

QUANTIFYING THE CHANGE IN ENDORECTAL MAGNETIC RESONANCE IMAGING-DEFINED TUMOR VOLUME DURING NEOADJUVANT ANDROGEN SUPPRESSION THERAPY IN PATIENTS WITH PROSTATE CANCER

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ABSTRACT

Objectives. To quantify the changes seen in the endorectal magnetic resonance imaging (erMRI)-defined prostate volume, predominant tumor volume, and secondary tumor volume during neoadjuvant total androgen suppression (TAS).

Methods. Between July 1997 and April 2001, 152 consecutive patients with clinical Stage T1b-T3cNXM0 prostate cancer were treated with 6 months of TAS and external beam radiotherapy. erMRI was conducted before and after 2 months of neoadjuvant TAS. The median values and percentage of changes in the erMRI-measured prostate volume and primary and secondary tumor volumes during neoadjuvant TAS were calculated and compared, using the Wilcoxon matched-pairs signed-rank method, for the patients overall and stratified by pretreatment risk group.

Results. All patients had a significant decline in their erMRI-defined median prostate volume (36.6 versus 25.7 cm³, $P < 0.0001$) during 2 months of neoadjuvant TAS. The median primary tumor volume decreased significantly in the intermediate-risk (0.77 versus 0.52 cm³, $P < 0.0001$) and high-risk (2.48 versus 0.83 cm³, $P < 0.0001$) patients. The median secondary tumor volume approached a significant decline in only the high-risk patients (0.45 versus 0.31 cm³, $P = 0.15$). Fourteen percent of patients had an increase in their primary tumor volume during neoadjuvant TAS.

Conclusions. The erMRI-defined primary and secondary tumor volumes generally decreased in the study population during neoadjuvant TAS. However, 14% of patients had an increase in their primary tumor volume during androgen suppression therapy. The clinical significance of this awaits further study. UROLOGY 62: 487-491, 2003. © 2003 Elsevier Inc.

Prostate cancer is the most commonly diagnosed cancer in men, and it is the second leading cause of cancer death in the United States. It is estimated that 220,900 new cases of prostate cancer will have been diagnosed with 28,900 deaths

from this disease in 2003.¹ The increased use of prostate-specific antigen (PSA)-based screening has allowed for the earlier diagnosis of prostate cancer, as reflected by the growing proportion of nonpalpable (clinical Stage T1c) prostate cancers diagnosed.

No single imaging modality to date has been accepted as the clinical standard in providing local staging information for patients with prostate cancer. Transrectal ultrasonography (TRUS), computed tomography, and body coil magnetic resonance imaging (MRI) have all been studied extensively.²⁻⁶ None have provided the adequate diagnostic accuracy needed to warrant its use in dictating clinical management. Rifkin *et al.*⁶ reported the results for a large multi-institutional

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study comparing the staging accuracy of TRUS and body coil MRI. They found no statistically significant difference in accuracy, which was approximately 60%, between the two imaging modalities in predicting for pathologic Stage T3 disease in patients with clinical Stage T1 or T2 prostate cancer.

MRI with the use of an endorectal coil (erMRI) was initially viewed with optimism, largely because of early, single-institution reports that documented overall staging accuracy as great as 83% to 93%.^{7,8} However, subsequent studies have not been as optimistic and have reported accuracy rates that range between 51% and 68%.⁹⁻¹² Specifically, a large multi-institutional study evaluated the staging accuracy of conventional body coil MRI, body coil MRI with fat suppression, and erMRI, and the investigators found the accuracy for erMRI to be 54% and not significantly different from the other two techniques.¹² D'Amico *et al.*¹³ found that the accuracy of erMRI findings varied with the pretreatment risk group. They reported that the presence or absence of extracapsular extension and/or seminal vesicle invasion on erMRI was a significant independent predictor of postoperative PSA failure and, if validated, may be useful in helping to stratify intermediate-risk patients into those at low or high risk of postoperative PSA failure at 5 years.

In this study, erMRI was obtained before and after 2 months of neoadjuvant total androgen suppression (TAS). We investigated the volume changes seen in the prostate, predominant (primary) tumor, and second-most predominant (secondary) tumor on sequential erMRI during neoadjuvant TAS as measured by an MR radiologist.

