Positron Emission Tomography of a Human Prostate Cancer Xenograft: Association of Changes in Deoxyglucose Accumulation with Other Measures of Outcome following Androgen Withdrawal

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ABSTRACT

The current means of assessing response in prostate cancer are imprecise because changes in tumor size are often slow and difficult to document, and alterations in serum prostate-specific antigen (PSA) levels do not always correlate with clinical outcomes. Using the CWR22 human prostate cancer xenograft model, serial changes in prostate tumor metabolism were assessed after androgen withdrawal by ²³H]deoxyglucose (DOG) accumulation in the tumors and noninvasively using positron emission tomodraphy (PET) with 2-[¹⁸F]fluoro-2-deoxy-D-glucose as a radiotracier. A decrease in ²³H]DOG accumulation was observed at 48 h after androgen withdrawal [62% of preandrogen withdrawal value (95% confidence interval: 0.59, 0.65)], reaching a maximum decline at day 10 [38% of preandrogen withdrawal value (95% confidence interval: 0.37, 0.40)]. Using PET, parallel changes in tumor metabolism were demonstrated and preceded changes in tumor volume and marked decreases in serum PSA. DOG accumulation returned to near baseline upon reintroduction of androgen. The decrease in DOG accumulation was associated with a decline in the proportion of tumor cells in actice cell cycle from >60% to <5% at 7 to 10 days after androgen withdrawal. No increase in the proportion of tumor cells undergoing apoptosis was observed during this time period, implying an arrest in a G₀/early G₁ state. DOG accumulation in tumor cells, measured directly and by PET, correlated with androgen changes in the host. The results suggest that serial monitoring of DOG accumulation using PET scanning may be useful as an early indicator of treatment efficacy and other outcome measures in prostate cancer.

INTRODUCTION

Current means of assessing treatment response in prostate cancer are imprecise because changes in tumor size may be difficult to document, and changes in serum PSA do not always correlate well with clinical outcomes. The insensitivity of current imaging modalities, particularly with regard to osseous metastasis, often necessitates the administration of multiple courses of therapy before a clear indication of response or progression can be determined. A method to assess response to therapy shortly after an intervention is needed.

Glucose is a polar molecule that relies on a family of transporters to cross the hydrophobic plasma membrane. Two different glucose transporter systems are present in human cells: GLUTs and a sodium-glucose cotransporter that is expressed primarily in the small intestine and in the kidney. GLUTs function in a bidirectional manner to transport glucose down a concentration gradient, in which the glucose molecule is enzymatically phosphorylated by the enzyme hexokinase and trapped inside the cell. One isoform, GLUT1, is overexpressed on many tumor cells, including prostate cancer (6). Glucose accumulation serves as a marker of tumor metabolism and can be assessed in vivo by noninvasive means using the nonmetabolizable glucose analogue FDG as a radiotracer and PET imaging (7–11). The increased tumor accumulation of DOG may be related to increased GLUT expression, an increase in hexokinase in the tumor, or a change in the level of phosphorylase. Although there is controversy as to how net FDG accumulation varies as a function of the degree of differentiation or rate of proliferation, it is generally accepted that, for a tumor to accumulate DOG, it must be viable. The change in DOG accumulation would, therefore, reflect a change in the viability of the tumor or its metabolic activity.

To study the effects of hormonal manipulations on glucose metabolism, we used the CWR22 human prostate cancer xenograft model (12–15). This model has many features of the human condition, including a dependence on androgens, and a correlation between measured levels of PSA in serum and tumor size. Following androgen withdrawal, PSA levels decrease to nearly undetectable levels, and tumor volumes decrease. Later, the tumor will regrow as an androgen-independent neoplasm, manifest initially by a rise in PSA and, later, by measurable tumor growth. In this study, we show that decreased glucose metabolism in the prostate cancer xenograft, assessed by the direct measurement of DOG level, and in vivo using serial PET scans, preceded changes in PSA and tumor volume following androgen ablation. The decrease in DOG accumulation was associated with an increase in the proportion of the cells in a G₀/early G₁ state.

