Hello, my name is John Davis. The title of this talk is “Prostate Cancer Survivorship: Surgical Management of Prostate Cancer and Late Effects of Surgery.” We’re at The University of Texas MD Anderson Cancer Center, where I’m an Assistant Professor in the Department of Urology.

There are three key objects to this talk: one, is to discuss the surgical treatments for prostate cancer; two, is to compare the outcomes according to surgical techniques including quality of life measures; and then, to review the MD Anderson cancer experience.

So where shall we start? With --- guidelines are certainly a helpful way to introduce a topic. So the American Urological Association has a --- a basic guideline consensus statement and to clarify what we’re mainly talking about today is patients who have undergone mostly cases --- PSA-based screening, and ultimately leading to a biopsy and were found to have clinically localized prostate cancer. So if they have metastatic disease, that’s a different topic, of course. But for the majority with screening that have clinically localized disease, the AUA recommends categorizing treatments into standard therapy versus alternatives. So the difference is mainly in the quality of evidence and the length of follow-up. So three standards have been identified, with the most robust follow-up that includes surgery, and they don’t spec --- specify the technique currently. That includes radiation and, again, that sort of is a broad group includes external radiation, BT or brachytherapy and then of course, watchful waiting. Now, alternatives could be cryotherapy where you’re freezing the prostate or --- and this is not FDA --- a non-FDA program called high intensity focused ultrasound. They do state, however, that for patients with localized disease, in the vast majority of cases, primary hormone therapy without localized therapy is really not advised. So going back up top really to focus on this talk, we’re going to speak from the viewpoint of the surgeon who is evaluating a patient, what sort of data should --- they’d be looking at. Obviously, there’s whole separate topics on which patient should undergo radiation and watchful waiting. So I’m mainly going to focus on surgery, that’s the most common version, and some comments on cryotherapy because that is FDA-approved and available in the United States.

So this is a slide that one of my colleagues in medical oncology generated and it --- it’s got some important themes. Its --- It doesn’t really make sense when you stare at it. But it’s the idea of what happens --- what would happen if you took radical prostatectomy and evaluated it like a drug? Meaning, you’d look how often is the drug actually needed and successful? How often is it needed and unsuccessful? How often is it not necessary? Or how often is it necessary but futile? So these are not from one study. These are pulled in from different studies. But if you look over here at this table, there’s four concepts. The idea of a true positive is when someone has clinically relevant disease and prostatectomy works. So this could be sort of summarized from the Swedish trial randomizing surgery versus observation. And you see that there’s a measurable benefit over --- over time. Now, true negative kind of
comes from this graft to the right that’s basically showing that there’re patients who failed surgery, but undergo salvage radiation therapy or immediate postoperative radiation therapy, and can --- compared to observation, can experience durable responses. So if you just think about this in the big picture, this means these patients were curable up front. Surgery didn’t do it alone but the combination did. So that would be a true negative. The surgery itself was not successful, but clearly it was relevant disease and there’s room for improvement. Now, unnecessary, that --- again, that’s sort of a made-up figure on a variety of studies and that figure could change. But the idea that surgery can be unnecessary and efforts to re-screen and re-evaluate patients and put them on active surveillance when appropriate wa --- is certainly relevant. And futile is another kind of interesting concept. Certainly, there’re people that undergo screening and treatment, and still fail surgery and ultimately die of prostate cancer. There’s a growing role, we feel, for surgery in this category but often it’s going to be later coupled with systemic therapies and a lot of the novel cancer drugs. So that’s one of the perspectives up front of thinking about surgery.

Now, a major problem the surgeons have when then sitting down with an individual patient and coming to recommendations is how good is our evidence.

Because a common question that a patient would want to know is whether or not they want an open or robotic procedure. And these little hash marks are meant to indicate that really is no randomized head-to-head comparison, so it’s --- it’s an open question. And people have tried many ways to study open or any type of surgery versus radiation. There is a trial in the United Kingdom underway that may shed some light on that. But even in a head-to-head comparison, this is an open question.

So often the surgeon is looking at, you know, lesser forms of evidence. Now --- And again, if you had to go back to the AUA guidelines I mentioned, it’s interesting that this document that’s over a hundred pages really centers on a handful of randomized studies. So there is a study of radical prostatectomy versus watchful waiting. There are studies of radiation where they look at different dosage, and often higher dosages are more successful. And there are trials that look at radiation specifically for intermediate to higher grade cancers where if you add hormonal therapy to the mix, the cancer-free and overall survival figures can be improved. But here’s the bottom line of the AUA guidelines that despite medical advances there’s emerged no consensus regarding the optimal treatment for the most common patient with prostate cancer. And currently, comparisons among the treatments are not possible for the purposes of rendering a single superior treatment. So often patients are counseled, and yes, sometimes the doctor can pull out a few medical situations that may point the treatment in favor of one over the other. But often it’s a combination of patient preference, and you know, sometimes it’s just a random distribution.

