INTERVIEW

Urologic cancers: where are we now and where is the field going?

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Badrinath Konety speaks to Laura McGuinness, Commissioning Editor.

Q What first attracted you to following a career in uro-oncology?

Ever since I was a little kid I have always wanted to be a doctor because my father is a surgeon; but at first I wanted to be a heart surgeon. After I completed my initial medical training and moved to the USA I wanted to do some research; I liked the idea of it and I hoped it would improve my chances of getting a good residency. It just so happened that the research placement I was able to secure was with someone working in urologic oncology research. I had not been exposed to the field before that time.

In my research placement I was working on prostate cancer. At the time, prostate cancer had become known as a very common cancer and prostate-specific antigen (PSA) had recently been discovered, so there was a lot of excitement in the field, a

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lot of new grant funding, and a lot of new research ideas. We were looking at treatment of advanced disease. We developed cell lines to study new types of treatments in the laboratory. We were looking to see how we could mitigate or limit the side effects of therapy for prostate cancer. We were looking at MRI for the diagnosis of prostate cancer, which was a fairly new approach back then. These were all completely new and unchartered territories – it was exciting.

During my research fellowship, I met other urologists who were great role models. This really got me interested in urology, particularly uro-oncology, because I really liked the idea of being able to continue work in prostate caner, as there was so much new science going on that I could get involved in.

Q How did your career progress from that point onwards?

Once I finished my research fellowship, I came to my residency at the University of Pittsburgh. That involved 2 years of general surgery training and then 4 years of urology training. During my residency I began work with a researcher from Johns Hopkins (MD, USA) who was doing a lot of exciting work in prostate cancer, as well as bladder cancer. Following the residency I worked in his lab for 2 more years studying bladder cancer markers, vitamin D and its effect on prostate development and prostate cancer growth inhibition. Following that, I went to Memorial Sloan-Kettering Cancer Centre to do a clinical fellowship in urologic oncology. At that time, Sloan-Kettering had the longest standing urologic oncology clinical fellowship in the country, it was the first one established so that was great training. I got to meet a lot of fantastic urologic oncologists. It was very inspirational; there are a lot of great people that come from Memorial. After, I was an assistant professor at Iowa, then at the University of California San Francisco and 2 years ago I moved to the University of Minnesota.

Q When you initially started your medical training you were living in India. Having trained in India & then worked in the USA for a number of years since, how do you think your education differed? Was there a difference in the kind of cases you came into contact with?

Absolutely, there is a huge difference. In India you see a lot more infectious disease and stones. A lot of very basic bread and butter urology. Here in the USA, we see a lot more oncology. You don't see tuberculosis; if you see that in the genitourinary tract here, for example, then it is an oddity whereas in India it is fairly common. The predominant majority of cases when I was training were infections. In terms of general surgical cases, it used to be bowel perforations or ulcer disease, not colorectal cancer, which is very common here. In terms of case load, it was very different; the case mix was very different.

The approach is also very different. It has changed now, even in India, but at that time we were heavily reliant on our cognitive skills for diagnosis, whereas here we are reliant on imaging and diagnostic testing to make our diagnosis. I would say this is probably the clearest distinction. In India many hours of training were spent learning how to do the proper physical exam and understand and identify subtle signs, whereas here it's, "Let's get a CAT scan." It is a lot more decision-making and a lot more protocol driven here. Where I grew up there was a lot more time spent trying to understand the symptoms and slowly mulling over them to come to a diagnosis as we couldn't afford all these tests.

Q Do you think that you received a good grounding by starting in that way?

Correct. I think it did help. You get the best of both worlds. When I started I learned to recognize all the physical signs and arrive at a diagnosis or treat patients with limited resources. Then I learned a different skill set in the USA, plus you have the advantage of having all the sophisticated imaging and testing facilities, which really makes you, I think, a much better physician because you have both sets of tools to utilize.

Q What are the main topics & the biggest projects that you are working on at the moment?

