline-to-creatine ratio >1.5:1 or choline signal-to-noise-ratio >5:1. To test the strength of association between MRSI results and the time elapsed since EBRT (TEFRT), PSA levels, Gleason score (GS), and stage, logistic regression (LR) was performed. p value <0.05 was statistically significant. The patients' outcomes were verified in 2011.

Results: MRSI documented MA in 84 of 109 and CM in 25 of 109 cases. LR showed that age, GS, stage, and initial and recent PSA had no significant impact on MRSI results which were significantly related to PSA values at the time of MRSI and to TEFRT. Patients were divided into three groups according to TEFRT: <1 year, 1–2 years, and >2 years. MA was detected in 54.1% of patients of group 1, 88.9% of group 2, and in 94.5% of group 3 (100% when PSA nadir was reached). CM was detected in 50% of patients with reached PSA nadir in group 1. Local relapse was found in 3 patients previously showing CM at long TEFRT.

Conclusion: MA detection, indicative of successful treatment because growth of normal or abnormal cells cannot occur without metabolism, increases with decreasing PSA levels and increasing time on HT after EBRT. This supports long-term HT in advanced prostate cancer. Larger study series are needed to assess whether MRSI could predict local relapse by detecting CM at long TEFRT.

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Introduction

The combination of adjuvant long-term hormone deprivation therapy (HT) and external beam irradiation (EBRT) in locally advanced prostate cancer (stage T3−T4N0M0, according to the American Joint Committee on Cancer/International Union Against Cancer TNM classification) is associated with improved disease-free and overall survival compared with EBRT alone (1−5). However, published studies disagree about the optimal duration of HT in these patients (3, 4). Adjuvant HT consolidates the efficacy of EBRT. Therefore, an appropriate monitoring of the prostate response to EBRT is desirable. Digital rectal examination (DRE) is a low-sensitivity test, showing 73% sensitivity and 66% specificity after EBRT (6). Decreased serum prostate-specific antigen (PSA) is the most commonly used method to verify prostate cancer remission. However, PSA response data are difficult to interpret in patients undergoing long-term HT because of the direct effect of HT on PSA production, which tends to decrease with the increasing duration of HT. PSA fluctuations within 1 ng/mL during the first year after reaching PSA nadir, typically <0.1 ng/mL (7), might not be worrying because they can be associated with ejaculation, proctitis, or recent invasive examinations.

Among the imaging techniques used during the follow-up of patients undergoing HT and/or EBRT, T2-weighted magnetic resonance imaging (MRI) is of limited diagnostic value because the diffuse reduction of signal intensity on T2-weighted images, caused by glandular atrophy and fibrosis secondary to treatment, makes it difficult to differentiate the tumor from the normal surrounding parenchyma, both of which appear hypointense on T2-weighted images (8). Magnetic resonance spectroscopic imaging improves MRI ability to monitor prostate cancer remission after treatment (8−10). A loss of prostatic metabolites, correlating with duration time of HT and PSA level reduction, has been documented in early prostate cancer investigations (9). Reported studies based on the hypothesis that metabolic atrophy (MA) is indicative of successful treatment because the growth of normal or abnormal cells cannot occur without metabolism, successfully demonstrated magnetic resonance spectroscopic imaging (MRSI) efficacy in assessing MA at biopsy after EBRT (11) or after permanent prostate seed implantation as compared to time to PSA nadir (12) and after HT (9).

The aim of this prospective blinded study was to correlate MRSI results with PSA levels at the time of MRSI examination and with the time since EBRT to verify a successful treatment by assessing the achievement of MA in patients treated with long-term HT and EBRT for locally advanced disease.

Methods and Materials

Study subjects

The institutional review board approved this study; tenets of the Declaration of Helsinki were followed. Written informed consent was obtained from all patients.

From November 2006 to November 2008, 109 patients (median age 70 years; range, 42−85) treated in our department with long-term HT and EBRT for histologically proven locally advanced prostate cancer were consecutively enrolled in this MRSI study protocol. In June 2011, clinical and diagnostic investigations at further follow-up controls were retrospectively analyzed for each patient to assess patient outcome. Patients' characteristics are displayed in Table 1. At diagnosis, clinical staging (T3−T4N0M0) was assessed by means of DRE, pelvic ultrasound, CT or pelvic and abdominal MRI, and radionuclide bone scanning. MRSI was always planned after a recent DRE and PSA testing, both performed within 15 days before MRSI.