Now, what else is relevant to discuss? This question has been open for a while about whether or not open versus robotic prostatectomy would be the --- the question to answer for patients choosing surgery. This has become more surgeon-dependent and I’ll show you some excerpts from this data. And often the head-to-head data that’s not
expert --- that's not randomized is often looking at high-volume experts. So you look at the highest quality open surgery versus highest quality volume robotic surgery. The alternative, and this is --- if you had to like really categorize the literature, you'll see really two major sets of outcome studies. One is expert versus expert. The other is administrative dataset. And what's relevant about these two? In expert datasets --- datasets, often the --- the chief surgeon and author is the one in control of the data and they often have very high quality detailed data. The --- Those are the patient that they've operated on and follow. So there's often very robust follow-up information and lots of interesting hypothesis-generating facts in those studies. And often, you know, the surgeons are, of course, identified by the study. Now, occasionally, you'll have handfuls or small collections of experts pool their results and that makes it more of a heterogenous surgeon subset to look at. But the other one you see more and more of is what we called administrative datasets. And that's where you look at large data collections systems --- systems that, quite frankly, are generally designed for billing purposes often to assist with insurance and claims and payers in the mix. So you often --- the benefit is you often have access to tens of thousands of patients. But you often have much more restricted sets of questions you can answer. Often, for example, these sets of data cannot tell you anything about functional outcomes of prostate cancer treatment. But they can certainly show you how long people are in the hospital or if they had subsequent complications. And then the reality of the patient beyond trying to look at the science of this is the fact that there is a lot of marketing and there's a large company that's, you know, developed this technology. And --- And ultimately, the interesting thing about devices in the U.S. that I --- I observe is that the FDA approves devices based on safety, whereas they approve drugs based on efficacy. So if --- if a company makes a robot, they have to prove it's safe, but they don't have to prove that it's superior to open. Often, if you're trying to get a drug approved, you have a much higher burden of evidence and consequently the companies have to raise significant dollars to fund very high quality comparisons. So what's developed out of this that I'll go through is what I'll just call agenda-based. A surgeon who doesn't have access to high quality data to answer these questions often just has to set an agenda of what do you want to fix. So patients, if you ask them what're --- what are their goals of treatment, they're going to resolve or mainly center around cancer control, maintaining good bladder function, maintaining normal sexual function. So the surgeon has to figure out strategies to improve all of these over time and to move the field forward.

So in --- on terms of optimizing outcomes, we want to look at someone's personal experience, training as well as technique. Because this is actually relevant. If --- if only a handful of surgeons can deliver very high quality surgeons and the rest are moderate to lower quality, then the overall effect of surgery gets very diluted. And that's back to that sort of drug analogy we started with. Ideally, every patient would get the same quality treatment, just like theoretically if they all take the same pill, they get the same effect. In my view, there's a very fine body of work from Peter Scardino and Andy Vickers at Sloan Kettering in New York, that have really shown that the higher volume a surgeon is and the higher volume a hospital is, then the more significantly improved their outcomes are. It does show that the radical prostatectomy when performed open, has a very steep learning curve and not all surgeons with an average volume can
meet that. So an open question is whether or not robotics is an effective strategy to level the playing field to improve the quality of surgery for a larger number of surgeons since the high volume experts practically can’t do every single case in the country, although many of them try.

So why --- in terms of generating a hypothesis, why is a robot better access? Well, the male pel --- pelvis, putting small 8 mm instruments into the pelvis and using a three dimensional camera provides significant advantages of seeing the anatomy and having very high quality instrumentation that can articulate and flex. And I would almost argue that this is not an outcome statement. But in terms of access to the pelvis in doing complex surgery, the engineering part of the robot is superior to open. And you almost can’t argue the point. If I --- When I have a patient in front of me, I usually give the analogy that if you hold an instrument that’s 18 inches long and hold that into the pelvis and expect to do a complex motion with your hand or wrist, compared to a robotic instrument, where the tip, if you can see my pointer over there, that’s --- see how this instrument can flex within only a centimeter or two of the tip of the instrument. So you’ve got tremendous ability to articulate and do complex motions. So these are the standard, you know, purported advantages, a robotic three-dimensional camera. Everything is stabilized and tremors are eradicated. And you can zoom to whatever degree or --- you --- you want to see. If you really want to hone in on the anatomy, you can, or you can back up for a broad view and you don’t have, you know, people crowded around a small incision with heads and headlights in the way. So that’s the --- my opinion on that.

Now, this is kind of what the general setup looks like for those who’ve not been in the robotic room. You have an operating console that the surgeon sits in front of. You have a tower of these instruments and the --- really the power of the robot is that the computer manipulates the inside of the instrument so that it moves exactly how the surgeon outlines in his motions in the box, and then instruments sort of basically comply with his arm motions. Using these foot pedals, the surgeon can basically move the instruments around as well as the camera and control a vast majority of the case. Now, in almost all robotic cases, prostate or not, there’s generally a patient-side surgeon who helps set up the robot, insert instruments, and often holds a couple of what we would just call assistant laparoscopic instruments to move the case along, hand them needles, suction, that kind of assistance.

