OLIGOMETASTATIC
Prostate Cancer

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Most surgeons, radiation oncologists and particularly medical oncologists regard prostate cancer as either confined to the prostate gland and curable, or widely metastatic and incurable.

However, we now know that there is an intermediate stage where the cancer has spread outside the prostate gland but is not widespread. This intermediate stage is called *oligometastatic* (the oligo- prefix comes from the Greek word for "few").

The concept of oligometastatic disease we have today derives from a paper written in 1995 by Samuel Hellman and Ralph Weichselbaum that established this concept (Hellman, S & Weichselbaum, RR J. Clin. Oncol 12:8, 1995). It is not written with a focus on prostate cancer, but rather on the broad spectrum of human cancers. We regard this as one of the classic papers in cancer treatment, and feel it should be required reading in every training program in surgical, radiation or medical oncology. Fortunately, the authors revisited their original concepts in 2011 when they reviewed the evolution of this way of thinking about cancer. The paper is relatively short, easy to read and available for free at http://www.nature.com/nrclinonc/journal/v8/n6/pdf/nrclinonc.2011.44.pdf.

The most important message of these two papers is that some patients with oligometastatic cancer have their survival markedly prolonged when the metastatic lesions are surgically removed or treated with radiation. A portion of patients with liver metastases removed by surgery have survived long enough that they are very likely cured. Similarly, among patients with lung metastases removed by surgery, between 20-30% were still alive at 15 years. It is important to note that neither paper looked at oligometastatic disease in prostate cancer patients.

Four years after the publication of this paper, Dr. Snuffy Myers was diagnosed with prostate cancer that had escaped the prostate gland and spread to several lymph nodes. At that time, the concept of oligometastatic disease had not been applied to prostate cancer, and this presentation was nearly always fatal in less than 10 years. *(continued on page 15)*

Faced with this grim future, Dr. Michael Dattoli offered to treat Myers with radiation to the prostate gland and lymph nodes in the pelvis. Surgery was used to eliminate the lymph nodes in the lower abdomen that might be involved. All of this was done after hormonal therapy had been used to reduce the total volume of cancer. The publication of this essay coincides with the 13th anniversary of the diagnosis, and Myers remains free of cancer.

This experience sensitized the authors of this essay to the possibility of oligometastatic disease in prostate cancer. During those early years, it was difficult to use this concept because it was difficult to image (therefore difficult to find) metastatic lesions.

This cancer commonly spreads to bone and lymph nodes in the pelvis and lower abdomen. Bone scans are widely recognized to be plagued by false positives, and require sizeable cancer deposits before they turn positive.

CT and conventional MRI are also notoriously insensitive, and require close to 1 centimeter of cancer for detection. At that time, the ProstaScint scan was available. While this was a marked improvement, ProstaScint scan's utility was limited by a 20% false positive and 20% false negative rate.

The next major advance came from the University of Rochester in New York, and it documented in detail the existence of oligometastatic disease in prostate cancer metastatic to bone (Singh, D, et al O Int J Rad Onc Biol Phys 58: 3, 2004).

The first observation was that men with five or fewer bone lesions had nearly the same 5-year survival as those with PSA-only recurrences.

They then went on to look at the natural history of bone metastases in those with five or fewer bone lesions (versus more than 5). An appreciable proportion of those with five or fewer lesions remained stable for up to several years before the cancer started to spread widely. Those with more than five bone lesions were much more likely to spread widely.

The authors proposed that stereotactic radiation to bone metastases in those with five or fewer may eliminate the bone metastatic cancer and make the patients disease-free for a prolonged period of time. This paper was followed by several papers involving a limited number of patients that show radiation can indeed control individual bone lesions. However, because of small patient numbers and limited follow-up, these papers offer no convincing evidence of improved survival.

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Our view is that if survival is going to be significantly changed, it is a strategic mistake to focus solely on bone lesions. From a wide variety of sources, we know that many men have lymph node metastases that are invisible to CT and MRI. Unless nodal disease is identified and eliminated, the cancer can continue to progress despite elimination of bone lesions by radiation.

Thus, translating the concepts of oligometastatic disease into a survival benefit for prostate cancer patients requires further improvement in our ability to locate the cancer. Further, the advances in imaging must be tightly linked with improved radiation therapy techniques. Fortunately, there have been advances in both bone and lymph node radiation therapy.

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The specific pattern of lymph node spread has been defined using multiple varied methods, with consistent results across these different studies. The most common sites involved are in a broad area surrounding the obdurator, common, external and internal iliac arteries where more than half of all nodal disease will be found. These nodes are within the pelvis, and easily targeted with modern radiation therapy.

Other nodal clusters in the pelvis are involved much less commonly. From the iliac/obdurator nodes, the cancer can then spread to the back of the abdomen to the retroperitoneal nodes. While this cancer can spread above the diaphragm, this is quite uncommon.

NEW IMAGING TECHNIQUES

Sodium F18 Bone Scan - The traditional bone scan uses Technetium (99mTc) medronic acid. The sodium F18 PET bone scan appears to be significantly more sensitive than the traditional bone scan.