MATERIAL AND METHODS

PATIENT SELECTION

Between July 1997 and April 2001, 152 consecutive patients were prospectively enrolled into this institutional review board-approved study. The eligibility criteria included no previous androgen therapy for prostate cancer; no previous chemotherapy or radiotherapy for prostate cancer; age 30 years old or older; performance status 0 to 2; and histologically proven American Joint Center for Cancer Stage T1b-T4bN0-NXM0 adenocarcinoma of the prostate. All study patients provided informed consent. A single genitourinary pathologist reviewed all the biopsy specimens. Table 1 lists the clinical characteristics of the study patient population.

TREATMENT PROTOCOL

All patients received 6 months of TAS with a nonsteroidal antiandrogen and a luteinizing hormone-releasing hormone agonist for 2 months before, 2 months during, and 2 months after external beam radiotherapy. Radiotherapy was delivered using a four-field technique, with at least 10-mV photons to a total median dose of 70.2 Gy (range 70.0 to 72.4) to the prostate gland using 95% normalization.

IMAGING

Each patient underwent erMRI before the start of hormonal therapy and again immediately after 2 months of hormonal

TABLE 1. Percentage distribution of pretreatment clinical characteristics

Characteristic	% (n = 152)
Age (yr)	
<60	10
60-70	43
>70	47
Clinical stage	
T1c	31
T2a	18
T2b	20
T2c	12
T3a	10
T3b	3
T3c	6
Gleason score	
≤6	29
3 + 4	26
4 + 3	21
≥8	24
Pretreatment PSA (ng/mL)	
0-4	8
>4-10	40
>10-20	28
>20	24
Positive biopsies (%)	
≤34	28
>34-50	24
>50	48
Risk group	
Low	6
Intermediate	37
High	57

treatment, before beginning radiotherapy. A 1.5-Tesla magnet was used for all imaging studies. Multicoil arrays were used to allow imaging of both the anterior and the posterior prostate. Two anterior 5-in. (12.7-cm) coils working with the endorectal coil and a single posterior coil (composed of two 5-in. [12.7-cm] coils combined with a T-connector) were used. A 10-cm field of view and a 256 × 256 matrix interpolated to 512 television pixels (256 pixel pairs) yielded a resolution of 0.4 mm per pixel pair. This can be compared with a 30-cm field of view when the body coil is used, which yields a resolution of 1.2 mm per pixel pair. Using this technique, the limit of detection of extracapsular penetration is 3 mm.

The long repetition time/echo time pulse sequences used in this study were as follows: fast spin echo, 4000/100_{eff}, section thickness 3 mm, interleaved acquisition (3-mm skip), field of view 10 cm, 256 × 256 matrix, right-to-left phase encoding, no phase wrap, flow compensation, 90° flip angle, and axial, sagittal, and angled coronal planes.

Prostate cancer was detected on T₂-weighted MRI as areas of hypointense signal; other causes of low T₂-weighted signal, such as postbiopsy hemorrhage, were ruled out by comparison with T₁-weighted images.¹⁴ The total prostate volume, primary tumor volume, and secondary tumor volume were measured along three perpendicular axes by one of two experienced body MR radiologists. The volumes were calculated using an ellipsoid approximation per the formula: $volume = \pi/6 \times length \times width \times height$. In cases in which an abnormal MR signal consistent with tumor was seen, but a discrete tumor volume could not be measured by the MR radiologist, the

tumor volume was recorded as missing and was not used in any data analyses.

STATISTICAL ANALYSIS

The median values for the total prostate, primary tumor, and secondary tumor volumes were calculated at baseline and at 2 months after TAS. A minimal 5% difference between a patient's baseline and follow-up erMRI-measured volumes was needed to qualify as a change in volume. In addition, for the primary and secondary tumor outcome comparison analyses, cases in which no tumor was visualized on erMRI either at baseline or at follow-up were excluded from the analysis.

Using the Wilcoxon matched-pairs signed-rank method, the preneoadjuvant and postneoadjuvant TAS median values for the prostate, primary tumor, and secondary tumor volumes were compared for the patients overall and stratified by risk group. The risk groups were defined as follows: low risk (PSA 10 ng/mL or less and Gleason score 6 or less, and Stage T2a or less), intermediate risk (PSA greater than 10 to 20 ng/mL or Gleason score 7, or Stage T2b), and high risk (PSA 20 ng/mL or greater or Gleason score 8 or greater or Stage T2c or greater).

RESULTS

erMRI-DEFINED VOLUME COMPARISONS

The median value of the total prostate volume at baseline and after 2 months of TAS was 36.6 cm³ (range 12 to 135) and 25.7 cm³ (range 11 to 112), respectively, for all 152 study patients (Table II). Similarly, for the 147 and 136 patients in whom a primary tumor volume was measurable, the value was 1.56 cm³ (range 0.1 to 78) versus 0.58 cm³ (range 0.01 to 133), respectively. For the 34 and 28 patients in whom a secondary tumor volume was measurable, the median value was 0.47 cm³ (range 0.1 to 11) versus 0.26 cm³ (range 0.01 to 4.4), respectively. The median values and ranges for the prostate, primary tumor, and secondary tumor volumes for the patients when stratified by risk group are given in Table II.

