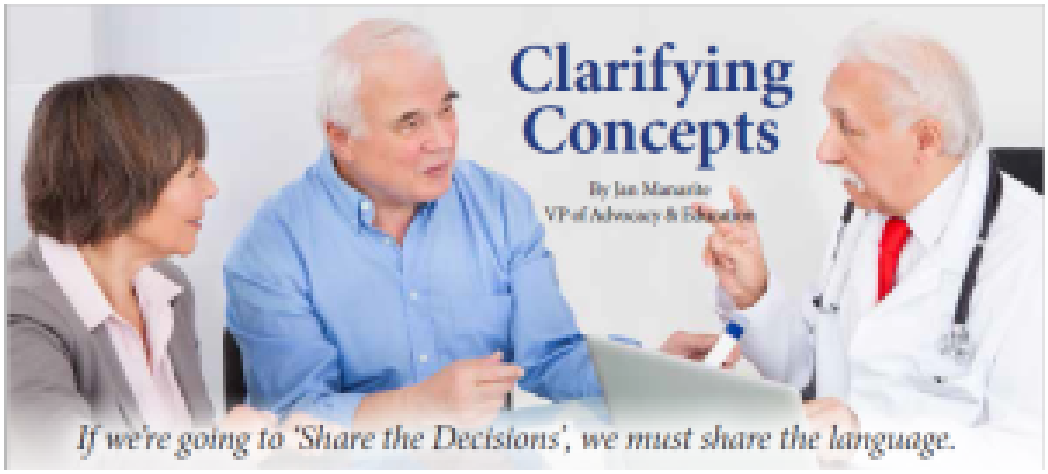
Clarifying Concepts – The word SYMPTOM means PAIN Jan Manarite, 2015



The word 'Symptom' usually means 'Pain' (in metastatic prostate cancer). Medical oncologists often use the words "symptomatic" or "asymptomatic." For the most part, they are simply referring to pain. On occasion, the word symptom may mean other things such as edema, urinary symptoms or fatigue, but mostly it means pain.

The reason this can be helpful for patients and caregivers to understand is that some advanced prostate cancer treatments are given or not given (covered by insurance or not covered), based on the patient's level of pain.

For example, PROVENGE (sipuleucel-T) is given to patients who are asymptomatic or minimally symptomatic. That usually means it's given to patients who have no pain or minimal pain (they cannot be on opioids, for example). The reason being is that how PROVENGE was studied in its Phase 3 clinical trials and that's where the data came from that led to its FDA

approval. Therefore, when PROVENGE was FDA approved, it was "labeled" for patients who are asymptomatic or minimally symptomatic, just like the patients in the Phase 3 clinical trials. Now, here's the final landing place – that's how insurance reimburses. **So, insurance usually doesn't cover or pay for a treatment when a patient doesn't "fit" the FDA label.** If PROVENGE is administered to a patient with a lot of pain or is on opioids for pain, it would be prescribed in a way that doesn't correspond with the FDA label (i.e. the way PROVENGE was studied), so that would be considered "Off-Label." use which is a term you may have heard before. Just to be clear, the other factors on the PROVENGE FDA label include prostate cancer patients who are (1) metastatic and (2) castrate-resistant or hormone refractory. REF

Another treatment for metastatic castrate-resistant prostate cancer (mCRPC) that has the word "symptoms" on its label is Xofigo (radium 223). Xofigo's Phase 3 trials (called ALSYMPCA) enrolled patients who had some type of pain (symptoms), so when Xofigo was FDA approved, it was labeled according to the data submitted from the Phase 3 trial in which it was studied. The FDA label for Xofigo says it is for patients who have symptomatic bone metastases. For the most part that means bone metastases that cause any level of pain. Since this is how it is labeled, this is what insurance requires in order for them to pay for Xofigo. Just to be clear, the other factors on the Xofigo FDA label include prostate cancer patients who are (1) castrate-resistant and (2) have no known visceral metastatic disease. REF (According to the NIH, visceral means "The soft internal organs of the body, including the lungs, the heart, and the organs of the digestive, excretory, and reproductive systems.") REF

The next time your physician asks if you have any symptoms, ask him if he means pain. If he (or she) asks you if you have any pain, ask if they mean symptoms. For us they are different words, but in the clinic they often mean the same thing.