So this would be a postoperative or immediate postoperative view of prostatectomy. This is the umbilicus here in the middle. This patient had a very large prostate so that’s about as large as these incisions are made. You just make it as small as possible to pull the prostate specimen out in a protective bag. These are all little 8 mm puncture wounds where the ports were inserted. In a --- In a gentleman like this, all this hair will regrow and these incisions will regress and be very low profile. The alternative is --- is depending on the surgeon, you’d make an incision here and extend it straight down here, and insert a retractor system for exposure.
So one the questions patients and other users always ask is, what about tactile sensation with robotic prostatectomy. I find this an interesting debate because in the pre-laparoscopy era, men we’re really --- robotics is really the second attempt to refine the prostatectomy operation. There was open as the standard. Then, there’s laparoscopic with hand-held instruments and then robotics after that. But before laparoscopy, most open surgeons agree that feeling the prostate anatomy in the middle of a surgery is not a very accurate staging system. For the --- For the most part, the surgeons would use nomograms and imaging. Mainly, you would either do an MRI exam of the prostate or you would just look at their clinical features of their biopsy and PSA testing to determine whether or not you felt like you could do a nerve-sparing plane or an alternative. Now the robot does provide resistant feedback. Meaning that if you push into anatomy or you grab an instrument, the hand controls give you that resistance and your mind is, of course, viewing this very enlarged anatomy, so your brain learns to basically make good substitutions. And the outcomes support this. In many hospitals, they’ve looked at palpable tumors with robotic or open assistance. And basically the outcomes of margin status are the same. So and ultimately, how can much can you really feel through a gloved finger? So there are many surgeons, myself included, that do all these cases robotically. Some will go back and forth. And there’s a handful that still prefer open surgery. When we designed this lecture, there was probably a 50-50 split. In recent months and years, it’s more like 70, 80% are done [in the] U.S. robotically. So ultimately, PSA is mainly a localized disease. The point here, that with PSA screening, we’re looking at smaller and small volumes of tumor in many cases.

Now, what about cost? Now, it is true that if you look at the purchase, the capital acquisition of a robot, it exceeds two million for the most updated equipment, with upwards of $200,000 a year of maintenance. There is --- I mean, I just find this interesting. There is what I would call the logic of distraction. There’s extra money involved with robotic surgery. An example that I hear at lectures on campus here – as we’re in Houston, where we have NASA, NASA spends three billion a year on space exploration but, you know, the country spends six billion dollars a year on Halloween. So it’s kind of an amusing anecdote. That it just depends on what you’re comparing to. So yes, robotic surgery costs another thousand dollars to $1,200 per case but if you look at what’s spent on drugs for advanced cancer or even the Proton Center incremental, then you’re talking about multiple orders of expense larger. Some of the advanced prostate cancer drugs are $100,000 to extend life by a handful of months. This technology, you know, per patient may upward be --- be upwards of $1,500 per case for potentially curative therapy.

So it’s difficult to get much deeper than that into cost. But this is the, you know, raw data. If someone asked how much would the any --- any of these technologies cost if you were paying cash in the door, proton radiation approaches $100,000. The standard IMRT is give or take, $50K. Robotic assisted is around $40K. The cheapest, actually, is the seed implantation which is going to be perhaps in the $30,000. But sorry, 30 --- yeah, $30,000 per case. So, for robotic surgery, again, depending on the year, it was 1.8 million purchase, a hundred to $200 of maintenance, and then the disposables. Proton is 200 million to purchase, 12 million dollars a year in maintenance. So cost
needs to be carefully monitored. But sometimes, that’s the price of getting new knowledge.

And ultimately, a lot of this is an assignment of value. For example, proton is $100,000 mainly because we’ve decided that that’s how much we’re going to pay for it. Robotics is more expensive, but part of this is about the it --- it is a monopolized company. So there’s only one vendor. They do have instruments that are programmed to basically expire after 10 uses, when they actually are still functional. So who knows, there may be incentives to decrease costs when there’s more competition in the marketplace. So ultimately, I --- I think what’s lacking, you know, from my perspective is often an --- an equivalent to what we call the relative value unit. It’s very difficult to put a metric on how productive physicians are in the office. So the relative value unit is meant to neutralize that and talk about work units rather than how much someone charged or how much someone was reimbursed. And you could do a similar with the cost of therapy. How much is the actual resource utilization? Yes, robotic surgery utilizes resources not only at the machine and the maintenance, but any surgery is going to require a surgeon, an assistant surgeon, an anesthesiologist, an OR team, you know, for anywhere from two to four hours. So you have to measure that against the cost of someone going to a radiation center for 40 treatments. It’s all going to be expensive but does need to be looked at carefully.

So as a practitioner working with patients, while monitoring costs, of course, we need to focus on what’s right in front of us and what we can hopefully make a difference in. That’s, of course, cancer control, optional [speaker meant to say “optimizing”] functional outcomes, minimizing complications, enhancing training and then, quite honestly, I sort of leave costs aside for the time being.

So my overall pro --- proposal has been to go through that personally. And you can measure some differences. So for example, this is actually me around 2001 training here in open surgery, again, with the headlight and magnified loops and, you know, me and the professor around the incision. To get to this point, I, of course, did a urologic residency where I assisted on 50 procedures as a resident, a hundred more as a fellow. These operations typ --- typically took four to five hours, the blood loss was about 1,200 cc – many patients were asked to donate ahead of time. We would leave one to two drains in place. As a resident, we left the catheter in for three weeks. There was a lot of non-nerve-sparing surgery because we were dealing with larger volume tumors. And often, there were many moves that as a trainee I could not see. It’s hard for me to demonstrate that point on the picture but maybe --- I mean, you can’t see the anatomy but I’ll tell you that standing where I was, there was half the operation I couldn’t see either. And we often did very brief lymph node dissections. I’ll come back to that, about what we’ve done with robotic surgery.

