Thank you for the opportunity to present. Today, I am going to talk today about the comparative harms of management options for localized prostate cancer and the implications for shared decision making.

None of the study investigators had any relevant industry relationships. We did have research funding from AHRQ and PCORI and we now have funding from the Movember Foundation for a related project. The CAESAR Study, which I’ll tell you more about that in detail, was published in *JAMA* in March 2017.

Source: Contemporary Treatment Options for Prostate Cancer, PCORI.org
Posted: September 2017
In terms of learning objectives, first we want to be able to identify the key components of shared decision making around the management of localized prostate cancer. Second, we’d like to describe the data regarding comparative harms of contemporary external beam radiation therapy (EBRT), radical prostatectomy (RP), and active surveillance (AS). And, finally, we would like for the listener to be able to participate with the treatment team in shared decision making around management of localized prostate cancer, incorporating patient preferences with what is known about functional outcomes, general quality-of-life outcomes, and oncologic outcomes.

So, what are the components of shared decision making for localized prostate cancer?
This model was developed by AHRQ. It encourages the provider to seek the patient’s participation, to help the patient explore and compare treatment options, to assess the patient’s values and preferences, and to reach a decision with the patient, and, finally, to evaluate the patient’s decision.

So, how does this pertain to the decision between surgery, radiation, or active surveillance for localized prostate cancer? The medical team provides knowledge and specifically provides knowledge about comparative effectiveness and oncologic outcomes such as progression-free survival, disease-specific survival, and overall survival.
And there are factors that influence the comparative effectiveness, such as the risk of disease progression, for example.

In addition, the medical team provides knowledge about the comparative harms, such as functional outcomes—urinary, sexual, and bowel function, general quality of life outcomes, anxiety and depression and so forth.
And, again, there are patient factors, baseline factors, that can influence these comparative harms; things such as patient age and co-morbidity; and baseline urinary, sexual, and bowel function.

What does the patient bring? The patient brings their own preferences and priorities. And, in addition, the caregiver, spouse, partner, et cetera, may have their own preferences and priorities to voice. And, of course, there are the patient factors that influence those elements.
And, finally, perhaps the biggest component is the communication between the patient and the provider and along with the caregiver, spouse or partner. And, of course, the provider factors that influence communication are profound. The provider not only has to be knowledgeable about comparative effectiveness and comparative harms, but has to be effective at communicating with the patient in getting that information across. They have to be effective at eliciting the patient’s preferences and priorities, hearing them out and trying to help them make a good decision. Patient factors that come into play here are things like healthcare literacy and self-efficacy. So, the communication is paramount.

Today, our study and the following talk really pertains to the functional outcome, the comparative harms of different treatments for prostate cancer. So, I want to point out that this is one component. We have good information, but it is only one component of this more complex
process that’s very important for helping them come to a good decision about how to manage localized prostate cancer.

I do want to say a word about comparative effectiveness before we dive into the comparative harms. Because comparative effectiveness is so important for men making these decisions. They want to know what the anticipated oncologic outcomes are if they choose surgery, radiation, or active surveillance. First, let’s say that this is highly controversial, because the data are limited in many ways. For sure, it depends on life expectancy. Is the patient expected to live more than ten years or not? And, of course, it also depends on the risk of cancer progression, which we can estimate based on the PSA level, the clinical stage, biopsy grade, and maybe other bio-markers and imaging. In other words, what is the likelihood of disease progression within the patient’s lifetime?
This is my interpretation of the available comparative data: Short-term outcomes are equivalent across treatments or even across observation and treatment. Five-year prostate cancer survival is about a hundred percent regardless of treatment. The longer-term outcomes are more variable and depend in part on the risk stratum. So, men with low risk disease, there’s no proven survival benefit for treatment versus active surveillance. However, for intermediate and high-risk disease we know that untreated disease is associated with risk of disease progression, metastasis, and death and that treatment mostly likely lowers the risk of adverse oncologic outcomes in these men. At present, we believe there’s equipoise between radiation and external beam radiation therapy with respect to oncologic outcomes. However, there are numerous caveats and nuances to that statement that go beyond the scope of this talk. There are situations in which because of patient factors or disease factors one treatment might be preferred over the other and that discussion with the patient is quite nuanced. I think at a minimum, one would want to be familiar with the references that are on this slide in order to appropriately counsel men about the comparative effectiveness.
How do we coalesce these bits of information on oncologic outcomes? Most guidelines and most practitioners do it as follows: For men with low-risk disease and a life expectancy greater than ten years we recommend active surveillance; for men with intermediate-risk and high-risk disease and a life expectancy greater than ten years we usually recommend surgery or radiation. And, of course, there’s a little bit of crossover here with some low risk men preferring treatment, some intermediate risk men preferring active surveillance, but the bottom line is that without being able to tell a patient which treatment option or which option is clearly best from an oncologic point of view, prostate cancer treatment is preference-sensitive. In that light, men incorporate the comparative harm information into their decision-making process, which is appropriate.
So, what are the comparative harms of contemporary management options for localized prostate cancer?