MATERIALS AND METHODS

Animal Studies. Four- to 6-week-old nude athymic BALB/c male mice were obtained from the National Cancer Institute-Frederick Cancer Center and maintained in pressurized ventilated cages at the Sloan-Kettering Institute. The CWR22 tumor line was propagated in the animals by the injection of minced tumor tissue from an established tumor into the s.c. tissue of the flanks of athymic nude mice, together with reconstituted basement membrane (Matrigel; Collaborative Research, Bedford, MA; Refs. 13 and 14). To maintain serum testosterone levels, the mice were administered 12.5 mg sustained-release testosterone pellets (Innovative Research of America, Sarasota, FL) s.c. before receiving tumors. Three to 4 weeks after inoculation, tumors of ∠1.5 × 1.0 × 1.0 cm can be measured. Androgens were withdrawn by surgical castration under pentobarbital anesthesia and removal of the sustained-release testosterone pellets, while androgens were repleted by reimplantation of the pellets. Control animals underwent a sham operation. Tumor size was determined by caliper measurements of height, width, and depth. PSA values were performed on the serum of the mice after tail bleeding using a Tandem-R PSA immunoradiometric assay (Hybritech, San Diego, CA). A karyotype analysis was performed to check for consistencies with the parental strain.

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The abbreviations used are: PSA, prostate-specific antigen; GLUT, facilitative glucose transporter; FDG, 2-[¹⁸F]-fluoro-2-deoxy-D-glucose; PET, positron emission tomography; DOG, deoxyglucose; FOV, field of view; ROI, region of interest; SUV, standard uptake value; TdT, terminal deoxynucleotidyl-transferase; TUNEL, TdT-mediated dUTP-biotin nick end labeling; ID, injected dose.
DOG Accumulation. Six- to 8-week-old BALB/c mice with established tumors were injected with 5 μCi (mouse) of [3H]DOG (2-[3H]deoxy-D-glucose, specific activity = 26.2 Ci/mmol; DuPont NEN, Wilmington, DE) into the tail vein. Animals were sacrificed at various time points after i.v. injection by cervical dislocation or CO2 inhalation. The tumors were dissected and homogenized in 70% methanol, while the serum fraction of blood was placed in 70% methanol for the DOG quantitations. The methanol-soluble fraction of the samples was processed for scintillation spectrometry as described (16, 17).

FDG accumulation was measured in vivo using a whole-body GE PET scanner (Advance; General Electric Medical Systems, Milwaukee, WI). The mice were first anesthetized with i.p. tribromoethanol (Avertin; Aldrich, Milwaukee, WI) anesthesia (250 mg/kg), and ~50 μCi FDG was injected into the tail vein. They were then placed in a dose calibrator (Capintec CRC15R, Ramsey, NJ), and the whole-body activity was recorded. At 50 min postinjection, a 10-min transmission scan was obtained and used for attenuation correction. This was immediately followed by a 10-min emission scan. The transmission scan was performed immediately prior to the emission scan to maintain the positioning and to also reduce the time period that the animals had to be anesthetized. Because the transmission scan was obtained in the presence of activity, the subsequent emission scan was used for correction. The emission images were reconstructed using a transaxial Hanning filter with 4-mm cutoff and a 13-cm FOV diameter with the filtered backprojection technique.

At each time point, two mice were imaged simultaneously by placing them in a marked holder that allowed reproducible positioning within the scanner. This allowed the section of the tumor that was used for quantitative analysis to be in the same location for each imaging session, as close as possible to the center of the scanner’s three-dimensional FOV. In this location, the greatest spatial resolution is achieved by acquisition of images in “high sensitivity” mode. Interleaved mode was used for both the transmission and emission scans to increase sampling in the FOV.

18F was produced at Memorial Sloan-Kettering Cancer Center by the acceleration of protons onto an [18O]water target in a CS-15 isochronous cyclotron. FDG of high specific activity was produced using a nucleophilic fluorination method (18, 19).