The therapeutic schedule consisted of three phases. Phase I: neoadjuvant HT, administered for 2 months before EBRT, using a depot formulation of luteinizing hormone-releasing hormone (LH-RH) analog administered subcutaneously every 28 days; therapeutic agents were triptorelin (Decapeptyl 3.75 mg; Ipsen, Paris, France) or goserelin (Zoladex 3.6 mg; Astra Zeneca, Wilmington DE) combined with oral bicalutamide (Casodex, Astra Zeneca; 50 mg daily) or with oral flutamide (250 mg 3 times daily; Eulexin, Schering-Plough, Kenilworth, NJ), administered only during the first month to prevent the flair-up phenomenon. Phase II: curative EBRT plus HT using an LH-RH analogue. Phase III: adjuvant HT administered for 24 months after the achievement of complete clinical response (achieving PSA nadir and a negative DRE) using an LH-RH analogue. In all phases, an alternative therapy was used in patients with osteoporosis or intolerance to LH-RH analogue or in patients <65 years with preserved sexual function (150 mg orally every day; bicalutamide [Casodex] Astra Zeneca). Total radiation dose delivered to the prostate was 73.8 Gy (1.8 Gy/fraction), and the dose to the seminal vesicles was 55.8 Gy (1.8 Gy/fraction) for T3a stage and 66.8 Gy (1.8 Gy/fraction), for T3b−T4 stage. Patients with intermediate- or high-risk cancer, according to National Comprehensive Cancer Network (www.nccn.org) criteria, received whole pelvic radiotherapy (45 Gy, 1.8 Gy/fraction), unless they had diverticular or inflammatory bowel disease. Study inclusion criteria were as follows: (*1*) locally advanced cancer, staged T3−T4N0M0; (*2*) enrollment at any time during the therapeutic schedule but after completion of Phase II (at least 3 months after the end of EBRT to reduce discomfort of endorectal coil placement); (*3*) PSA

Table 1 Patients' characteristics

N (%)	109 (100)
Median age (range)	70 (42−85)
Stage (%)	
T3a	61 (56.0)
T3b	39 (35.7)
T4	9 (8.3)
Median Gleason score (range)	7 (5−9)
Median PSA at diagnosis (range)	10.3 ng/mL (1.6−154)
Median PSA at MRI (range)	0.07 ng/mL (0−12.97)
Median time to MRSI after EBRT (range)	14 months (3−68)

examination within 15 days before MRSI; (*4*) no evidence of metastasis. In all patients, PSA testing was performed in our hospital. Clinical evaluation was performed by one of the same two radiotherapists, with approximately 30 years' experience in the field of prostate radiation therapy. MRSI exams were performed by one of the same two radiologists expert in prostate MRI and spectroscopy who reached a consensus evaluation, blinded to the most recent clinical information (last DRE and PSA results). A physicist with expertise in MRSI supported the radiologists. MRSI and PSA results were compared at the end of each MRSI examination.

MRI and MRSI techniques and MRSI data processing and analysis

Characteristics of MRI and MRSI sequences are detailed in Tables 2 and 3.

All MRSI data were analyzed using the Functool 4.5.1 software (GE Medical Systems, Milwaukee, WI). Spectra were superimposed on the axial high-resolution T2-weighted fast spin echo images and the corresponding spectral arrays were plotted. Voxel data analysis was always performed at the apex, middle gland, and basal region of the peripheral zone in both prostate lobes, with special attention to the site of original tumor. When necessary, the position of the spectral grid was retrospectively changed to better include the region of interest. For each data set, for selected voxel spectra the peak area integral of creatine, choline, and citrate was calculated (arbitrary units) by numeric integration; noise was defined as the standard deviation of the signal value in a frequency range free of metabolites signal (0.9−0.4 ppm). For selected voxel spectra, signal-to-noise values were calculated for the main metabolites as the ratio between the integral of the metabolite peak and the noise value, and choline to creatine peak area ratios were evaluated.