**Background**

- Prostate cancer management is preference-sensitive.
- Historically, side effects of treatment are common
  - Sexual; urinary; bowel; hormonal (ADT)
- Newer treatments are now available.
  - Robotic RP; intensity-modulated EBRT; AS

Historically, side effects of treatment have been common and, in some instances, severe in terms or sexual, urinary, bowel, and hormonal side effects. However, there are new treatments now available. Robotic radical prostatectomy has come up in the last ten or fifteen years. External beam radiation therapy has evolved quite a bit in terms of use of intensity modulated therapy, image-guided therapy and use of hormone therapy concomitantly. And active surveillance is an advance over prior surveillance modalities of “watchful waiting.”

**Objective**

Compare functional outcomes and adverse effects associated with radical prostatectomy (RP), external beam radiation therapy (EBRT), and active surveillance (AS) in a contemporary, population-based cohort of men who survived prostate cancer.

So, with that in mind, the CAESAR Study aimed to compare the functional outcomes associated
with radical prostatectomy, external beam radiation therapy, and active surveillance in a contemporary population-based cohort.

We developed a prospective population-based cohort study. Subjects were recruited from five SEER Registries and the Capture Registry from 2011 to 2012. We collected patient questionnaires at baseline, six months, twelve months, and three years and, specifically, we collected the EPIC 26, which is a validated questionnaire for us in men with prostate cancer to assess function. It has urinary, sexual, bowel, and hormonal function domains, each of which is scored from zero to one hundred, with a higher score indicating better function. And when we interpreted our results, we did so not just with statistical significance in mind, but with clinical significance in mind using thresholds that were developed in prior publications in order to identify minimum clinically important differences in functional scores. The medical charts were reviewed at 12 months to gather clinical and treatment data and we also linked up the data to the SEER Registry to get mortality outcomes.
So, you can see here that the inclusion criteria were aged less than eighty, that the patient enrolled within six months of diagnosis; he was able to participate in English or Spanish; the PSA had to be less than fifty; and the stage was localized. We excluded men from this analysis who had other treatments and two hundred men who did not complete a follow-up survey. In terms of the baseline characteristics, as expected, men undergoing radical prostatectomy were younger than men in the other groups.

About twenty-five percent of our cohort was non-white, reflecting the diversity of the underlying population. Men who underwent external beam radiation therapy group tended to have higher risk disease compared to those who underwent surgery and those who underwent active
surveillance. The active surveillance group appropriately is mostly low risk. And, finally, 45 percent of men in the external beam radiation therapy group had hormone therapy within the first year.

Let’s talk about the functional outcomes first with the urinary incontinence domain. What you see on the left side is just a trajectory of average scores following treatment for the active surveillance, external beam radiation, and radical prostatectomy groups. For the urinary incontinence domain, you can see on the unadjusted trajectory plot that they all start at about the same level. The men who underwent radical prostatectomy take a sharp dip in their urinary incontinence domain score and they rebound a little bit, but on average do not get back to baseline. The other two groups preserve their urinary continence function. On the right side is a forest plot that shows the predictors of three-year domain score. The dotted lines indicate the threshold for minimum clinically important difference. So, you can see from this plot that the factors that predict a clinically significant difference in 3-year outcomes are treatment with radical prostatectomy, which results in on average about a fifteen-point decline in functional domain score. And, men who started out with a high baseline domain score, tended to have a clinically significant higher 3-year domain score. Overall, 14 percent of men undergoing radical prostatectomy reported a moderate or big problem with urinary incontinence at 3 years compared to 5 percent for EBRT and 6 percent for active surveillance.

Source: Contemporary Treatment Options for Prostate Cancer, PCORI.org
Posted: September 2017
Urinary irritative domain scores actually get a little bit better with radical prostatectomy. These are symptoms like having to wake up at night to use the bathroom, urinary urgency or frequency or burning when they urinate. These are, to some degree associated with BPH and so it’s not surprising that removing the prostate alleviates some of these symptoms. And, you can see again on the forest plot the factors that have a clinically significant impact on 3-year scores for treatment with radical prostatectomy, this time to the favorable side and baseline domain score again.