Tumor FDG concentration was obtained by having a blinded observer draw a ROI around the tumor at its greatest cross-sectional area, as determined in the pretreatment PET study. This same ROI was then placed on corresponding PET slices at subsequent time points. The 18F tumor activity concentration, obtained for each animal, was divided by the total 18F injected, as determined by the dose calibrator measurement, and divided by whole body weight. The resulting value is equivalent to the SUV used in human studies (20).

Histopathology. Normal and tumor tissues were fixed in 10% buffered formalin and embedded in paraffin. Tissue sections (5 μm) were stained with H&E. There were three tumors analyzed at each time point. The following well-characterized mouse monoclonal antibodies were used at the indicated final working dilutions: anti-Ki67 monoclonal antibody MIB1, 1:50 (Immunotech SA, France), and anti-GLUT1, 1:200 (Charles River East Acres Biologicals, Southbridge, MA). MlgS-Kpl, a mouse monoclonal antibody in the same subclass as MIB1, was used as a negative control (1:50; PharMingen Laboratories, San Diego, CA). Sections were subsequently immersed in boiling 0.01% citric acid (pH 6.0) for 15 min to enhance antigen retrieval, allowed to cool, and incubated with primary antibodies overnight at 40°C. Biotinylated horse antimonouse IgG antibodies and (biotinylated horse antirabbit antiserum for GLUT1) were applied for 1 h (1:500; Vector Laboratories, Burlingame, CA), followed by avidin-biotin peroxidase complexes for 30 min (1:25; Vector Laboratories). Diaminobenzidine was used as the final chromogen, and hematoxylin was used as the nuclear counterstain. Nuclear immunoreactivities were assessed by counting tumor cells displaying a positive staining in different fields, analyzing over 650 tumor cells in each time point of the study. Data were recorded as continuum data. Ki67 proliferative index was considered high when >20% tumor cells displayed a positive MIB1 nuclear staining pattern. Flow cytometry assays for assessment of S-phase fraction and cell cycle analyses were done on tumor blocks from each time point after androgen withdrawal, and tumor tissue was microdissected to avoid normal tissue contamination and necrotic material. Three consecutive 60-μm-thick sections were cut, and the nuclei were disaggregated, stained using propidium iodide,
Fig. 3. Change in FDG accumulation in the CWR22 tumor after androgen withdrawal as assessed by PET before changes in tumor volume and marked declines in serum PSA. A, tumor volume (-----) did not change in the time period studied, and the serum PSA value (-----) did not decrease >20% in this time period. B, FDG accumulation of the tumor ROI declines with time after androgen withdrawal. Data points, representative experiments in which each line is an experimental animal (■, M5; □, M6).

and analyzed on a Coulter Excel using a multicycle soft program for assessment of cell cycle profile (21).

To study the microanatomical distribution of apoptosis, consecutive sections from the blocks used for Ki67 proliferative assay were assayed by the method of TUNEL. The TUNEL assay was performed using a modification (22) of the method originally described by Gavrieli et al. (23) and is based on the specific binding of TdT to 3'-OH ends of DNA, ensuring the synthesis of a polydeoxynucleotide. Briefly, after the exposure of nuclear DNA of histological sections by proteolytic treatment, TdT was used to incorporate biotinylated deoxyuridine at sites of DNA breaks. The signal was amplified by avidin-biotin peroxidase complexes and visualized by diaminobenzidine deposition, enabling conventional histochemical identification of reactive nuclei by light microscopy. Nuclear staining was assessed as per Ki67 scoring, counting different fields and evaluating >650 tumor cells (24).