Data interpretation

As previously established (8, 13), spectral voxels with choline, creatine, and citrate peak area-to-noise ratio <5:1 are to be considered free of metabolites and represent metabolic atrophy (MA). As previously assessed (13), in voxels without detectable citrate (citrate peak area-to-noise ratio <5:1), CM is defined as choline-to-creatine ratio >1.5:1 if creatine was detectable, and choline peak area-to-noise ratio >5:1 if creatine was undetectable. These criteria were based on the reported elevated choline levels in recurrent prostate cancer after HT and on the described metabolic changes after EBRT in prostate cancer (8, 9, 14). It is known that citrate and polyamine spectral peaks decrease rapidly and progressively with time after EBRT or HT, at a faster rate than choline and creatine levels (8, 13, 14). Therefore, the choline+creatine/citrate ratio, which is used in the characterization of cancer in nontreated patients, is of limited use after treatment (15).

To test the strength of association between MRSI results and the time in months elapsed from EBRT, as well as between MRSI results and clinicopathological characteristics of the disease such as PSA levels, Gleason score (GS), age, and stage, logistic regression was performed using MedCalc software (MedCalc Software, Mariakerke, Belgium). A p value <0.05 was considered statistically significant.

Results

In the total study population (109 patients), PSA values at diagnosis ranged between 1.6 and 154.0 ng/mL (median, 10.3 ng/mL), whereas PSA values at the time of MRSI examination ranged between 0 and 12.97 ng/mL, with a median value of 0.07 ng/mL. GS at diagnosis ranged between 5 and 9 (median, 7). In 58 of 109 patients, PSA value at the time of MRSI was <0.1 ng/mL, stating that PSA had stabilized at its lower level (PSA nadir).

The achievement of MA (choline, creatine, and citrate peak area-to-noise ratio <5:1) was diagnosed by MRSI in 84 of 109 cases (77.0%), whereas prostate metabolism suggesting CM (choline-to-creatine ratio >1.5:1 or choline peak area-to-noise ratio >5:1) was identified in 25 of 109 cases (23.0%). Citrate activity, previously reported during HT administration (10), or polyamine activity, was never found in the present study.

Logistic regression showed that age, GS, stage and initial PSA had no significant impact on MRSI results, whereas MRSI results were significantly related to PSA values at the time of the examination (odds ratio [OR] 4.1; 95% confidence ratio [CI], 1.40−12.34; $p = 0.009$) and to the time elapsed from EBRT (OR 0.9; 95% CI, 0.86−0.96; $p = 0.0008$). This relationship was maintained when both variables were combined in a multiple logistic regression (PSA: OR 3.4; 95% CI, 1.14−10.38; $p = 0.02$. Time elapsed from EBRT: OR 0.88; 95% CI, 0.82−0.95; $p = 0.0009$), suggesting that MA achievement as assessed by MRSI is associated with decreasing PSA and increasing time after EBRT.

The total study population (109 patients) was then divided into three groups according to the time elapsed from EBRT: group 1: <1 year (37 patients); group 2: 1−2 years (36 patients); group 3: >2 years (36 patients). As showed in Fig. 1, MRSI detected MA in 20 of 37 patients of group 1 (54.1%), in 32 of 36 of group 2 (88.9%), and in 34 of 36 of group 3 (94.5%), whereas prostate metabolism suggesting CM was found in 17 of 37 patients of the first group (45.9%), in 4 of 36 of the second group (11.1%), and in

Table 2 Magnetic resonance: Sequence characteristics

Sequence	TR/TE (msec)	ST (mm)	Matrix	FOV (cm)	NEX	IG	Coil
Sagital T2 FSE HR	3625/85	3	256 × 224	14	4	−	endorectal
Axial T2 FSE HR	3800/85	3	256 × 256	14	4	−	endorectal
Coronal T2 FSE HR	3000/85	3	256 × 256	14	4	−	endorectal
Axial T2 FSE	4500/85	4	320 × 256	24	2	1	pelvic
Axial T1 SE	550/9-26	4	384 × 256	24	2	1	pelvic
Axial T2 FSE body	3600/100	5	256 × 224	24	2	1	Pelvic

Abbreviations: FOV = field of view; FSE = fast spin echo; HR = high resolution; IG = intersection gap; NEX = number of excitation; TR/TE = repetition time msec/echo time msec; ST = section thickness.