This enhanced sensitivity comes with an increased risk of false positives. The risk of false positives can be reduced if the CT shows areas of increased bone formation and the MRI shows tumor occupying the marrow cavity. However, there are cases where a positive F18 bone scan needs to be confirmed by a bone biopsy. If you want to delve further into this promising technique, the Society for Nuclear Medicine has issued a Practice Guideline that is available at http://interactive.snm.org/docs/Practice%20Guideline%20NaF%20PET%20V1.1.pdf

Magnetic Resonance Imaging - MRI has become a powerful tool in medicine. Compared to CT scan, MRI generally does a much better job at visualizing soft tissue details. For example, MRI excels in visualizing such things as muscle damage or a cancer mass pressing on the spinal cord.

Unfortunately, MRI has not done very well at visualizing cancer invading lymph nodes because most cancers have the same MRI characteristics as the lymph nodes. Thus, MRI only picks up cancer invasion of lymph nodes when the node becomes too large. In practice, this means the node is greater than 1 cm (0.4 inches). Gadolinium, a contrast agent commonly used in MRI, is also taken up equally by normal and cancerous lymph nodes.

The goal of MRI with Feraheme or Combidex is to identify those lymph nodes that are considered normal by conventional MRI size criteria, but demonstrate abnormal signal after the administration of either the Combidex or Feraheme reagent.

Combidex Scan - The story of the development and subsequent death of Combidex as an imaging agent is one of the major tragedies in prostate cancer oncology.

Combidex is a very small iron particle (nanoparticle). When administered intravenously, it is taken up by lymph nodes throughout the body. Prostate cancer in a lymph node does not take up this iron. With MRI, the contrast between the iron-free cancer and surrounding lymph node is quite significant. As a result, lymph node metastases down to 2 mm can be visualized.

Harisinghani et al (J Magn Reson Imaging 7:161, 1997) first reported successful imaging of prostate cancer via Combidex in 1997. This elicited considerable interest and more than 400 papers were published on Combidex, including its ability to detect lymph node metastatic disease from a variety of other cancers. Jelle Barentsz at the Radboud University Nijmegen Medical Center in the Netherlands specifically focused on perfecting the use of Combidex in prostate cancer patients. ***(continued on page 17)***

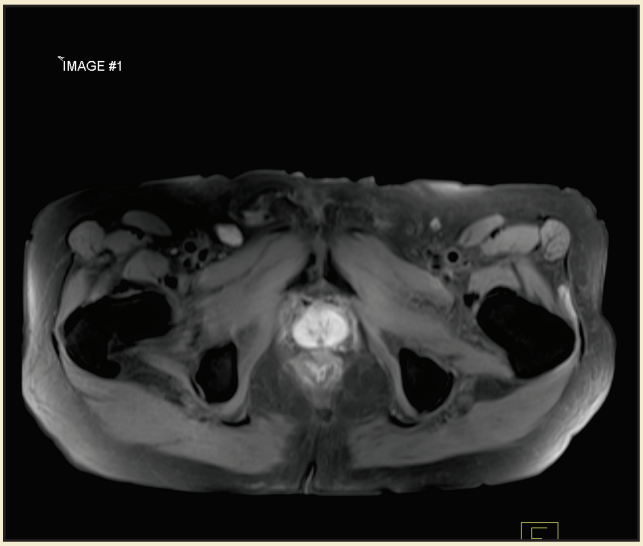

FIGURE 1

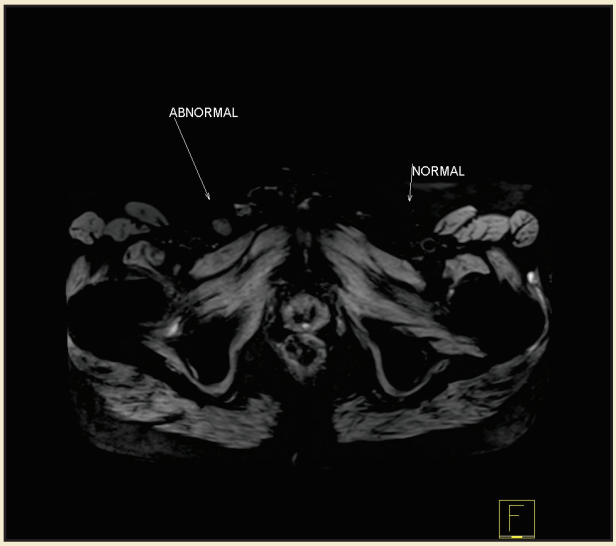

FIGURE 2

The published record clearly indicates that Combidex represented a major improvement in the detection of lymph nodes in prostate cancer and other cancers. So, why did this agent disappear?

When the Combidex results were presented to the Oncology Drugs Advisory Committee (ODAC) at the FDA, members of the committee voted not to approve it. Members of the Committee involved in imaging voted for approval. The medical oncologists voted against approval. We think this split nicely illustrates a cultural divide between those involved in imaging research and those involved in cancer treatment.

As a medical oncologist, Snuffy Myers would also have viewed the material presented before ODAC as too limited for FDA approval. Ideally, you need a fairly large number of patients imaged, and the presence of cancer in the lymph nodes confirmed by biopsy to determine the false positive rate. You should then present information that this resulted in improved treatment. It would be even better if you show improved survival.