Statistical Analysis. The bootstrap resampling procedure was used to generate 95% confidence intervals for this study (25). The bootstrap was selected over the conventional asymptotic normal methodology because it provides more accurate confidence intervals when the number of subjects is small. Confidence intervals were used to estimate the relative average ID/g of

Fig. 4. Representative PET scans of a nude mouse (mouse M2) with CWR22 human prostate cancer xenograft immediately before and after androgen withdrawal and reintroduction. Shown are successive 2.125-mm sagittal slices of the subject animal. A, the mouse shown with CWR22 xenograft underwent PET scanning 30 days after tumor implantation for baseline FDG accumulation measurements (day 0). B, the mouse was then imaged by PET scan again 6 days after androgen withdrawal (day 6). C, testosterone pellets were reimplemented in the mouse and the mouse underwent a PET scan 6 days later (day 12). *, tumor.
tissue following androgen withdrawal and androgen reintroduction. Computation was performed when there were at least six mice in each group.

RESULTS

A karyotype analysis of the CWR22 tumor was performed to check for consistency with the parental strain. The current modal karyotype of 48–50,XY,+t(1q10),−2,add(4)(q33),+7,+8,+12,+add(18)(p11) differs slightly from that described previously (14).

The kinetics of DOG accumulation were as follows. The optimal tumor:serum DOG accumulation ratio in the xenograft (~5:1) occurred ~50–60 min after injection. At this point, the serum levels of the radiotracer were low, and the tumor had trapped significant radiotracer DOG (Fig. 1). The 60-min time point was chosen to evaluate tumor DOG accumulation in later experiments, at which point ~2.5 ± 0.2% (mean ± SD) of the DOG (expressed as percentage of ID/g of tumor tissue) was shown to accumulate.

After androgen withdrawal (48 h), the percentage ID/g of tumor tissue declined to 62% (95% confidence interval: 0.59, 0.65) of the preandrogen withdrawal value and 39% (95% confidence interval: 0.37, 0.40) of the preandrogen withdrawal value. Androgen was reintroduced into mice 6 days after initial androgen withdrawal and there was an ~64% increase (95% confidence interval: 1.57, 1.73) in the tumor DOG accumulation to near preandrogen withdrawal levels (Fig. 2B). DOG accumulation in brain, liver, and the serum was not affected in these experiments by androgen withdrawal or its reintroduction. Sham castration and sham androgen reintroduction groups were included and showed that surgery or anesthesia did not effect DOG accumulation (data not shown). In the time period studied, measured tumor volume did not change (Fig. 3A). Serum PSA values decreased during this time period but did not fall by >20% from baseline in any experiment (up to 8 days after androgen withdrawal).

FDG accumulation of the CWR22 tumor, relative to the mouse whole body-injected radioactivity, demonstrated a time-dependent decrease after androgen withdrawal (Fig. 3B). In this study, there was a fall in the FDG accumulation ratio of tumor:whole body of ~30%, as early as 48 h after androgen withdrawal, and reached a reduction of 75% at ~8 days after androgen withdrawal.

The baseline FDG accumulation was measured in animals with established CWR22 xenografts by PET scanning ~30 days after tumor implantation (day 0; Fig. 4A). The animals were reimaged 6 days (day +6) after androgen withdrawal (Fig. 4B) and, again, 6 days after reimplantation of testosterone pellets (Fig. 4C). At day +6, FDG accumulation in the tumor decreased by 35% in the five animals who showed a decrease compared with the baseline (day 0) value. An increase in FDG accumulation was observed in one. Following androgen repletion, tumor FDG accumulation increased by 34% in 6 days (Table 1). However, the percentage change in FDG accumulation after repletion varied from 27 to 55% (Fig. 5). One tumor (M3) demonstrated an increase in FDG accumulation after androgen withdrawal (Table 1). The tumor in this animal was necrotic, and it was not possible to draw an ROI solely on an area of clinically viable tumor.

