Non-metastatic (M0 CRPC): Where are we today and where are we going?

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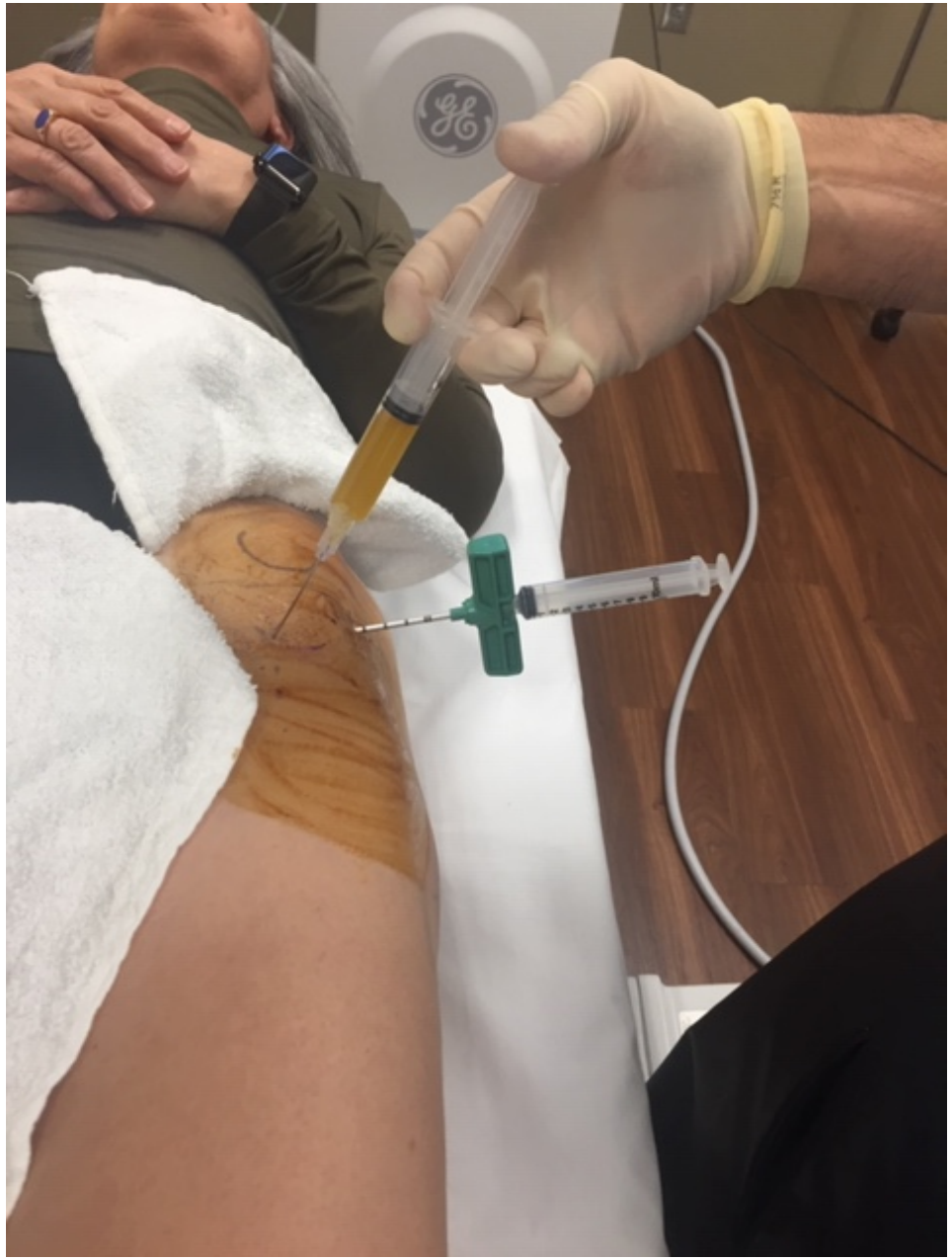