The erMRI-defined prostate volume was noted to decrease significantly across the study population overall ($P < 0.0001$), as well as across the low, intermediate, and high-risk groups ($P = 0.01$, < 0.0001 , and < 0.0001 , respectively). The primary tumor volume decreased significantly in the intermediate and high-risk patients ($P < 0.0001$ and < 0.0001 , respectively), and the secondary tumor volume approached a significant decline only in the high-risk population ($P = 0.15$). Table II summarizes the results of the Wilcoxon matched-pairs signed-rank test for all of the outcome measurements.

The median percentage in reduction in the prostate, primary tumor, and secondary tumor volumes in the study population overall was 28%, 64%, and 76%, respectively. Of the 95% (132 of 139) of patients who had a measurable change in their primary tumor volume, the median percentage decrease among the low, intermediate, and high-risk

TABLE II. Comparison of median values for prostate volume and primary and secondary tumor volume during neoadjuvant TAS

Outcome Measurement	All Patients (n = 152)		Low-Risk Group (n = 9)		Intermediate-Risk Group (n = 57)		High-Risk Group (n = 86)	
	Median (cm ³)	P Value	Median (cm ³)	P Value	Median (cm ³)	P Value	Median (cm ³)	P Value
Prostate volume								
Baseline*	36.6 (12–135)	<0.0001 (n = 152)	38.3 (22–72)	0.01 (n = 9)	36.0 (15–99)	<0.0001 (n = 57)	36.7 (12–135)	<0.0001 (n = 86)
Follow-up†	25.7 (11–112)		26.0 (15–52)		25.8 (11–94)		25.6 (11–112)	
Primary tumor volume								
Baseline*	1.56 (0.1–78)		2.34 (0.1–62)		0.77 (0.1–78)		2.48 (0.1–67)	
Follow-up†	0.58 (0.01–133)	<0.0001 (n = 139)†	2.14 (0.1–31)	0.20 (n = 9)†	0.52 (0.01–133)	<0.0001 (n = 52)†	0.83 (0.03–47)	<0.0001 (n = 78)†
Secondary tumor volume								
Baseline*	0.47 (0.1–11)		0.73 (0.5–0.9)		0.37 (0.1–11)		0.45 (0.1–5)	
Follow-up†	0.26 (0.01–4.4)	0.69 (n = 42)†	0.20 (0.1–0.3)	1.00 (n = 3)†	0.20 (0.01–1.9)	0.46 (n = 17)†	0.31 (0.03–4.4)	0.15 (n = 22)†

KEY: TAS = total androgen suppression; erMRI = endorectal magnetic resonance imaging.

* Pretreatment volumes as measured on erMRI.

† Volumes as measured on erMRI immediately after 2 months of neoadjuvant TAS.

‡ Cases with no erMRI-measurable tumor at baseline and at follow-up were excluded from analysis.

TABLE III. Percentage of patients experiencing increase, decrease, or no change in primary tumor volume, stratified by risk group

Outcome Measurement	Low-Risk Group (n = 9 of 9 [†])			Intermediate-Risk Group (n = 52 of 57 [†])			High-Risk Group (n = 78 of 86 [†])		
	Increase	Decrease	No Change*	Increase	Decrease	No Change*	Increase	Decrease	No Change*
Primary tumor volume (%)	11	78	11	12	82	6	17	79	4

* No change defined as <5% difference between baseline and follow-up endorectal magnetic resonance imaging (erMRI) volumes.

[†] Cases with no erMRI-measurable tumor at baseline and at follow-up were excluded from analysis.

TABLE IV. Review of literature regarding TRUS or MRI-visualized percentage of decrease in predominant tumor volume during androgen-suppression therapy

Investigator	Year	n	Imaging Modality	Androgen Suppression (mo)	Measure Used to Report Percentage of Decrease	Decrease in Predominant Tumor Volume (%)
Pinault <i>et al.</i> ¹⁶	1992	17	TRUS	3	Median	81
Chen <i>et al.</i> ¹⁷	1996	10	erMRI	3	Mean	61
Nakashima <i>et al.</i> ¹⁸	1997	48	erMRI	4	Not reported	75
D'Amico <i>et al.</i> ¹⁹	1998	21	erMRI	3	Mean	35
Padhani <i>et al.</i> ²⁰	2001	56	Body coil MRI	3	Median	65
Present study	2002	152	erMRI	2	Median	64

KEY: TRUS = transrectal ultrasonography; MRI = magnetic resonance imaging; erMRI = endorectal coil MRI.

patient group was 32%, 69%, and 64%, respectively. Of the 98% (41 of 42) of patients who had a measurable change in secondary tumor volume, the median percentage reduction for the low, intermediate, and high-risk patient group was 76%, 13%, and 80%, respectively.