Immunostaining of the CWR22 tumors, with an anti-Ki67 cell cycle-specific monoclonal antibody, demonstrated that >60% of the tumor cells were in active cell cycle in the intact (noncastrate) host (Fig. 6A). Androgen withdrawal caused a time-dependent decrease in the percentage of cells in active cell cycle to ~21% by 5 days (Fig. 6B) and <5% by 7–10 days (Fig. 6, C and D; data are summarized in Table 2). After androgen withdrawal, the tumor cells did not demonstrate proliferative markers, implying a G0/early G1 state. No evidence of apoptosis was observed at the time intervals sampled using the TUNEL assay, up to 10 days after androgen withdrawal (Fig. 6, E–H; summarized in Table 2). Flow cytometric analysis of the CWR22 tumor cells using propidium iodide incorporation also showed a decrease in the percentage of cells in S-phase fraction from 22% preandrogen withdrawal to 5.8% 5 days after androgen withdrawal to 4% 10 days after androgen withdrawal (data not shown).

Changes in GLUT1 expression did not parallel the changes in DOG accumulation during the time period studied. The expression of GLUT1 was scored as 1+ on the preandrogen withdrawal (Fig. 6f) and day 1 and 2 postandrogen withdrawal specimens and 3+ on tumors obtained 5–7 days (Fig. 6, J and K) after androgen withdrawal. The tumor GLUT1 expression decreased to 2+ at day 10 (Fig. 6j; Table 2).

DISCUSSION

Androgen withdrawal is a standard therapy for human prostate cancer that results in a decrease in tumor volume, a decline in the PSA, and an improvement in cancer-related symptoms in the majority of cases (26). Unfortunately, these responses are rarely complete because a proportion of the cells within the tumor are resistant to androgen ablation at the time treatment is begun (27). This, in part, explains the inevitable relapses that occur. This study recapitulates the human condition in a xenograft model and presents a novel system for studying the biology of prostate cancer and the evaluation of different therapies without sacrificing the animal. In this trial, significant declines in tumor DOG accumulation were demonstrated 48–72 h after

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Table 1 Tumor:whole-body FDG activity concentration ratios (SUVs) in CWR22 tumor xenografts

<table>
<thead>
<tr>
<th>Mouse no.</th>
<th>1 day preandrogen withdrawal</th>
<th>6 days postandrogen withdrawal</th>
<th>6 days postandrogen reimplantation</th>
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<tr>
<td>M1</td>
<td>1.37</td>
<td>1.02</td>
<td>ND*</td>
</tr>
<tr>
<td>M2</td>
<td>1.08</td>
<td>0.51</td>
<td>0.78</td>
</tr>
<tr>
<td>M3</td>
<td>0.53</td>
<td>0.64</td>
<td>0.82</td>
</tr>
<tr>
<td>M4</td>
<td>1.00</td>
<td>0.57</td>
<td>0.77</td>
</tr>
<tr>
<td>M5</td>
<td>0.98</td>
<td>0.59</td>
<td>ND*</td>
</tr>
<tr>
<td>M6</td>
<td>0.93</td>
<td>0.49</td>
<td>ND*</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.98 ± 0.25</td>
<td>0.64 ± 0.18</td>
<td>0.79 ± 0.03</td>
</tr>
</tbody>
</table>

* ND, not done.
androgen withdrawal. The decline in DOG accumulation preceded the marked decline in PSA and decrease in tumor volume, standard measures used to assess treatment effects. The decreased DOG accumulation was also associated with a decrease in the proportion of proliferating cells within the tumor from >60% to <5% over a 10-day period. No evidence of apoptosis was observed using the TUNEL assay and flow cytometry at the time intervals studied during the postandrogen withdrawal period. These results, together with Ki67 staining, implied that the tumors were arrested in a G2/early G1 state. The cells were not dead, as proliferation resumed when androgens were repleted.

DOG accumulation was measured with [3H]DOG as the radiotracer, and the optimal tumor:serum ratios were determined to occur 60 min after injection. Successive experiments used FDG PET scans of the tumor bearing mice to demonstrate tumor metabolism. The noninvasive serial PET scans were able to quantitatively follow the decrease in tumor DOG accumulation after androgen withdrawal and the increase of DOG accumulation after androgen repletion.