With regard to sexual function, this is interesting. You can see that on the unadjusted trajectory plots, men who underwent external beam radiation therapy actually started out with lower scores compared to the active surveillance and radical prostatectomy patients. Actually, overall scores were pretty low to begin with for all groups. The radical prostatectomy patients take a sharp dip
in their sexual function within the first year and they rebound only a little bit. The radical prostatectomy and external beam radiation patients end up with about the same average scores, but since the external beam patients started much lower, the drop in scores is much more significant for the surgery patients. And that’s reflected in the forest plot on the right where you see radical prostatectomy is associated with a clinically significant decrement in three-year function. And, again, notice that baseline domain score is the strongest predictor of the three-year functional outcome. So, men who started out with a high score ended up with a high score.

Looking at that in more detail, one point of interest is that that 39 to 56 percent of men started out with erections insufficient for penetration. More than forty percent of men had erectile dysfunction before treatment. In addition, 45 percent of men who underwent EBRT had hormone therapy. Those men completely lose their libido and are not sexually active, at least during that period of time in which they’re being treated. The plot on the left is men with the highest baseline sexual function in the top quartile. For them the difference between surgery and radiation is statistically significant and clinically meaningful. However, for the remaining 75 percent of men who had less-than-perfect baseline function, their 3-year scores are about the same, whether they had surgery or radiation. So, the bottom line is that sexual function differences are not clinically relevant for all men. And baseline function should be considered when individualizing a recommendation.
What happens to bowel function? It takes a small, but clinically significant dip in men who get external beam radiation therapy, but rebounds in large part after the first year.

Similarly, with hormone therapy you see a small, but clinically meaningful dip in their hormone domain score within the first year to 18 months, but it recovers and is comparable to active surveillance and radical prostatectomy patients thereafter.
What other outcomes? General quality of life. we saw no difference between treatments. Disease-specific survival, no difference between treatments. In fact, there were only three prostate cancer deaths in this 3-year follow-up in the whole cohort.

So, in summary, we see that radical prostatectomy is associated with higher rates of urinary incontinence than with external beam radiation or active surveillance – a moderate or big problem reported by 14 percent of men who underwent radical prostatectomy compared to 5 percent for EBRT and 6 percent for active surveillance. Radical prostatectomy is associated with a small improvement in the irritative urinary symptoms and is associated with a higher rate of sexual dysfunction compared to external beam radiation therapy or active surveillance. However, again, the difference is significant only for men who started out in the highest quartile of baseline
sexual function. EBRT is associated with worse bowel and hormonal outcomes, but that appears to be significant only in the first year. And we saw no differences in general quality of life or survival at 3 years.

In general, despite technological advances, our treatments still have significant side effects. Baseline function and treatment are the strongest predictors of 3-year functional outcomes. So, we really need to consider the baseline function and patient preferences when individualizing a treatment recommendation. Men with poor sexual function at the beginning may not prioritize their sexual function outcomes. Men with bad BPH symptoms may prioritize having that alleviated and so forth. One interesting point we found is that population-based outcomes in this study particularly for sexual function appear to be worse than those reported from single center or specialized multi-center series. This raises a question whether those single center, multi-center series may have some bias in them, but it also raises the question of whether we ought to consider referral to specialty centers or experienced providers to try to maximum those outcomes. And, finally, and probably most importantly, the bottom line is that our treatments have side effects. And, so, in patients where the disease is not expected to progress within their lifetimes we should strongly consider active surveillance for those patients in order to preserve their function.
Now, finally, what are the implications for shared decision making? The CAESAR Study, along with the NC ProCESS Study provide data to inform the comparative harms of contemporary treatment. So that one key component of the shared decision-making process we now have very good and clear data to guide men in that regard. However, we also need to be well informed about the comparative effectiveness data and be facile in explaining the nuances and limitations of those available data. We need to be able to elicit the patient’s preferences and priorities and engage them in the process. We need to be able to communicate effectively. And we need to individualize treatment recommendations based on those factors. You can consider using the available online tools, some of which are listed here.

And, finally, I just wanted to thank and acknowledge my co-investigators from the Vanderbilt coordinating center and the CAESAR site investigators. And I also wanted to thank the folks at AHRQ and PCORI for sponsoring our study. Thank you very much.