So again, when we compiled a lot of data for this study in 2010, what I’ve done as a faculty member, you know, basically forwarding almost a decade ahead, the prostate itself only takes about 60 minutes. The fastest I’ve ever clocked is 45 minutes and, you know, if it’s difficult, it can take two hours. The extended lymph node dissection’s
around 30 to 45 minutes now. But these patients stay one day in the hospital. A select group of patients we can do in a pre-peritoneal approach and they may may go home the next day. We leave the catheter in for only seven days unless they leave the state. And we may be drag in a couple of extra days just so they don’t have a risk of urinary retention. But now, the blood loss is a median of 200 cc, only a half percent are transfused. And I don’t have it on the slide. But I would say the other interesting thing about open surgery was that if the average was 1,200 cc, the range at the best hands often was only 500 cc, but in a really difficult case, could be over 2,000 cc, with intraoperative transfusions. The blood loss robotically is around again, a median of 200 but the range is very tight, meaning in good cases, it’s 100 and on difficult cases, it’s maybe 400. So they really don’t get close to the transfusion threshold. Overall, we still see about 1% major complications and about 4% minor. Major would be anything that was preoperative or requiring invasive radiology, or was a major medical event, such as a vein thrombosis or cardiac event. We do a lot of these cases on aspirin if they have a cardiac history, and I think this result is probably under 1% now. But there are minor complications, minor infections, having to, you know, deal with the slow GI or gastrointestinal return, that kind of thing. Also, what’s changed is that the --- we do consent the patients that the robotic occasionally fails. We’re now on a third generation machine. The original would fail maybe 2.2% of cases, the second generation less than a half, and probably the third generation similar or better. And --- And basically the risk to the patient is generally very minimal during the surgery but there is some risk of being rescheduled if you’re the next case. So the idea is that in the middle of a case, you might have a problem with an arm, but like a computer, you can reboot the system and often finish the case. Afterwards, of course, the technicians are going to have a look at it. And they may want to replace something and not let you do the next case unless you have an extra robot not being used. So occasionally, there is some inconvenience, but it’s much less than it was even four years ago.

So obviously as we’re looking at our own data, we often look at other people’s publications and pull excerpts from what we find interesting. Henry Ford in Detroit published a large series of over 2,000 cases in 2007. And this was one of the earliest institutions that made the leap to robotic surgery. Overall, for example, they saw that if the cancer was contained, so, in nomenclature, that’s pathologic T2, 13% had positive margins. If the patient had what we would consider favorable sexual function or --- or erectile function and on a 25-point scale inventory, 25 being perfect, if they were greater than 17, then the post-op success was around 80%. They had 93% of patients having one pad or less a day. The median time to control was actually a fairly impressive three weeks. Now, another colleague that we know well, David Wood, looked at a --- a good experience of his own open surgery versus robotic. He didn’t see any specific time increments to activity, driving, or pain at two or six weeks. So, again, some --- some of this looks favorable, some looks neutral. But on the other hand, at Vanderbilt, another very high-volume center, they made the switch from open to robotic. And they saw positive margin rates go from 9% down to 24%. So there’s multiple different endpoints to look at and kind of a mixture of conclusions.
Again, this is back to the concept we introduced earlier where you can look at disease experts, their own series versus administrative data --- datasets. So one publication that came out of JAMA by Jim Hu was published in JAMA, 2009. And here’s a study that I’ll just compare from Tina Shih who was at MD Anderson, she has since left. But she put together a nice study that is now out in Value Health, 2012. They both looked at large insurance and other billing-related datasets to try to get a handle on what’s the difference between open and robotic surgery, not between experts, but when, you know, hundreds of different surgeons are being looked at. So the Hu study is a Medicare dataset. So by definition, it’s a little skewed because the patients have to be 65 years and up. By contrast, my median age for my patients is about 60, having surgery, so me --- more than half of them are less than 60. But they looked --- they saw that the utilization of minimally invasive prostatectomy during their study period, basically in the last seven years, went from 9% to 43%. Hospital stays for robotic were about a day shorter for robotic, two versus three. Transfusion was 2.7% versus 20%. Complications, you see, was a percent or so lower. Urinary strictures or scarring of the urinary tract was 4 --- 5.8% versus 14% favorable to robotic. And where the study got a lot of headway was the fact that in terms of just coding office visits, they showed a slightly higher rate of incontinence and erectile dysfunction with robotics. Now, that --- that actually translated into a lot of media’s coverage including New York Times, showing that the robotic surgery had some advantages but not with sexual function or uri --- urinary function. Now, since that’s been published, even a high-impact journal, most experts would say that you really can’t look at billing codes to substitute for function. You really have to do survey studies. So those studies are clearly underway and --- and, you know, I’ll show you some examples of what we’ve seen but I think that higher quality studies are needed. Rates of radiation are basically the same and tha --- that’s a bit of a deeper topic because they don’t all represent treatment failure. Sometimes, that’s just adjuvant therapy for risk and doesn’t --- it’s not really a measure of quality like it --- it would, but another day, another lecture. Now, in the MD Anderson review, again, we looked at insurance data set that looked at all ages and, again, the utilization of minimally invasive went from 5% to basically 50%. Again, shorter hospital stays, fewer complications, fewer strictures, and we basically didn’t think we could evaluate functional status. We did show less radiation use after robotics but, again, that’s not a hard indicator of quality anymore.