The decrease in DOG accumulation was associated with an increase in the cell surface GLUT1 staining of the tumor. GLUT1 is a bidirectional transporter, and DOG can only accumulate in tumor cells, at the time points studied, if phosphorylation and trapping occur. Thus, the change in DOG accumulation could either be related to (a) a decrease in the intracellular trapping of DOG through phosphorylation, by down-regulation of hexokinase enzyme; or (b) an increased efflux of DOG through GLUT1 from the tumor cells.

This study demonstrates that early changes in DOG accumulation predict for response of an androgen-dependent human prostate cancer xenograft to androgen withdrawal. The change in DOG accumulation, assessed noninvasively in vivo using PET, was paralleled by a decrease in the percentage of cells in active cell cycle and increase in cells in a G2/early G1 arrest. The metabolic changes in the tumor cells occurred in the absence of tumor cell death or a change in the tumor volume or marked decreases in serum PSA levels.

The xenograft model has a high growth fraction compared with human prostate cancer and, therefore, may allow easier PET visualization, but the difference in host size will significantly improve tumor localization in the human and, thereby, allow monitoring of disease metabolism. This study demonstrated tumor imaging of approximate volumes of 1.5 X 1.0 X 1.0 cm and followed relative rather than absolute changes in DOG accumulation. At the tumor dimensions used in this study, the recovery coefficient of the radioactive counts

<table>
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<tr>
<th>Days after androgen withdrawal</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
<th>+5</th>
<th>+7</th>
<th>+10</th>
</tr>
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<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ki67 staining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ (%)</td>
<td>495 (62)</td>
<td>497 (65)</td>
<td>453 (64)</td>
<td>467 (64)</td>
<td>157 (21)</td>
<td>36 (5.5)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>- (%)</td>
<td>295 (38)</td>
<td>270 (35)</td>
<td>254 (36)</td>
<td>261 (36)</td>
<td>602 (79)</td>
<td>619 (94.5)</td>
<td>734 (99.2)</td>
</tr>
<tr>
<td>Total</td>
<td>790</td>
<td>767</td>
<td>707</td>
<td>728</td>
<td>759</td>
<td>655</td>
<td>740</td>
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<td></td>
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<tr>
<td>+ (%)</td>
<td>1 (0.2)</td>
<td>5 (0.7)</td>
<td>5 (0.7)</td>
<td>4 (0.6)</td>
<td>6 (0.8)</td>
<td>4 (0.6)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>- (%)</td>
<td>712 (99.8)</td>
<td>738 (99.3)</td>
<td>719 (99.3)</td>
<td>693 (99.4)</td>
<td>735 (99.2)</td>
<td>632 (99.4)</td>
<td>683 (99.3)</td>
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<tr>
<td>Total</td>
<td>713</td>
<td>743</td>
<td>724</td>
<td>697</td>
<td>741</td>
<td>636</td>
<td>688</td>
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<td>GLUT1 staining</td>
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<td>2+</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
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</tbody>
</table>

*The data shown represent the mean of three tumors in each experimental group. Ki67 and TUNEL assay data were recorded as continuum data.
rises very steeply as a function of tumor size. An adjustment of the radioactive counts based on the estimated recovery coefficient, therefore, would be highly susceptible to minor changes in the volume of the region drawn. Instead, we chose to keep the ROI constant through the region drawn. Instead, we chose to keep the ROI constant through the current study is evaluating the change in metabolism of existent tumors, though, has shown that a change in tumor DOG accumulation after effective treatment could be demonstrated by a change in metabolism, before any decrement in tumor size (32).

Serial assessments of tumor metabolism may allow treatment effects to be determined earlier than is currently possible in clinical practice and to decrease patient exposure to potentially toxic and ineffective therapies. It may be particularly useful to determine the optimal biological dose of drugs and treatments for which the maximal tolerated dose or MTD may not be appropriate for dosing determinations. Cytostatic drugs, such as inhibitors of angiogenesis and receptor tyrosine kinase-mediated signaling, are entering clinical trials, for which there is a need for a biological end point. Serial changes in [18F]DOG accumulation measured by PET is currently under study as an intermediate end point in clinical trials for men with prostate cancer receiving a variety of antitumor agents.

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