Asking better questions always gets you better answers. Stay empowered.

Clarifying Concepts – Every Drug has 2 Names, Jan Manarite, 2015

Every Drug has 2 names. From antibiotics to chemotherapy, every drug has a brand name and a generic name. For the patient, **this can be confusing**, especially when trying to research a treatment, which is essential in developing better questions, and essential in Shared-Decision Making with physicians. If we are going to 'share the decision,' we must share the language and share the information. Sometimes this is harder than it should be for the patient or caregiver. The table to the right is a tool you can use to help recognize both names of a treatment or drug as you are doing research, whether it is on the internet, or at a medical library. This list is not all-inclusive, but hopefully illustrates an important issue in your cancer research, which is that every drug has 2 names, and even a third name in its earlier clinical trial days. So don't let this confuse you – look to recognize both names, the generic name and the brand name.

Don’t be discouraged if you ‘Google’ one name, and find the other. As always, continue to research your ideas and questions before you ask your physician(s). A researched question is a better question. And a better question always gets you a better answer.

FOR SOME EXAMPLES OF TREATMENTS & DRUGS OFTEN USED IN BPH & PROSTATE CANCER PLEASE SEE THE CHART BELOW.

BRAND NAME	GENERIC NAME
Proscar	finasteride
Avodart	dutasteride
Jalyn	dutasteride + tamsulosin
Flomax	tamsulosin
Rapaflo	silodosin
Hytrin	terazosin
Casodex	bicalutamide
Eulexin	flutamide
Nilandron	nilutamide
Nizoral	ketoconazole
Firmagon	degarelix
Lupron	leuprolide acetate (intramuscular injection)
Eligard	leuprolide acetate (subcutaneous injection)
Trelstar	triptorelin pamoate
Zoladex	goserelin acetate
Zytiga	abiraterone acetate
Xtandi	enzalutamide (MDV3100 in trials)
PROVENGE	sipuleucel-T
Xofigo	radium 223 (alpharadin in trials)
Taxotere	docetaxel
Jevtana	cabazitaxel
Zometa	zoledronic Acid
XGEVA	denosumab (larger dose)
Prolia	denosumab (smaller dose)
Cipro	ciprofloxacin
Levaquin	levofloxacin
Tylenol	acetaminophen
Aleve	naproxen sodium
Advil, Motrin	ibuprofen
No brand name in U.S.	aspirin

Look for other upcoming articles on **Clarifying Concepts** to help patients and caregivers in their research, formulation of

questions and Shared Decision Making with their physicians.

Update: C11 Acetate Pet/CT in Prostate Cancer Fabio Almeida MD, 2015

In a previous December 2012 article published in PAACT's newsletter I had the opportunity to discuss the preliminary results of our imaging work with Carbon 11 Acetate PET/CT. In this article, I provide an update to our study and give some case examples of patients to help illustrate the utility and options provided by this advanced imaging for prostate cancer recurrence.

The treatment landscape for prostate cancer has been revolutionized by the arrival of multiple novel treatment approaches and agents over the last few years. After initial treatment with surgery or radiation however, up to 40% of patients will unfortunately experience PSA relapse. For these patients, treatment options tend to be limited, usually including salvage radiation and/or hormone therapy. In addition, the PSA relapse can occur in the setting of a negative CT Scan and/or bone scan, leaving patients and

physicians guessing about the location of cancer recurrence, and the number and size of metastatic lesions.

Oligometastatic prostate cancer is a relatively new term referring to the detection of a limited number of metastatic sites developing at PSA relapse after primary treatment. **Oligometastasis refers to 1- 3 or at most up to 5 lesions in lymph nodes or in bones.** The concept emerged in the 1990s from observations that there were some patients with just a few sites of metastases with slowly progressive disease who experienced very favorable long-term outcomes with local therapy (usually radiation) targeted to these few sites. Observations of this sort spawned the hypothesis that there may exist an intermediate stage of cancer between primary disease and widespread metastases that could be treated successfully with limited therapy, delaying or avoiding long-term androgen suppression, or hormone therapy.