What was interesting, I won’t go through every piece of this, I’ll just summarize it. If you want to study, you can, or --- or refer to Dr. Shih’s full manuscript. But the idea is that on day one of a robotic prostatectomy versus open, you spend more money on robotics. But when you calculate all the costs of taking care of complications and hospital stay, by the time you get out to three and six months, then the cost is neutral and per --- perhaps even favorable to robotic surgery. So that would be favorable to the payers involved in the care even if the hospital pays more disposable cost in the capital expense up front.

Now, let me just turn on topics. Now, back to the idea of technique improvement as well as training, And I think what is needed, again back to the model of turning the operation into sort of a drug model where it’s very codified and --- and, you know, you write down
what you’ve done and you try to tweak it and improve it over time. So what we do for
training and for internal monitoring is to basically break the operation down into 11
different steps. For each one, you state the objectives of the step. It’s usually getting
access to the prostate, of course, dividing the bladder connection, the urethral
connection, the nerve bundles, then suturing everything together, and then the lymph
code dissection. So each of those steps gets described when --- when it starts and
stopped, what are the allowed motions. So one of the important concepts of any nerve-
sparing prostatectomy is to really avoid two sources of trauma. One is heat. So
there’re various thermal energy devices that seal blood vessels, so it’s a very ---very
well vascularized organ. But if you used cauterized heat near nerve bundles, then you
get nerve damage and you get poor sexual function. So we usually use clips or sharp
division and sutures. So that gets codified about how you --- how you’ve done those
parts of the operation. More and more, we’re appreciating the fact that we need to
reduce tension on the nerve bundles and that’s --- that’s a more recent objective. So
we codify the instruments, what --- what --- what to avoid, how much time that should
take, what’s the expected progress of a trainee. Ultimately, if you’re going to train
surgeons, they need to demonstrate proficiency, not just that they’ve driven the robot
around a little bit and done introductory steps several times but that they have multiple
skill sets. I mean, you could really I --- I --- in my mind, I think of four skill sets. One is
just basic driving the robot, one is more advanced dis --- dissection skills. Then, there is
suturing and then there is recognizing the correct anatomic planes. So part of training is
learning all four of those and getting proficient.

Over time, of course, we try to codify modifications to each step and why they’re
significant. So for example, you can take one step. You can actually codify how long it
takes now. How long it takes a trainee. And they generally take, you know, upwards of
50% longer. What’re the rules? What’re the objectives? So for example, even if you’re
getting around the prostate in --- in the pelvic fascia plane, you know, a very detailed
step, there’re ways to do that to try to release nerve bundles early, to try to protect them
from cautery as well as from stretch. So if you can do that successfully and teach that,
then hopefully the quality of the operation goes up.

This is a good slide just showing the multiple zones of anatomy that the --- the prostate
surgeon has to master. If you look at the --- this is a cross section. The prostate glands
are here in the middle in the tan. The urethra runs right through the middle. The purple
line basically shows the idea of the capsule of the prostate and some of these tumors
are right up against it. Here in the corner is where the nerve bundles are. And then this
green line would be sort of the fascial covering of how the surgeon gets into the plane.
So if the patient has locally advanced cancer, the surgeon may plan, you know, to take
a very wide margin out here. If they have a very favorable early stage cancer that still
needs therapy, then you may come through this green layer all the way to the purple
layer and try to spare this nerve bundle even as it’s sending arterial branches towards
the prostate. This is more of a surgeon’s view, looking from the side, where you see the
rectum below. And you see this cutout window that’s meant to just display how the
surgeon has to get through multiple, almost like onion peel layers to get down to the
capsule to identify all these vessels penetrating in. And then, here you see the yellow
nerve bundle line that has to be sort of released and pushed gently out of the way as the prostate gets pulled up. This diagram, by the way, is a very famous diagram from the Brady Institute at Johns Hopkins.

So here’s some estimates of outcomes that we’ve encountered. So when we look at open prostatectomies at MD Anderson from ’02 to ’07 with multiple surgeons, we’ve looked at laparoscopic when that was done for about three years, and then the initial two years of --- or really three years of robotic surgery from two of the higher volume individuals including myself and then Surena Matin. So for organ-confined disease, open surgery has about 10% positive margins, laparoscopic was 13%, and robotic was 7.4%. If you looked at my best year in the study or more recent, it was 3%. So these can improve over time. The laparoscopy is a little bit --- bears explanation just because not only was it a new technique. But it was a new surgeon in first years of practice. And even in open surgery, some of the doctors in the earlier practice may have slightly higher pos --- positive margins, but with plenty of high-volume users, that was the average.

Now, if the cancer is not contained to the prostate, it’s about 25% positive margins for all of the modalities and a lot of that is driven by biology. And I’ve seen numbers like that in almost every series published on the topic. The location of the positive margin is generally equivalent. So both the open and the robotic surgeons, it would seem, have good access to the apex, which is the farthest removed in the anatomy versus the bladder that’s easier to get to.