The biggest area I have been successful in working on has been bladder cancer and looking at diagnostic testing for bladder cancer and outcomes from bladder cancer, in the area of diagnosis and management, particularly in older people. One of the things that I am particularly proud of is that when I was in Iowa, I was part of a state-wide effort to develop consensus recommendations on how to diagnose and manage older men with prostate cancer, the first of their kind for older men, which was a very useful experience for me.

Q What are the key differences between diagnosing prostate cancer in an older man compared with a younger patient?

The conundrum in older people who get prostate cancer is that you don't know if they are going to die from other diseases associated with old age or from the prostate cancer itself. You don't know how aggressive you need to be at first finding the cancer and once you find it, treating the cancer. A lot of people, including all the guidelines committees, don't even bother finding prostate cancer in these old men, as they assume that the patient will die of something else and that they probably have insignificant cancers. But this is not true in everybody. If you look at the different types of cancer that older men get, approximately half of them actually have some pretty aggressive forms of prostate cancer that will kill them in a fairly short timeframe of 5–7 years. Even though somebody is 75 years old they could easily make it to 85 years of age. If you ignore an aggressive cancer in these men they will either die from it or suffer from the side effects of the cancer that is untreated within their lifetime. So that is the problem – it is about how you decide to not start turning every single stone to find there is nothing under a lot of those stones, yet making sure you don't miss those men who have aggressive disease. Developing an algorithm or a paradigm that allows you to do that is very important.

A second issue is once you do find the cancer, how do you discriminate between the group of people who will actually be helped by further treatment and the other group that you are better off leaving alone. That also requires the physician to exercise a lot of discretion. A lot of physicians seem to know that we need to not treat everybody the same way, yet practice is very different. It is still a challenge and I don't profess to have the answer, but I try to continue to chip away at that. We are trying to develop methods in which you say, "Well, we are not going to treat this person, we're going to watch them." We then need to figure out the correct protocol to watch these people; is it imaging, biopsies or markers? Then when do you act? And how do you act? Do you have to do surgery? Do you have to use other types of local treatment? Those are all the protocols we're working on right now.

Q You mentioned the difference between treating elderly prostate cancer patients & younger prostate cancer patients. Is there a difference in bladder cancer patients as well?

Yes, there is not so much an age-related difference with bladder cancer patients, because everybody realizes bladder cancer needs to be treated, but there is controversy in bladder cancer patients in terms of appropriate surveillance and treatment. You have aggressive and less aggressive bladder cancer regardless of age. What we find, paradoxically, is in types of bladder cancer that are not very aggressive, the treatment and the surveillance is inordinately aggressive. These patients are treated, overtreated, watched too closely, given too many tests, whereas in patients who have got very aggressive forms of bladder cancer, we do too little. People do not seem to adhere to the guideline recommendations, they don't watch them closely enough, they don't do scans frequently enough, so it seems like a real paradox; we need to work out why this is happening. It seems counterintuitive, it seems like everybody is reading the same literature, so why are they not following it?

The second issue is then how do you improve care from treatment of advanced or aggressive bladder cancer in which you need more aggressive surgery, such as removal of the entire bladder. What are the factors that lead to better outcome from that sort of surgery? I believe that of all the operations urologic oncologists do, which are relatively common in bladder cancer surgery, bladder removal is the most complex operation that is associated with the highest percentage of complications. It's also the most expensive cancer to take care of. If we can figure out how to improve outcomes of bladder removal surgery and keep the cost low, I think we can translate that across many other cancers. Some of our research has shown that the surgeons who do a good job with bladder removal surgery or cystectomy are also adept at prostate removal or kidney removal. It does seem to translate across.

Q You mentioned that, in your opinion, even though everyone is reading the same literature, the same practices are not being put into place. Do you think the guidelines are sufficient as they are? Are there changes that could be made that could help?

There need to be some changes. First, one problem is that there are approximately half a dozen guidelines. Every set is subtly different and some are very different. That has got to stop. It's like two parents giving different messages to the same child, the child doesn't listen to either of them as both are equally important. It is important for us to better congeal around one single, uniform message without too much ambiguity. That would at least avoid the confusion coming from different sources giving different messages. Then we have to educate people about adherence to the guidelines.