Knowing the precise location of a cancer recurrence is therefore important since recurrence in the prostate bed or pelvic lymph nodes may be amenable to additional focal therapy. Finding lesions outside of the pelvis (distant metastases) may require systemic treatment with hormones combined with radiation or other focal treatment, such as radiation.
The primary difficulty is that standard imaging techniques such as technetium (T99) bone scan, CT scans and MRI are usually unable to see small recurrent tumors outside the prostate, or metastases. These studies are therefore very limited in terms of directing focal treatment and so also limit potential treatment options. An accurate global (total body imaging) assessment is needed to identify all locations of metastases. The recent development of whole body imaging with C11-Acetate PET/CT appears to facilitate the identification of early, limited recurrent prostate cancer and appears to provide a tool to help better guide individualized treatment options.

C11-Acetate & C11-Choline

Over-expression of certain enzymes in prostate cancer (fatty acid synthase and choline kinase) results in increased cell membrane lipid production. Tumor cells depend on their ability to produce their own lipids. Different PET tracers, such as Carbon-11-Acetate (C11-Acetate) and Carbon-11-Choline (C11-Choline) have been developed that take advantage of this metabolic pathway and allows for lipid membrane imaging in prostate cancer. These metabolic agents used in PET/CT imaging provide for direct detection and measurement of the cancerous lesions, and additionally have the advantage of a more comprehensive review of the body – evaluating the lymph nodes, the prostate gland region, other organs such as the lungs, as well as the bone.

At the Phoenix Molecular Imaging Center in Phoenix Arizona, a large scale FDA-approved clinical trial investigation of C11-Acetate PET/CT imaging has continued to demonstrate excellent results and has led to direct benefit to many patients that would not have been achievable with standard imaging techniques.

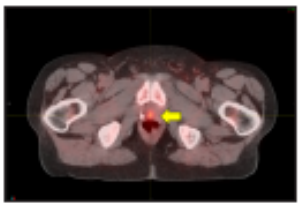
In this study, over 560 men with recurrent prostate cancer (as evidenced by a rising PSA) have now been studied using a high resolution PET/CT camera and Carbon 11 Acetate. This study represents the largest single site prostate cancer PET molecular imaging evaluation conducted in North America. **Our results have demonstrated an overall detection rate for the site of recurrence of 88%. In 59% of these studies locally recurrent or regional lymph nodes were found with no evidence of distant metastases.**

The PSA level is being shown to have an influence on the C11-Acetate detection rate. When the PSA is > 1.0 ng/mL the detection rate increases to 92%. With a PSA of 0 – 0.4ng/mL the rate is 64% and when the PSA is 0.4 – 1.0 ng/mL this is 75%. The PSA doubling time (or rate of PSA rise) also appears to have an influence, such that when the PSA is <1.0

and the PSA doubling time is < 3 months, the detection rate is 95%. To calculate your own PSA doubling time, simply calculate how long it takes a rising PSA to double, or search online for one of the many PSA doubling time calculators.

C11-Acetate appears superior to C11-Choline. The overall detection rate for cancer recurrence or metastatic disease with C11-Acetate (88%) has been 14% higher than that reported for C11-Choline (74% – as reported by Mitchell et.al [J Urol 189(4): 1308-1313]). Lesions detected at lower PSA levels (<1.0ng/mL) are of particular clinical interest. It is at this low range where many treatment decisions are made, such as otherwise "blind" radiation to the prostate bed or the
initiation of hormone therapy. C11-Choline performance in this range is poor, with a detection rate of only 44%. C11-Choline is therefore generally not recommended when the PSA is less than 1.5-2.0 ng/mL. C11-Acetate performance inthis low PSA range on the other hand is significantly higher
with a detection rate of 75%. Additionally, when performed in the context of a low doubling time (<3 months), the detection rate for C11-Acetate in this low PSA range is excellent, at 95%. This higher performance in the low PSA range makes C11-Acetate better suited for earlier detection for recurrence.

Case Example 1
Mr. V is 76 years old and was diagnosed with Prostate Adenocarcinoma (PCa) in 2000. His Gleason score was 8 (4+4) and his PSA was 4.0. He underwent a prostatectomy in 2001 and his PSA remained <0.1 for several years. His PSA then began to rise and by 2011 his PSA was 3.3 ng/mL and PSA doubling at a rate of 10.9 months.