Now, in terms of lymph node dissection, this is another part of the operation that has changed over time. And if you can focus in on this diagram, this is sort of a cutout as if you were --- if you had half the male pelvis and you’re looking at it from the side. So this would be the aorta or the major vena cava aorta coming down. Now, this line coming over is the ureter. It always crosses over the common iliac artery. Then, as you really get into the true pelvis, then the artery makes a major split, so the external iliac vessels go through the pelvis. And they’re on their way out to the leg. Then, there’s an internal branch that basically dives deep into the pelvis and it --- and it feeds all the pelvic structures. It used to be that prostate surgery involved sampling the lymph nodes where you see the --- the Roman numeral I and these were just a common --- we called it the obturator fossa. You could spend 10 minutes plucking out lymph nodes in here and that was considered a lymph node dissection. Then you would proceed on with the prostatectomy. Now, then, some surgeons mostly in Europe and Switzerland, for example, started doing a more detailed lymph node dissection and mapping it. So if you see this dotted line, you can see that there’s a Region II that incorporates the hypogastric. Now, there are --- if you really made the whole operation into a cadaver plane, you know, you can identify other areas. But in --- in summary, if --- if you go to Region I, you’d probably only get about get about 25% of the drainage of the prostate. If you do I and II, you’d probably get about 75%, according to one study. So adding this --- this region significantly improves the capture of possible lymph node drainage from the prostate. And what these authors found is that your --- your positive lymph node rates went up significantly, and about a third of positive lymph nodes were only seen in
this region II. Believe it or not, that actually anatomically makes sense because these are the lymph nodes that are anatomically the closest to the prostate and theoretically the tumor has to go through here to get up to Region I. Now, Region I is easier to do. So it’s been done commonly. But we worked at it here robotically and feel like we’re making good progress at doing a good Region I and II lymph node dissection.

And here’s some samples of what we found. So if we looked at a cohort from early in robotic experience that had standard nodes versus 150 extended, well matched for PSA and Gleason score and staging, then we had about eight lymph nodes harvested from standard and 17.4 extended. So you roughly doubled your lymph node count. And then the percent positive went in the higher risk patients from 6.8% to 20%. I don’t think I have this on a slide specifically. But if you look at individual risk groups, the patients with the highest risk cancer, the positive lymph node rate actually approaches almost 40%, whereas it used to be, you know, say, 6 to 8%. So you’re getting more nodes and more positive nodes, and perhaps learning more about the biology of the disease, perhaps improving outcomes that will require longer study.

So I mean, this is sort of a flow chart of when we apply this --- this extended lymph node dissection to a --- a prostatectomy operation, specifically in the context --- context of high risk prostate cancer. So these are patients with Gleason 8 to 10 on the Gleason score or PSA over 20. And a handful of them have just advanced stage when you examine them. So we looked at a hun --- the first 118 and here’s your initial split between the cohorts, about 30. Again, this --- in this case, it was 36% had positive lymph nodes or N1 staging, whereas 64% were negative. So already you’ve --- you’ve made a major division between patients with sort of potentially early metastatic cancer versus hopefully organ-confined or at least regionally-confined disease. Now, if you follow out the lymph node positive patients, yeah, some of them have organ-confined primary stage or maybe they don’t. And --- but the idea is that most of those patients you’re going to observe and you’re going to give hormone therapy basically in response to their PSA over time, their velocity, that kind of thing. The role of radiation for this population is a little bit less clear. If they’ve got extensive positive margins and we feel like they need local control, sometimes we’ll add that. But many of these patients will just be observed and --- and basically be treated appropriately with hormone therapy to prevent metastatic progression. Now, if they don’t have lymph node involvement, then you see about 40% are still contained to the prostate. So we still think many of these patients could be observed. There’ll be some relapses, but reasonably good cure rates for surgery up front. And these patients generally have not had to have systemic therapy. Now, some will have extra-prostatic disease with high-risk and with negative margins and, you know, that’s debatable whether or not you give radiation, adjuvant versus salvage. What’s more clear is there is obviously a cohort of people with extra-prostatic disease and positive margins. And in those cases, many of them should really strongly consider adjuvant radiation. But observation with early salvage is a --- is a --- is appropriate as well. So you can see how the --- the surgery not only is potentially curative. But the lymph node adds a lot of downstream information that helps sort of direct traffic and make long-term disease decisions.
Let’s summarize briefly about the --- the quality of life parts we’ve looked at. Now, we believe in the --- the method of using survey-based instruments. It’s not the perfect assessment. But it has been validated and published many ways. And basically the idea is that the patient fills out their own assessment of quality of life using questionnaires that have been, you know, carefully studied and have metrics of their performance. So the one that we often use was developed, the --- the initial one was done at UCLA in California. And then a group in Michigan kind of updated it to be more applicable to multiple treatment choices. So this is called the EPIC and it's basically an expanded prostate cancer index. And the major domains rel --- related to prostate cancer, of course, are urinary control, bowel, and sexual function. So it's --- you know, in our practice, we do have a very regional and national practice, some internationals. So we have plenty of baseline data, but obviously over time, we have fewer patients. We’re adding to this mix and we’ll probably be able to double all these numbers in the next few months. But as an early look, and we look at urinary control, that’s important to just learn about what you can learn in urinary con --- control. It’s not all about incontinence. It’s also about how much the system bothers them. How much there’s irritative or obstructive symptoms. So in the scale results, the way its set is 100 will be perfect and zero would be the worst. Okay, so higher numbers are always better. And these numbers are actually very typical for people with or without prostate cancer who are over age 50. They typically have baseline scores of 80 to 90. Obviously, they go down at six weeks and they recover up towards a year. If you look at specific scales, notice that their irritative/obstructive numbers baselined at 87, they went down to 80, but then they go up to 90 and 92. So the idea is you’ve removed prostate tissue; the urine flow generally is stronger. Then there’s a follow-up study that’s published in the New England Journal of Medicine by Marty Sanda that nicely shows that men with bigger prostates actually do potentially have a significant improvement versus those choosing radiation. If they've got normal function then, you know, maybe that’s not a deciding factor. Now, incontinence, of course, they baseline at 91. They do have a six-week deficit getting cut in half and then they recover up to 84 in this case. Now, we consider, and some experts have put out the notion that if --- if two different scores are less than 10 points apart, there’s probably not a major clinical difference between that. Even, you know, if you study enough patients, you can always make these statistically significant, but can a patient tell a difference between 84 and 90 or 91? Probably not. So for bowel function, you can look across these numbers. We almost ought to stop looking. For surgery patients, they basically have minimal baseline or follow-up differences. Obviously, that’s an important thing to study for radiated patients but less so for surgery. Now, for sexual function, it’s interesting that on the baseline score, the average score coming in the door is 60. Its 55 if you just look at function. And, yes, they go down by more than half to 20. And they recover up into the 30s. Now, if you only look at the higher baseline functions of 70s, they will recover up to 40s. And these patients, you know, some of them are se --- are sexually functional. Others do will --- will just say that it works but not as good as it used to. Clearly, surgery does have sexual side effects unless you really tease out the youngest patients with the best function and can spare both nerve bundles. So we do --- we try not to overstate or oversell the concept of --- of sexual dysfunction after surgery. It is a risk and has to be weighed against the alternatives of observation versus radiation and the like.
So what’ve other people published? Steve Frank in the Radiation Department just looked at all comers from different modalities within the first five years. So it was kind of a --- a after-the-fact idea so we did not have pre-treatment function. But if you just looked at the first five years, the brachytherapy patients had an average score of 37 for sexual function; radiation was 28; surgery was 25.