There are also other changes we have to make in terms of the guidelines themselves. However, the guidelines are being reviewed continually. Some are reviewed every year, others every 2 or 3 years, but there are changes being made. Incremental steps, although I don't believe any significant changes are in the offing.

Q Could you tell us more about your research that has been based around identifying biomarkers for the detection of bladder cancer & how that area is developing right now?

There has been a lot of excitement over the last 10–20 years in terms of bladder cancer and developing biomarkers for it, particularly urine-based biomarkers, as urine is easy to obtain and to test. There have been a lot of new markers identified and tests commercialized. The biggest problem is encouraging people to use these new markers, although usage is slowly increasing. Recent data suggest that finally approximately 26% of patients are now exposed to the biomarkers. What has happened is that we have identified all these biomarkers, but we don't yet know how best to use them. They do not work equally well in all situations, so to identify the right situation for them to exploit their unique attributes is important. We've got a lot of exciting biomarkers that are already commercialized. Now comes the process of figuring out "What slot do you fit each one into?"

Q Is the field of biomarkers developing as quickly for prostate cancer & other cancers?

In terms of prostate cancer, there is a huge need for biomarkers, mainly for two situations. One is early on to figure out who has aggressive cancer and who does not. There is a lot of work going on in that area and a lot of good biomarkers have been found. Then, in advanced disease we have patients who come back and you think they have a recurrent cancer but you cannot see anything on x-ray and you want to see if the cancer has returned. Right now we have PSA, but PSA just tells you there's cancer there. It doesn't tell you where the cancer is, so if we can get a marker that can help distinguish the location of the cancer that would be great.

In kidney cancer, again, there's a lot of work going on trying to figure out if a kidney cancer is only in the kidney or if it has spread. There are promising markers that are being developed here as well.

Q The use of PSA levels as a screening tool in prostate cancer is controversial amongst physicians. What is your opinion on this debate? What issues need to be resolved in order to clarify the association of PSA levels with prostate cancer?

It is a very controversial issue obviously and it's almost like a political debate, both sides argue very vociferously that they are correct. The truth of the matter is, there is clearly is some benefit to screening, except that the benefit is small. It depends on personal perspective. If you feel that, "Well, I need to have 'X' benefit" and this doesn't meet the criteria, then it's not useful. But if any benefit is a benefit, then yes it is useful.

Last week I saw a gentleman who was 46 years old and seemed completely healthy. He went into a urologist's office and they found he had a PSA score of 8.6. He has an extremely aggressive prostate cancer that has already spread outside the prostate. This gentleman will most likely die of his disease, but maybe we can help him live a little longer by treating him with multiple approaches. If he had not gone into a doctor's office at 46 years of age and randomly got a test, then he would never have known. I think at the individual patient level, for them it is a black and white thing.

However, at a population level, we can argue all we want but only approximately 5–10% of patients are being helped. For that 5% who are going to be helped, the chance of being helped is 100%. It's very important that we maintain perspective and in my opinion this is one of the problems with the guidelines. In recent years young men have been encouraged to carry out self-examination of their testicles in order to identify signs of testicular cancer. If testicular cancer is identified early enough, the cure is nearly 100%. However, since the incidence of testicular cancer is so low, it has been found that self-examination of the testicles is not really beneficial, so at a policy level it is now being suggested that we dissuade men from examining themselves. At a practical patient level this is nonsensical; it causes no harm and can be done by the patient themselves.

This is just one example of what can happen when you do medicine by committee and medicine policy, causing one to lose touch with clinical reality. As responsible physicians this is something that we have got to stop.

Q Moving from diagnosis to treatment; you were talking before about bladder removal as a treatment for bladder cancer. You have done some work on prostatectomy as well. Could you explain how surgical treatments are progressing & what new advances there are in the area at the moment?