Table 3 Three-dimensional magnetic resonance spectroscopy: Sequence characteristics

Sequence	TR/TE (msec)	SR (cm^3)	PES	FOV (cm)	NEX	SV (mm)	Coil
PROSE	1000/130	0.32	16 × 8 × 8	11	1	110 × 55 × 55	Endorectal

Abbreviations: FOV = field of view; NEX = number of excitation; PES = phase encoding steps; SR = nominal spectral resolution; SV = spectroscopic volume; TR/TE = repetition time msec/echo time msec.

2 of 36 (5.5%) of the third group ($p < 0.0001$). In 58 of 109 patients, PSA nadir (<0.1 ng/mL) was reached at the time of MRSI. MRSI results in this subgroup of patients (Fig. 2) revealed prostate metabolism suggesting CM in 8 of 16 patients of the first group (50.0%), in 2 of 18 of the second group (11.1%), and in 0 of 24 of the third group ($p = 0.0002$).

Retrospective analysis of clinical and diagnostic investigations at further follow-up documented that 109 of 109 were alive in June 2011. However, 13 of 109 patients relapsed. Among these patients, 10 of 13 showed increased PSA levels and lymph node and/or bone metastasis that were diagnosed by radionuclide bone scanning and CT or MRI. In the last 3 of 13 patients, a local relapse was suggested by increased PSA levels associated with negative radionuclide bone scanning and positive DRE and MRI. In no case was biopsy performed. In these last three patients, the retrospective analysis of the results of MRSI performed during treatment showed prostate metabolism suggesting CM at long time on adjuvant HT after EBRT (15, 17, and 31 months).

Discussion

MRSI capability of documenting MA at biopsy after EBRT and brachytherapy (11, 12) and after short, intermediate, and long-term HT (9) has been clearly documented in patients with early prostate cancer. Some authors (11, 13) reported that CM is still detectable at biopsy in prostate after EBRT completion, suggesting that detection of residual cancer at an early stage after treatment could allow earlier intervention with additional therapy providing a more quantitative assessment of therapeutic efficacy. Other studies state that prostate metabolism is still detected after HT (10), suggesting that HT had not reached its full deprivation potential in those cases.

It is also widely accepted that the combination of HT and EBRT represents the best therapeutic approach for locally advanced prostate cancer (5), even if there is no agreement on androgen suppression administration modalities and treatment duration, which is not free from side effects. There is no doubt that long-term HT can be associated with adverse events or side effects (16–18), which, when in combination, satisfy the criteria for metabolic syndrome, with an increased risk of mortality due to ischemic heart disease (19). Duration of adjuvant HT should consider side effects and toxicity. In a recent study, Bolla and colleagues (20) demonstrated that immediate androgen suppression with an LH-RH agonist, given during and for 3 years after EBRT, in patients with high metastatic risk improves 10-year disease-free and overall survival, without increasing late cardiovascular toxicity.

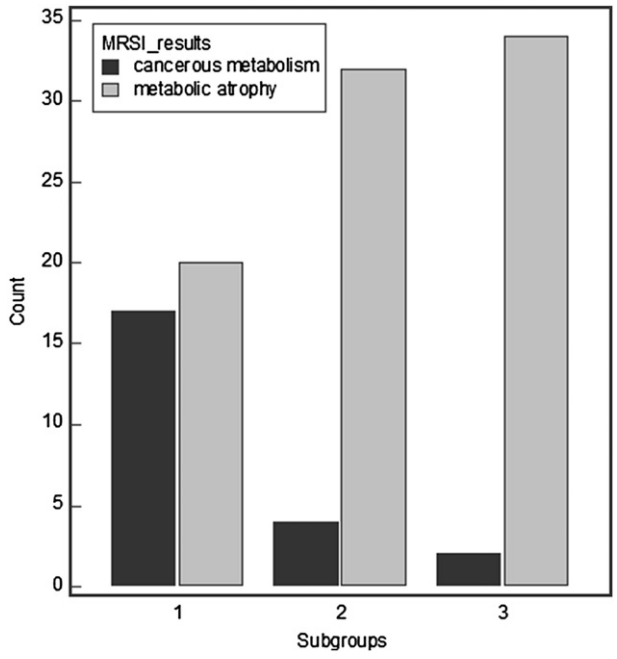

Fig. 1. Magnetic resonance spectroscopic imaging (MRSI) results according to the time since external-beam radiation therapy (1: <12 months; 2: 12–24 months; 3: >24 months). Total study population (109 patients).