Noted that in this study, it was higher, so it was 32, then 40 for a good baseline. So it just depends on which subset you’re looking at. It’s always the point of these numbers here. And again, control populations. So that the sexual function obviously has a lower baseline score out of 100 in on --- on --- on the way they ask those questions.

Now, another different topic is, of course, complications, and this has become --- it’s interesting, we’ve always tracked complications. But I’ll just add a caveat to this slide. Recently, the --- there’s a what we --- they call the U.S. Preventative Services Taskforce and they’re charged with looking at all types of screening and prevention programs, weighing the evidence, and writing guidelines for --- it’s supposed to be for clinicians. You know, there --- there --- there is some language and debate about whether or not those guidelines translate into public policy. But they did release prostate cancer guidelines. They gave it a D rating for PSA screening indicating that they didn’t see a benefit. That’s been very controversial and in --- in the opinion of most of the experts at MD Anderson, we would give it a C recommendation, meaning it’s beneficial for a subset of patients. That’s a bit outside the scope of the lecture. But it was interesting that when the guidelines put together not only their analysis of the randomized trials of PSA screening. But they also --- they really divided into four questions: What are the benefits of screening? What are the harms of screening? What are the benefits of treatment? What are the harms of treatment? So when they looked at what are the harms of treatment, then you --- you arrive at looking at detailed complication rates. And they looked at some old studies and quoted that one in 200 patients who have a prostatectomy die within 30 days of the operation, 0.5%. And you know I went and there was three citations, I looked it up and, wow, I was shocked. Yeah, a half percent in those studies. Now, there’s newer data and in expert hands, I’m going to say that the --- the true rate’s probably 0.05%. So it --- there are --- whatever is published is valuable to study but, you know if --- if experts really put their minds to it and look at specific ta --- changes, not only in the procedure, but in patient selection, we should be able to improve these numbers. Why do I --- And, why do I do that big aside? Well, if the incremental value of screening and treatment is small, in the sense that if you have to screen a large number of people and do a large number of surgeries to save cancer mortality, then you certainly can’t have treatment mortality. Every wh --- every time you have that, you’re undoing --- first of all, it’s a bad event. Second of all, you’ve really destroyed the metrics of the benefit of PSA-based screening and treatment. So we looked at the initial robotic series here: Overall, 8.4% complication rate, 2% major, 6.4% minor. No mortalities, which I’m happy about. But, over time, you could make major complications go from 5% to 1.3% when you looked at the first 100 versus the next 400. You could make minor complications go from 14 to 4.5%. If you went and reviewed each and every complication, you would estimate that, in this case,
45% of those complications led to a specific change in technique or selection. And sometimes, they’re very simple. I mean, one of the early deep venous thrombosis cases we had, when we interviewed the patient, we discovered that he got in his car after surgery, with his wife, and they drove to Arkansas in one stop, without stopping to stretch their legs. And when he got there, he had a swollen leg and had to be treated with blood thinners. You know, five years later, he’s alive and well. But since then, you know, we --- part of our written discharge information talks about not being immobilized for hours at a time and obviously we follow all standard guidelines in terms of preventing deep vein thrombosis with embolism stockings. And if they have specific risk factors, maybe they’ll have Lov --- Lovenox. There’re other changes to suture technique, to patient positioning, multiple ways to try to move this down. And I would say the other big impact in the --- in the subsequent, you know, basically a thousand patients after this cohort was analyzed, which show that again --- if patients have a cardiac history, stents in place, that kind of thing, we just leave them on aspirin and we’ve really not had cardiac events in the immediate post-op period. So that’s --- all those metrics and I think they’re very valid.