Of note, some patients showed progression in their erMRI-defined tumor volume between the two sequential erMRI scans. Overall, 14% (20 of 139) of patients had an increase in their primary tumor volume. Table III stratifies the patient population by risk group to report the percentages of patients who experienced progression, decline, or no change in their erMRI-defined primary tumor volume during TAS.

COMMENT

Large randomized trials have shown that erMRI does not yield high accuracy when used generally for staging of clinically localized prostate cancer. As Chelsky *et al.*¹⁰ discussed, this is often the result of microscopic extracapsular tumor spread that cannot be visualized by erMRI but is found in pathologic specimens. However, Chelsky *et al.*¹⁰ found that erMRI had relatively high accuracy in assessing macroscopic cancer spread to seminal vesicles, and Sommer *et al.*¹⁵ found a significant correlation when comparing the prostate tumor volumes seen on MRI with those measured in pathologic specimens. Thus, although erMRI may not be highly accurate in local staging because of microscopic

disease, it may provide accurate volumetric information about macroscopic tumor volumes.

This study quantified the erMRI-defined tumor volume changes resulting from 2 months of TAS as read by an experienced prostate MR radiologist. The results of this study showed that with neoadjuvant TAS, the total prostate volume decreased across all risk groups, the predominant tumor decreased significantly in intermediate and high-risk patients, and the secondary tumor approached a significant decline only in high-risk patients.

Our finding of a 64% median reduction in erMRI-visualized primary tumor volume is similar to findings in previous studies.^{16–20} Table IV compares the findings of previous studies that used an imaging technique to measure changes in primary tumor volume after hormonal therapy. The documented percentage of tumor volume changes in these studies ranged from 35% to 81%.

No prior studies to date have evaluated the radiologic changes in secondary prostate tumor volume in response to TAS. Our study found that the erMRI-measured secondary tumor volume change approached statistical significance in high-risk patients. This was likely a result of high-risk patients having secondary tumors large enough to be measurable with erMRI. As patients' PSA, biopsy Gleason score, and clinical stage increase, the probability that they will have secondary tumor volumes large enough to visualize a measurable change also increases. The small number of patients in our

study in whom a secondary tumor was visualized with erMRI may account for the reason the change in secondary tumor volume did not attain statistical significance in the high-risk group.

In our study, although most patients had a decline in tumor volume, 14% of the study population showed progression of primary tumor on sequential erMRI measurements during neoadjuvant TAS. This supports the results of a previous pilot study in which 17% of the patients had progressive disease.¹⁹ A study by Saitoh *et al.*²¹ previously found that tumor volume change as measured by TRUS during external beam radiotherapy had prognostic significance; specifically, those patients who had a decline in their TRUS-visualized hypoechoic lesions of more than 60% within the first 6 months after treatment had a lower progression rate of prostate cancer. If the erMRI-measured change in primary tumor volume is found to correlate with cancer control outcome, erMRI changes in tumor volume may offer information useful for the selection of patients who require new forms of systemic therapy to improve their outcome.

Our study was limited by its relatively small number of patients, particularly in the low-risk cohort. This may explain why the change in primary tumor volume did not attain statistical significance in this risk group. In addition, low-risk patients are less likely to have macroscopic disease, and thus, changes in their tumor volumes are not as readily measurable by erMRI. Finally, the cost of two sequential erMRIs needs to be substantiated by a clinically relevant endpoint such as PSA failure-free survival, disease-free survival, and finally, overall survival.

CONCLUSIONS

This study measured changes in erMRI-defined tumor volumes after 2 months of neoadjuvant TAS and found that tumor responsiveness, as measured by erMRI, varied among patients in different risk groups. A novel finding was that 14% of all patients had MRI progression of their primary prostate tumors during TAS. Whether changes in erMRI-defined tumor volumes are associated with cancer control outcome after radiotherapy and androgen suppression and whether the cost of sequential erMRI studies is warranted in patients with clinically localized prostate cancer require additional study.

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