EDITORIAL

Prostate Cancer CRPC Stage M0 and M1: Do We Need Stage M0.5?

Progress in the management of advanced prostate cancer is occurring rapidly. Consequently, clearly defined clinical disease stages are becoming blurred by advances in next generation imaging and new therapeutic agents in disease states where no treatments existed before.

Men with biochemical failure after local therapy for prostate cancer are often treated with androgen deprivation. While many men experience a long period of remission based on an undectable PSA and a castrate testosterone level, some will demonstrate disease progression known as "castration resistant prostate cancer" or CRPC. CRPC is defined as prostate cancer progression based on rising serum prostate-specific antigen (PSA) levels despite low levels of testosterone (< 50 ng/dL) due to surgical or medical castration. CRPC is further classified in the TNM system as M0 CRPC when there are no radiographically identifiable metastases. Once radiographic metastases are found, the disease is reclassified as M1 CRPC. Agents such as sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, and radium 223 are often administered in this next disease state as their approved use is for M1 CRPC.

With the advances in imaging we can detect metastatic prostate cancer much earlier than ever before. The identification of the transition from M0 to M1 CRPC is becoming less clear. The standard of care for radiographic imaging of prostate cancer metastasis is the technetium-99MDP bone scan and CT or MRI of the abdomen and pelvis to evaluate for soft tissue metastasis. Conventional bone scans are rarely positive for metastasis when the PSA is less than 10 ng/mL. Unless grossly enlarged, lymph nodes on CT or MRI cannot be reliably identified as containing metastasis. The recent clinical availability of new positron emission tomography (PET) imaging agents to identify metastatic prostate cancer in bone or soft tissue much earlier than our traditional standard of care radiographic studies is shortening the duration of M0 disease.

PET/CT or PET/MRI use in prostate cancer has advanced through the development of more specific prostate cancer radiotracers. Novel agents include ^{68}Gallium PSMA, ^{11}Carbon and ^{18}Flouride choline, ^{18}F Sodium fluoride, Fluciclovine (^{18}Flouride-FACBC), ^{64}Copper VPAC and others. These newer imaging agents can identify local recurrences or metastasis at PSA levels far below the PSA levels of traditional imaging such as CT or bone scan. Some of the new PET agents can identify metastatic lesions at PSA values as low as 0.2 to 0.5 ng/mL allowing the identification of M1 CRPC much earlier than before.

Further challenging traditional management of CRPC is a new FDA approved oral agent, apalutamide, the first approved therapy for patients with M0 disease. Apalutamide can significantly delay the development of radiographic metastasis in men with M0 CRPC based on bone scan and CT or MRI.

How do we address this paradigm shift of earlier identification of metastatic disease through these new PET scans? Should we define M1 CRPC based solely on traditional imaging or should we consider a new classification based on a PET based schema: M1 with traditional imaging and M0.5 to denote PET scan detected metastasis before traditional imaging? The National Comprehensive Cancer Network (NCCN) 2018 recommended guidelines for the evaluation of progression in M0 disease includes many different modalities from the traditional bone scan and CT or MRI through the consideration of PET imaging such as ^{11}Carbon choline or ^{18}Flouride fluciclovine PET/CT or PET/MRI soft tissue disease and ^{18}F Sodium fluoride for bone evaluation. The clinical utilization of prostate cancer specific PET scanning will take some time to become a standard of care. Until everyone is followed with the potentially more accurate PET scans, using different imaging modalities when evaluating treatment options may challenge patient care.

The earlier identification of metastasis in the transition between the M0 and M1 disease has significant implications. These include the use of advanced M1 CRPC therapeutics earlier that previously used and the challenge of comparing historical clinical trials of advanced prostate cancer in the context of the early metastatic identification on PET scans. While the focus of this commentary is on radiographic imaging in CRPC, evolving liquid biopsy technology will likely move the identification of progressive metastatic disease to before any detectable increase in PSA. A new liquid biopsy based CRPC stage might also be worth considering in the future.

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