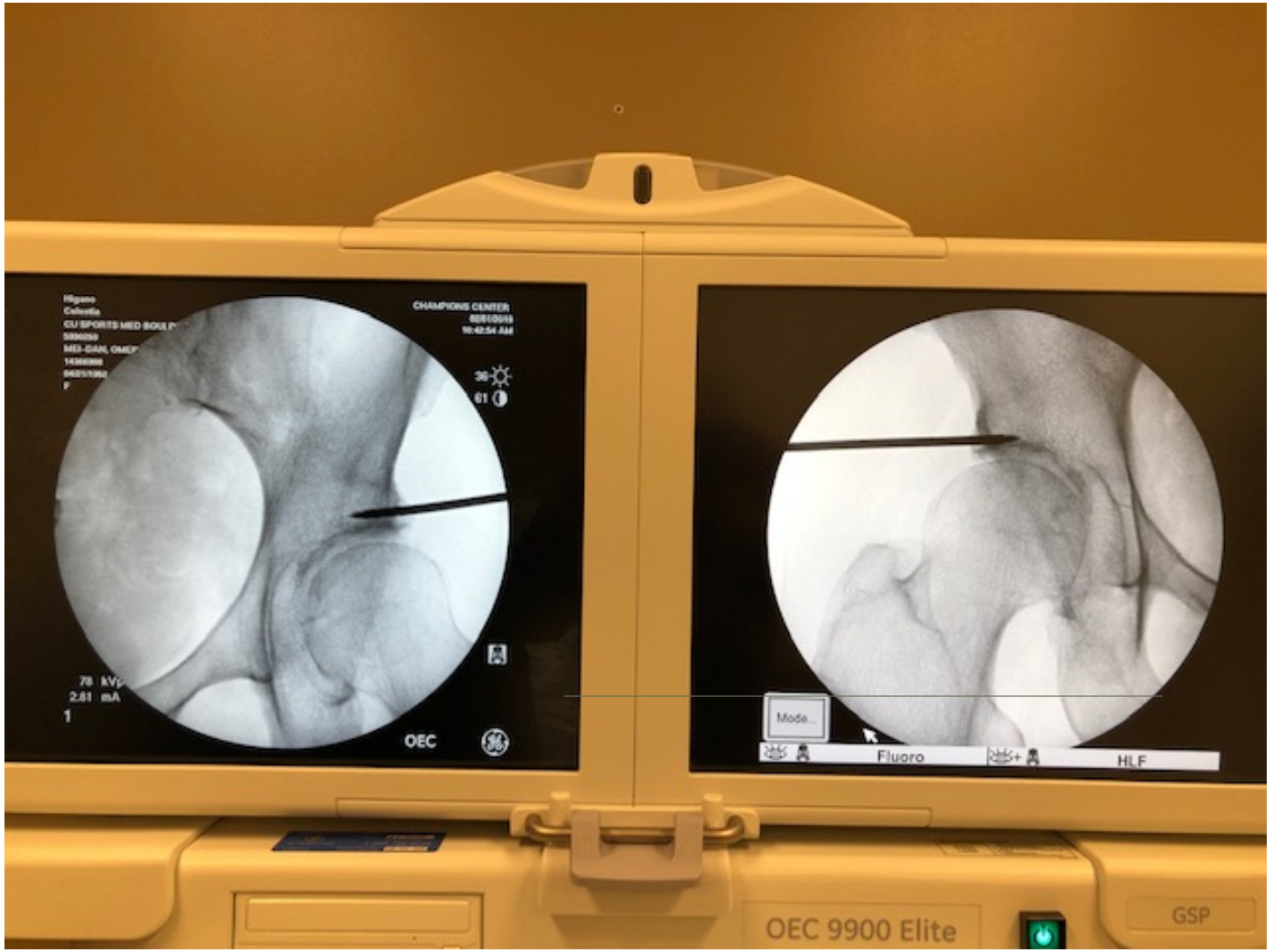
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Background

- Until recently there wee no standard of care treatment options
- In 2018 apalutamide was the first drug approved by the FDA for treatment of M0 CRPC
- First time use of an intermediate endpoint, MFS (metastasis free survival) WITHOUT survival data
- Subsequently, enzalutamide and darolutamide also FDA approved for M0 CRPC

What are some of the questions and challenges?