Together, the coauthors referred more than 50 patients to Dr. Barentsz for evaluation. More than half proved to have lymph node oligometastatic disease and were treated with radiation. Within the next two years, the follow up on these patients will be sufficient to look at survival. Unfortunately it is too late for those results to save the Combidex.

Feraheme MRI - Feraheme is also known as Ferumoxytol and it is a nanoparticle Fe3O4 preparation. It is already FDA-approved as a treatment for iron-deficiency in patients with renal disease. Thus, it is readily available and its safety is well-documented.

As with Combidex, Feraheme is taken up by normal lymph node tissue, but not by prostate cancer invading those lymph nodes.

However, there are several differences. Most importantly, Feraheme is available and the Combidex reagent is not. At least initially, the Combidex reagent showed better resolution. However, as the use of Feraheme has undergone optimization, the two appear to be equivalent.

Figure 1 shows an MRI done using Gadolinium as a contrast agent. Two lymph nodes are visible as white masses, the left larger than the right.

In Figure 2, the same patient is imaged following Feraheme injection. Using the T2* MRI imaging technique, normal nodes appear black, while the cancer shows up as white. In image 2, the right lymph node is black, indicating a normal node. The left node is white, indicating the presence of cancer. This was verified by biopsy: the right node was normal and the left contained cancer.

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Carbon-11-Choline PET Scan- Prostate cancer cells take up choline. This has been widely used in MRI spectroscopy as the cancer has a higher choline content than the surrounding normal tissue.

In a landmark study, Hara et al compared carbon-11-choline with fluorine-18-deoxyglucose PET in patients with prostate cancer (J Nucl Med 39: 990, 1998). The utility of the fluorine-18-deoxyglucose PET scan was compromised by intense radioactivity in the urine that overwhelmed cancer uptake. In contrast, the prostate cancer showed marked uptake of the choline label and very little of the isotope was found in the urinary tract.

There are now more than 70 papers on carbon-11-choline PET scan scanning for prostate cancer. Several papers have provided pathologic documentation that the abnormalities detected represent prostate cancer. R. Jeffrey Karnes from the Mayo Clinic has imaged several hundred prostate cancer cases and has shown this approach will detect cancer not seen on routine MRI or CT scan.

How does the carbon-11-choline PET scan compare with the Feraheme-MRI? There are no direct comparisons, so a definitive comparison is difficult. The two imaging approaches have different inherent strengths.

In favor of Choline PET, the image is based on a real biochemical characteristic of prostate cancer. In favor of the Feraheme MRI is that MRI using a 3 Tesla machine has inherently much better resolution than current PET technology. MRI can be problematic if the patient has a pacemaker, unless one of the newer MRI-safe pacemakers is used. PET poses no risk for patients with a pacemaker.

What is the best way to treat oligometastatic prostate cancer?

It is our view that surgery has limited utility in the management of oligometastatic prostate cancer.

First, it would not prove a useful approach to bone metastatic lesions. While surgery has a long history in diagnosing lymph node involvement in men with prostate cancer, evidence that this surgery offers improved cancer control is not impressive. At the same time, radiation therapy techniques are improving rapidly and we will focus on this as a treatment option.

External beam radiation has undergone a virtual revolution, primarily as a result of it being a computer-driven modality. Newer software and hardware have enabled the formulation of extremely complex treatment plans with the ultimate goal being to improve the therapeutic ratio (that is, maximal sparing of normal tissues while eradicating cancer).

Early Cobalt-60 therapy in the 1950s based on isotope decay gave way to mega-voltage radiation in the early 60s using linear accelerators allowing for higher energy photons and higher doses of radiation. Three Dimensional Conformal Radiation (3D-CRT) was popularized in the 1990s followed by Intensity Modulated Radiation (IMRT) beginning in 2000. With IMRT, the beam intensity is varied across the treatment field rather than being treated with a single large uniform beam.

Hundreds and even thousands of microbeams the size of a cubic millimeter (called Voxels) are utilized for dose delivery. Moreover, each microbeam can have a different dose intensity. IMRT treatment planning allows for dose delivery to match the shape of the target while maximally sparing adjacent normal tissues.

Zelefsky et al. reported on the superiority of IMRT over 3D-CRT with respect to patient morbidity (Int J Rad Onc Biol Phys: 70(40) 1124-9). Numerous other investigators have since demonstrated the superiority of the higher dose levels that can be achieved with IMRT compared to 3D-CRT.

Even more advanced versions of IMRT are now commercially available. Image Guided IMRT (IG-IMRT or IGRT) and especially Dynamic Adaptive Radiotherapy (DART) allow for the use of real-time 4D imaging to better track the target. DART accomplishes this most effectively, allows the microbeams to reach the target(s) and is capable of doing so even when the targets are in motion. Using the most advanced technologies, DART allows multiple built in 4D tracking systems. Aided by sophisticated 4D technologies, DART enables dose delivery between treatments ("inter-fraction"), but also during the actual treatment ("intra-fraction").

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