Case Example 1: Small Recurrence in Prostate Bed

A C11-Acetate PET/CT imaging study was performed which showed a small recurrence of the cancer in the prostate bed (yellow arrow on image). No involved lymph nodes were detected and no lesions were seen on the C11 study to suggest distant metastatic disease. Based on the results of the C11-Acetate imaging study, Mr. V proceeded with Intensity Modulated Radiation Therapy (IMRT) to the prostate bed. The radiation therapy plan was modified from the typical "blind" application of radiation to this region. Instead, the area of recurrent cancer identified on the imaging study was targeted by the radiation and less radiation was then given to the surrounding areas, including the urinary bladder and rectum.

How has he done?
After his radiation treatment, the PSA fell to 1.1 ng/mL and has remained stable at that level for 3 years. He experienced no side effects from the radiation treatment and no other treatment has thus far been necessary. He is pleased that he has not yet needed to start hormone therapy.

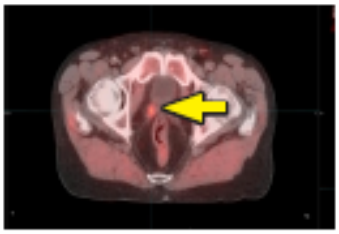
Case Example 2
Mr. S is 69 years old and was diagnosed with PCa in 2010. His Gleason score was 8 (4+4) and his PSA was 4.8ng/mL. He underwent a prostatectomy at which time extracapsular extension was found. After surgery his PSA was initially undetectable, but it began to rise a few months later and within a year his PSA had risen to 0.5 ng/mL, with a PSA doubling time of 3.18 months.

Mr. S's urologist told him it was most likely that the cancer had metastasized, and probably involved the bone given how quickly his PSA was rising. A technetium bone scan was

performed, which was negative for bone metastasis. Even so, he was advised by his urologist to begin hormone therapy as his only option.

Mr. S was not ready to start hormone therapy based on the above
information…

A C11-Acetate PET/CT imaging study was performed which showed a small focus of increased metabolism in the right seminal vesicle bed (yellow arrow on image below). This indicated locally residual cancer left behind after surgery which was now growing. There were no involved lymph nodes on the scan and no lesions were seen on the C11 study to suggest distant metastatic disease to the bone or elsewhere. In other words, he had no known metastatic disease.



Case Example 2: Recurrence in Right Seminal Vesicle Bed

Based on the C11-Acetate imaging study, Mr. S underwent IMRT. The radiation therapy was performed to the entire prostate bed region but also with a radiation "boost" targeted to the area of cancer noted on the imaging study.

How has he done?
After his radiation treatment, his PSA fell to <0.1 ng/mL and has remained stable at that level for 1.5 years so far. He experienced no side effects from the radiation treatment and has not yet had
to start any hormone therapy.

Case Example 3
Mr. W is 72 years old and was diagnosed with PCa in 2006. His Gleason score was 9 (5+4) and his PSA was 10.8. He underwent a

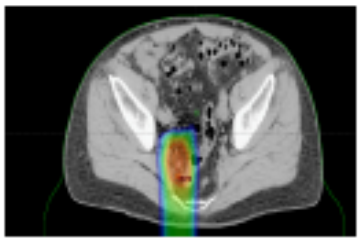
prostatectomy and his PSA remained <0.1 ng/mL for 7 years. His PSA then began to rise, and by 2013 it was 0.63 ng/mL with a PSA doubling time of 9.3 months.
An abdominal and pelvic CT scan as well as technetium bone were negative. A C11-Acetate PET/CT imaging study was performed which showed a small metabolic 9 mm lymph node to the right of and next to the rectum (yellow arrow on image below). A small 5 mm metabolic node was also seen higher up in the left pelvis (not shown). No metabolic lesions were seen in the prostate bed and no lesions were seen on the C11 study to suggest distant metastatic disease.

Case Example 3: Recurrence in Lymph Node to Right of Rectum

In most cases such as this, IMRT radiation treatment to the prostate bed with radiation extending to the pelvic lymph nodes has been the recommended course of action, with good results. Mr. W's case was however more complicated. He has a history of ulcerative colitis and recently had a bout of this requiring treatment with steroids. In this scenario, standard radiation would be problematic as it would likely make his bowel inflammation much worse. Radiation was essentially considered contraindicated for him. His urologist suggested hormone treatment, but Mr. W is a working professional and felt that this would interfere significantly with his work and travel.