What is the definition of non-metastatic (nm)CRPC?

Who should be treated with nmCRPC CRPC?

What should they be treated with?

What future directions should be undertaken in this disease state?

What is the definition of non-metastatic or “M0” CRPC?

- Serial rising PSAs despite a castrate level of testosterone
- No evidence of metastatic disease by conventional imaging
  - Technetium bone scan, CT chest, abdomen, pelvis
- What about more sensitive imaging, eg. fluciclovine, PSMA PET?
  - RCTs were done with conventional imaging
  - More sensitive imaging could identify “pseudo-M0” disease but there is no current data for this population
- Clinical trials definition vs what might be used in clinical practice

Questions and challenges for the future

Will earlier treatment of patients with “pseudo-M0” disease really benefit from earlier use of drugs for mCRPC?

Will earlier use of these agents hasten the development of drug resistance that ultimately develops?

Can “pseudo-M0” disease be treated with directed therapy such as SBRT to delay use of second line AR targeted therapy?

Who should be treated with nmCRPC?

- Patients should be assessed for risk status (PSA-DT)
- Co-morbidities should be ascertained and documented
- Patients with high risk nmCRPC (PSA-DT ≤ 10 months)
  - Should be offered second gen ARI's : apalutamide, enzalutamide, or darolutamide
  - Prolonged time to MFS and possibly OS
  - Information regarding potential side effects
- Patients with PSA DT > 10 months
  - May be good candidates for observation
  - ? role SBRT or other focally directed therapies, immunotherapy
- Patients who have PSA anxiety may "feel better" if PSA declines

If it is decided to proceed with a second generation ARI, which agent should be used?

- No head to head studies showing:
  - Improved efficacy
  - Improved tolerance
- Underlying co-morbidities are very important
  - Cardiovascular disease
  - Hypertension
  - History of falls or seizure
  - Frailty
  - Presence of osteoporosis or osteopenia

Question from Dr. Concepcion:

Any comments on lower rate of fatigue and asthenia in the placebo arm of ARAMIS vs that documented in PROSPER/SPARTAN?

Data from NEJM phase 3 trial reports

Adverse event	apalutamide	enzalutamide	darolutamide
	Tx vs PBO (%)	Tx vs PBO (%)	Tx vs PBO (%)
Grade 5 AE (death)	1.2 vs 0.3	3 vs 1	3.9 vs 3.2
Fatigue, any	30 vs 21	33 vs 14	12.1 vs 8.7
Fatigue, gr 3-4	0.9 vs 0.3	3 vs 1	0.4 vs 0.9
Asthenia	NR	9 vs 6	NR
HTN, any	24.8 vs 19	12 vs 5	6.6 vs 5.2
HTN, gr 3-4	14.3 vs 11.8	5 vs 2	3.1 vs 2.2
Falls, any	15.6 vs 9	11 vs 4	NR
Falls, gr 3-4	1.7 vs 0.8	1 vs 1	NR
Fracture, any	11.7 vs 6.5	NR	NR
Fracture, gr 3-4	2.7 vs 0.8	NR	NR

Going forward

We will need a better understanding in the post market setting about the toxicities of these agents relative to each other…registry?

Are there genetic, pharmacogenomic, or other biomarkers that can predict specific toxicities?

What is the OS for these phase 3 trials?

How does earlier use of these agents impact the natural history of mCRPC?

Must one consider use of the ARI's THE standard of care or A standard of care?

Role of molecular imaging and directed therapies to delay use of ARIs?