The biggest thing to happen to urology surgically over the last 20 years is the advent of laparoscopy, and more recently over the last 10 years or so, robotics. Laparoscopy was the first step where we actually started thinking that we could handle some of the cases in different ways, and then robotics made this much easier. It really increased our options. It has really revolutionized how we do urologic cancer surgery. We take out prostates, bladders, parts of kidneys, all of kidneys, and we do it all robotically.

Now there are other refinements going on, in terms of the equipment available and in terms of the techniques that we use, which will allow us to do a better job. Even open surgery has benefited from some of these robotic techniques because we try some things robotically and if that works then we think, "Why can't this work when it's open?"

Now the newer-generation technologies are about "How do you get feedback?", because with a lot of these technologies you can't touch the tissue, and now there is software that helps you feel like you're touching tissue and feeling the texture, which makes for a more realistic experience.

I believe the advances also allow for easier transfer of knowledge and training, because people can see things better and students can observe. There are robotic consoles in development where you can have a situation similar to that of a pilot and a copilot, where the main surgeon can regain control while the second person or trainee continues to operate. They sit side by side, use the same setup controls, which are separate for each of them, then one person can keep operating and if the other person feels, "We need to

make a change here," they can just jump in and correct the course. So this technology is advancing at a really exciting pace.

Q There are clearly a lot of merits to the new surgical techniques, but are there any drawbacks?

There is the expense and the learning curve. Not everybody can pick the techniques up that quickly, particularly some of the senior surgeons who may not have the time it takes. This may mean you'll have to slow down your case speed, or you may have a higher level of complications in the beginning because you are unfamiliar with the new technique. So those are the drawbacks. You have to relearn, you have to make a huge capital investment and a time investment.

Q What kind of projects do you hope to be working on in the next few years?

We are working on projects that are less and less invasive for treating cancers. We're continuing in that trajectory and we're trying to develop, for example, in prostate cancer, the means to image cancers and treat them locally, by just using lasers and other techniques, so you avoid making cuts at all and you do not need to take the whole organ out. We are trying to say, "If there's only one part involved, why are we destroying the whole organ? Let's just destroy the part that's involved;" similar to a lumpectomy but for prostate cancer. We're trying to become less intrusive and invasive.

The growing realization is that it is okay to watch some cancers, not all cancers are going to kill everybody right away. That is, I think we're going to continue with regards to who can be watched and how can we watch them best.

We are also working on developing new ways of treating really advanced disease, and investigating new drugs, new gene therapy approaches to treat patients who've got advanced disease or cancer that has spread.

We don't want to overtreat people who don't need treatment and we need to figure how to identify those people who we really don't need to worry about it too much. At the other end, we need to find out how to cure the people that we currently think are incurable.

Q What do you predict are going to be the biggest changes in the field over the next 5 years, in terms of diagnosis & treatment?

In all urologic cancers, particularly in kidney cancer, the biggest advance over the last several years has been the advent of a new class of drugs to manage advanced kidney cancer; antiangiogenic agents – what we call tyrosine kinase inhibitors. These are drugs that are essentially biological targets. They stop biological processes; stop blood vessel growth and either shrink the tumor or sometimes even make it completely disappear. I would be surprised if whoever came up with the discovery that allowed this new class of drug development didn't win the Nobel Prize some day. It is probably one of the most significant discoveries in all of cancer and it started with kidney cancer. That is where I think we're making a lot of headway.

There is also a lot of excitement surrounding the treatment of advanced cancers. We're going to get a better handle on treating advanced cancers and actually saving more lives and preventing people from dying, or at least converting aggressive disease into a chronic disease similar to diabetes – you have to keep taking your medicine, but as long as you keep doing that you'll be fine. I mean, look at HIV – I have patients who have been surviving for approximately 25 years since they were diagnosed with HIV. It was a death sentence 25 years ago, and now they're just like normal except they take a pill a day. I think we can do that with cancer.

Financial & competing interests disclosure

BR Konety is a consultant to Spectrum Pharmaceuticals, Allergan (who are developing treatment for localized bladder cancer) and a speaker for Amgen (who has a product for advanced prostate cancer). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.