Mr. W opted to undergo a different form of radiation treatment – Protons – with the newest (Intensity Modulated) generation of this technique (available at Scripps in San Diego California) having the ability to be conformal in a similar way to IMRT, but offering a level of precision not possible with standard radiation with IMRT. The proton therapy was

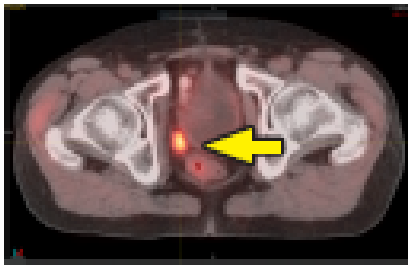
performed only to the pelvic lymph nodes detected on the C11 Acetate imaging study and with the C11 Acetate PET/CT imaging electronically integrated into the treatment plan to help guide the proton therapy. The image below shows the targeting of the proton beam treatment (color areas), which is narrow and avoids the intestine.



Case Example 3: Intensity Modulated Proton Therapy Beam (Targeted to Lesion Found on C11 Acetate PET)

How has he done?
Nine months after his proton radiation treatment, his PSA has decreased to 0.1 ng/mL. He experienced no side effects from the radiation treatment and most importantly, has not had any exacerbation of his ulcerative colitis. He will continue to follow his PSA.

Case Example 4
Mr. G was 48 when he was diagnosed with prostate cancer in 1995 with Gleason 7 (4+3) disease and a PSA of 58. He had a prostatectomy at that time. His PSA rose in 2001 for which he subsequently had radiation treatment to the prostate bed. In 2013 his PSA was again rising. A CT scan showed enlarged nodes in the pelvis and abdomen. These were treated with additional radiation and he was started on hormone therapy.



Case Example 4: Recurrence in Right Seminal Vesicle Bed

He completed Provenge treatment in 2014. The PSA continued to rise to a level of 2.96 ng/mL with a PSA doubling time of 1.25 months. Bone metastasis were suspected by his doctor but could not be seen on standard imaging.
A C11-Acetate PET/CT imaging study was performed which showed a small but focally metabolic lesion involving the right seminal vesicle bed region (yellow arrow on image below). No metabolic lesions were seen in the prostate bed and no lesions were seen on the C11 study to suggest active distant metastatic disease.

Mr. G's prostate cancer appears resistant to hormone therapy (castrate resistant) and a second line hormonal treatment (Xtandi) was recommended by his oncologists. He starting this medication. Finding only a single active area of cancer in the pelvis however also prompted the addition of focal IMRT re-irradiation to the right seminal vesicle region. With the ability to focally identify the recurrent cancer region, the application of radiation to an area previously radiated is now being performed by many radiation oncologists with good results and low side effects. Only with the information from the C11-Acetate scan could this have been possible.

How has he done?
After completing the radiation treatment, his PSA has decreased to 0.2 ng/mL. He experienced no side effects from the radiation treatment and he will continue to follow his PSA.

Summary
C11-Acetate PET/CT imaging appears highly useful in men with recurrent prostate cancer and can help provide treatment options that otherwise would not be available. It has a high detection rate even at very low PSA levels, and in many cases identifies areas of recurrent or regionally metastatic disease that can be treated with radiation or other focal therapy. Treatment with hormone therapy may be avoided or significantly delayed. In other cases, C11-Acetate may show evidence of

distant metastatic disease not seen by other techniques, thereby helping to better identify situations where systemic/hormone therapy may be the most appropriate course of action. Case example #4 also shows that C11-Acetate may reveal areas of resistant disease in the context hormone treatment and various other treatments, which may also benefit from additional focal treatment.

For more information about C11-Acetate imaging you can visit our web site www.phxmi.com, the clinicaltrial.gov web site https://clinicaltrials.gov/ct2/show/NCT01304485. You can also call our office in Arizona at 602.368.3055, open 8:00 am – 5:00 pm Mountain Time.