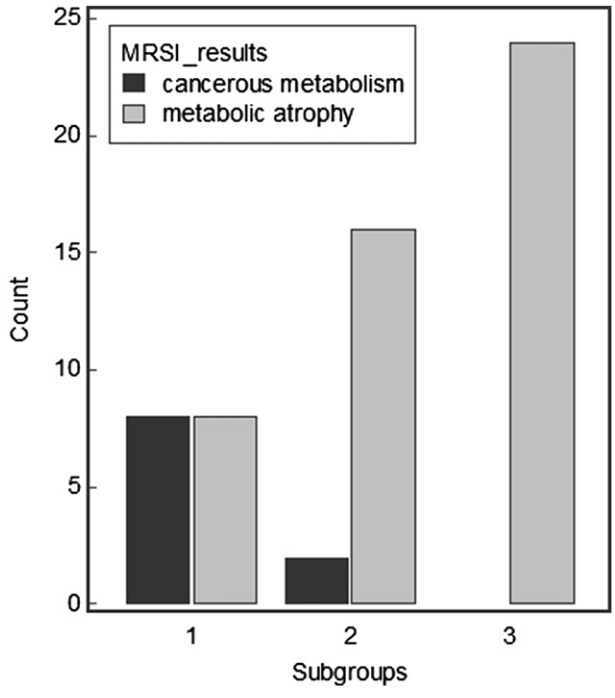

Fig. 2. Magnetic resonance spectroscopic imaging (MRSI) results according to the time since external-beam radiation therapy (1: <12 months; 2: 12–24 months; 3: >24 months). Subgroup of patient with reached prostate-specific antigen nadir (<0.1 ng/mL) at the time of MRSI examination.