Now, another topic that I don’t have detailed slides for this talk would relate to simulation and training. We certainly don’t want new pilots that get off course.

And --- And, there are new products on the market. This is actually a robotic simulator device and it’s on my desk in my office. This was tidied up for a picture. If you went there now, you’d probably see papers everywhere. But the --- you know, this is actually the hand grips and the view and the pedals, and they can basically go through simulated exercises. Now, can it simulate the whole operation? No. What it can help them with is how to drive the robot, how to do basic skill tasks, and how to suture. So that can knock off about a third or so of the major tasks to learn. They still need, obviously, formal training on top of that. And as video experts know there is in gaming -- I guess if people in game technology can get into medicine, perhaps you really can simulate more and more of an operation, just like pilots have to do before they, you know, take people on a commercial ride.

Now, I did want to go over some of the data regarding alternative treatments, cryotherapy and HIFU are on the list. Cryo’s the one that’s clinically available.

In terms of patient selection, you know, it’s still considered a localized treatment option with an attempt at cure. The grade doesn’t perhaps matter, but there’s limited data if they have clinical Stage T3. They don’t advocate hormone therapy unless you’re just trying to reduce the size for technical reasons. And there’s no specific large gland cutoff. That’s going to depend on the skill of the --- of the cryotherapy surgeon. And these are summarized data from a Best Practice Statement that, again, the American Urological Association has put forth.

If they have a higher PSA or grade, they would say consider do --- also doing a lymph node dissection, perhaps as a separate procedure. The best results, and what’s mostly published on cryotherapy, are for patients who were screened and have a PSA less
than 10. If they’ve had a prior transurethral resection of the prostate, that’s a relative contraindication in terms of urinary outcomes. And the overall panel of cryotherapy experts that wrote the Best Practice Statement recommended to select patients who either do not want or are not good candidates for an actual prostatectomy operation, generally due to comorbid conditions or obesity or pelvic surgery. And it’s also possible to use for patients who’ve failed radiation. But they would also state there’re some patients who are not candidates for primary radiation. Colorectal disease would be a good example. So then that cryotherapy could be one of their alternatives.

And in terms of oncologic outcomes, in contrast to all of the metrics I just went over, it’s a little trickier to do this on cryotherapy. The panelists wanted to emphasize that you don’t --- you don’t get a surgical result, meaning the PSA doesn’t drop down to zero like it does after surgery. There’s no --- and, there’s --- there’s limited metastasis-free or overall disease-free survival reported. Mainly, we have is, “what’re the odds of the cryotherapy lowering the PSA to a low range that’s si --- that’s similar to the methods that radiotherapists use for looking at their outcomes?” So if patients have low-risk disease, they can --- depending on the definition, they may have 85 to 91% disease control. Intermediate-risks, 70 to almost 80%, and high-risk, 70 to 62%. And these --- they’re just two different published definitions of what’s a PSA failure after a treatment.

In terms of complications, for short-term, they can have urinary retention, some genital swelling, sometimes paresthesias. The fistula rate is now 0.5% or less. That was a major concern until multiple technical generational improvements have been made. Incontinence is --- is kind of the driving factor here. Using pads after this is less than 10%. On the other hand, erectile dysfunction typically is higher, usually more than 50% at a year. And it’s --- most of the panelists would say it’s --- it’s not generally recommended for men concerned with erectile function. If that’s the case, they usually should consider something else on the list. They can get urethral sloughing because of the --- the necrotic effect of the treatment, but most of the techniques would use a warming catheter and that’s usually kept at less than 15%. It does heal but if it occurs, is --- is going to --- is going to be discomforting.

In terms of quality of life, there are --- there’re a handful of comparative studies. Again, they’re not randomized. One from the Journal of Endourology in ’06 looked at five different treatments and overall, you could show that cryotherapy is the same as brachy at six months. With urinary function, they may have slightly AUA symptom scores for irritative issues, and brachy usually does better on sexual function. So there’s some com --- comparison there. Another com --- comparison in ’02, again, shows lower sexual function scores, but no delayed complications. So we usually use it for men older than age 70. They can’t have radiation and it’s one way to potentially have less urinary morbidity or overall complication rate compared to surgery with prostatectomy, open or robotic.

So the conclusions for the cryotherapy, the therapeutic effect is, I think, what’s been established in the literature. But there’s a lack of level 1 evidence. The morbidity profile is clearly reduced with the technology, and there’s upwards of ten years biochemical
disease-free survival published and available. It’s still --- I don’t have it on this slide set, but it still represents maybe only 3 to 4% of overall treatment selected at MD Anderson. The majority ones are now surveillance, which is upwards of 15%. And then the remaining somewhat equally divided between surgery and radiation.

So, this comes to the summary slide for the overall concept of --- of what’re the issues related to surgery for patients with localized prostate cancer and what might be some of the long-term outcomes they would affect our understanding of survivorship, which is the overall theme for this course. Prostatectomy is again indicated for cure of appropriate patients with prostate cancer, has to be weighed against the --- the --- the relative value of radiation, cryo, and other alternatives. Quality of life measures do differ according to therapy and patients can prioritize them differently. We basically offer all of these canc --- cancer treatments to our patients, -especi ---. When I say all, I really mean the standard ones, and even some of the alternative ones, and can come to, I think, a good recommendation that patients will be satisfied with. As a last statement, I just want to thank you for your attention, and we do value your feedback regarding the content of this program. Thank you.