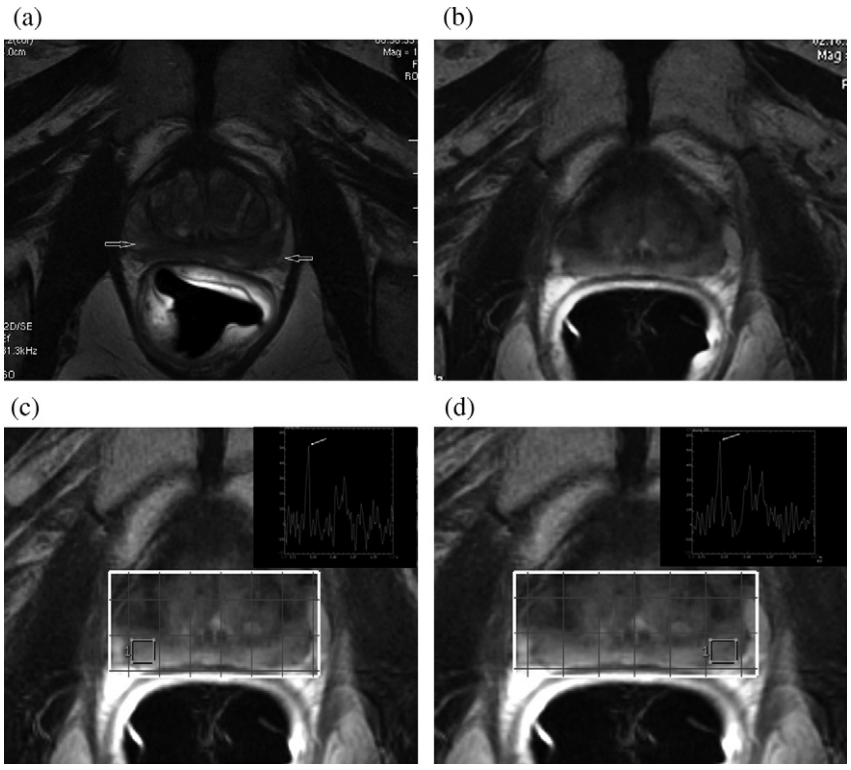

Fig. 3. Pretreatment MRI (a) in patient with biopsy-proven prostate cancer at the midgland of the left and right lobe and magnetic resonance spectroscopic imaging (b—d) performed in the same patients during adjuvant hormone therapy (HT) shortly after external-beam radiation therapy (EBRT). Transverse T2-weighted high resolution fast spin-echo MRI with endorectal coil (a) shows hypointense areas in the peripheral zone (arrows) at the midgland, according to histopathologic findings. After 5 months on adjuvant HT following EBRT, transverse T2-weighted high resolution fast spin-echo MRI with endorectal coil (b) documents the diffuse reduction of signal intensity related to the effects of the treatment; no focal hypointense areas are detectable in the peripheral zone. On the same transverse T2-weighted fast spin-echo images as in panel b with overlaid MR spectral grid (c, d), corresponding spectra show elevated choline peaks (c, d, arrows), suggesting cancerous metabolism.

The results of this study seem to support long-term treatment with hormonal therapy in advanced prostate cancer, because MA detection increases with decreasing PSA levels and with increasing time on HT after EBRT. Among the total study population (109 patients), approximately 94.5% (34/36) of patients who underwent MRSI more than 2 years after EBRT showed MA (Fig. 1, subgroup 3), and 100% of patients who underwent MRSI more than 2 years after EBRT showed MA when PSA nadir was reached (Fig. 2, subgroup 3).

These results seem also to suggest that during HT MRSI might provide a more quantitative assessment of therapeutic efficacy than PSA nadir, because prostate metabolism suggesting CM was still detected (Fig. 3) at short time after EBRT (<1 year) in 50% of patients with reached PSA nadir (<0.1 ng/mL). This is not surprising because PSA is hormone-dependent, whereas prostate cancer clearance is slow. It has been reported that cancer cells are found in biopsies performed a few months from the end of EBRT (21) and also that prostate cancer progression in the presence of undetectable or low serum PSA levels, albeit rarely (22).

In our study, only the absence of prostate metabolism (*i.e.,* MA) or prostate metabolism suggesting CM was found at MRSI examination. Neither citrate activity, which is reported in other studies performed during short-term HT administration, nor polyamine activity were found. This could depend on the phase of the therapeutic schedule at the time of MRSI, which was always planned in Phase III after completion of EBRT and during adjuvant HT administration (median time to MRSI after EBRT, 14 months; range, 3—68 months). Because it is known that citrate and polyamine spectral peaks decrease rapidly and progressively with time after EBRT or HT more quickly than choline and creatine levels do (8, 14), it is not surprising that citrate or polyamine activity was never found in this study.

Investigation of patient's outcome at follow-up controls documented resolution of the disease in 96 of 109 patients, whereas 13 of 109 patients relapsed. In patients locally relapsed (3 of 13), the retrospective analysis of results of MRSI performed during treatment showed prostate metabolism, suggesting CM with long-term adjuvant HT after EBRT (15, 17, and 31 months). However, whether detection of CM within the prostate with long-term adjuvant HT after EBRT can predict a local relapse should be confirmed by larger study series, including direct prostate biopsies.

In conclusion, this study seems to support the use of MRSI to detect MA in patients with locally advanced prostate cancer treated with long-term therapeutic modalities, in which PSA levels decrease as a direct effect of HT on PSA production and radiation-induced anatomic changes limit the utility of conventional morphologic MRI. MA detection by MRSI increases with decreasing PSA levels and with increasing time on HT after EBRT, which validates long-term treatment with HT in locally advanced disease. MRSI might be added to the methods currently used for monitoring prostate response to therapy because its

capability (9,11,12) of detecting MA can add reliable metabolic information that may contribute to the therapeutic strategy in locally advanced prostate cancer and can gain a special role in theragnostics (targeted imaging and targeted therapy) for radiation oncology (23).

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