INTERVIEW

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Challenges and prospects for liver cancer management: treatment, prevention and collaboration

Shahid A Khan*: Dr Shahid Khan qualified in Medicine at Guys Hospital Medical School (London, UK) in 1994. His studies in liver cancer led to a PhD from the University of London in 2003 and he was appointed Consultant in Gastroenterology and Hepatology at St Mary's and Hammersmith Hospitals, Imperial College London Healthcare NHS Trust; and a Clinical Senior Lecturer at Imperial College London in 2007. Dr Khan has lectured on liver disease nationally and internationally at hepatology and gastroenterology conferences, including state-of-the-art and invited presentations. He is the lead author on the

UK National Guidelines for biliary cancer and was on the International Liver Cancer Association panel for the International Guidelines. He has published extensively in the medical literature, including original research articles, reviews and book chapters. Dr Khan is a Fellow of the Royal College of Physicians of the UK, and a member of the British Medical Association, the British Association for the Study of the Liver, the British Society of Gastroenterology, the European Association for the Study of the Liver, the American Association for the Study of the Liver Diseases and the International Liver Cancer Association.

Q You are currently a Consultant Physician at St Mary's and Hammersmith Hospitals and a Clinical Senior Lecturer at Imperial College London; how do you divide your time between your various roles?

I have been in my post for almost 7 years, and have been very fortunate that over time, and with the help of colleagues, I have been able to shape my role. I primarily see myself as a clinician; however, I am also involved in conducting research and teaching. I spend approximately 50% of my time on direct clinical work (clinics, ward rounds and some endoscopy time), approximately 20–25% of my time on research (by which I mean meeting students, writing grants and reading papers) and the remainder of my time on teaching. I am the Director of Clinical Undergraduate Studies at St Mary's and am also Deputy Admissions Tutor for the medical

school. Obviously my role is not a 9 am to 5 pm experience, and work does tend to spill over into evening and weekends.

This is how the role has evolved and it is how I have wanted it to evolve. I have had opportunities to take roles involving more research that would have meant reducing clinical work, and vice versa; but my current role reflects my preference. For everyone the balance is different and I personally really enjoy the clinical work; I see myself primarily as a clinician, but I like the cutting edge of translational research. I feel I have the balance right, but it has taken several years to evolve my role into its current form.

Q What led to your specialism in gastroenterology and hepatology?

I trained at Guy's Hospital Medical School 20 years ago and during this time was tremendously interested in oncology and

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becoming an oncologist. As such, as a House Officer and Senior House Officer I applied for roles in cancer units. However, this experience actually put me off moving into oncology as a career, as I felt it was quite difficult and I missed the diagnostic aspect; by the time a patient reaches you as an oncologist the diagnosis has already been made, their disease has been staged and they can be fitted into a prearranged treatment strategy. I found this technically unsatisfying. Another aspect is that, of course, many patients do not respond very well; and in addition, you have missed the boat on disease prevention. Although I found the subject fascinating, I decided not to pursue oncology for my career.

Following this, I tried various different specialties and actually left medicine for a short period to work in the pharmaceutical industry and got extremely bored! I returned to medicine and the first job I found was as a locum registrar in gastroenterology at St Mary's in 1998. This was the first time I had been a registrar and as part of this role I was able to conduct endoscopy work, which I really enjoyed. So it was really by luck I moved into the role of locum registrar in gastroenterology and I found that I loved it; I loved being a physician and being responsible for the diagnostic work-up of the patient and I have always loved practical and technical skills, such as endoscopy (so much so, at one point I had also considered retraining as a surgeon). In this role, I found I had the perfect balance of everything. And of course gastroenterology has a huge proportion of work related to cancer; two of the three most common causes of death from cancer are gastrointestinal and hepatology related.

My subsequent move into hepatology was again really by serendipity. My mentor is Professor Simon Taylor-Robinson, who is now Professor of Translational Medicine at Imperial. He was my registrar when I was a Senior House Officer, and was appointed at Imperial as a young senior lecturer in the mid-to-late 1990s. We kept in touch and he was looking to conduct some research in cholangiocarcinoma in the late 1990s. He wanted to know if I was interested in coming to do

a PhD at Imperial as a junior registrar. I thought this sounded interesting, due to my ongoing interest in oncology. At that point I did not know much about cholangiocarcinoma, and I thought no-one would be interested in such a minor cancer! But I decided to pursue it, and we found through this research that the occurrence of cholangiocarcinoma was increasing, and we were the first people in the UK to report this. This of course led to my ongoing interest in cholangiocarcinoma and working on the first ever national guidelines on this disease.

Doing a PhD on liver cancer, one got interested in liver disease generally, and I decided to subspecialize in hepatology. I find hepatology particularly interesting because it has such a diverse range of conditions; you see people with liver disease and that could be metabolic (fatty liver), it could be alcohol-related, it could be genetic, it could be infectious disease-related (hepatitis B, C, D, E, HIV, and so on) and of course anyone with chronic liver disease is at risk from cancer. And in contrast to many specialties, you can actually cure some of your patients, which is not something you can say about a lot of medical specialties! I find it has everything I would want from a specialty.

Q What would you consider to be your greatest achievement to date?

If my work and publications over the last 15 years have helped to bring cholangiocarcinoma to the fore, I am proud of that. In the late 1990s, it was really a little known disease, and I am proud to be part of the team that has shown that its incidence is rising rapidly here in the UK and internationally, and then being part of the first ever guidelines anyone, anywhere in the world had written. Obviously I am not the only person to have contributed to this, but I was there at the beginning of the wave. There is still a long way to go to give cholangiocarcinoma the pre-eminence that, for example, hepatocellular carcinoma (HCC) has. I am proud that I have been part of the community in the last decade that has really helped to make liver disease more relevant and important in people's thinking.

Q You have been involved in the creation of national and international guidelines for the management of biliary cancer; what has your role involved?

The national guidelines came approximately 15 years ago. The British Society of Gastroenterology regularly, like many national societies, publishes national guidelines on various topics. A member of the gastroenterology committee was aware of the work we were doing on cholangiocarcinoma and asked whether we might consider working on guidelines for this disease. This was while I was doing my PhD on cholangiocarcinoma and so I, probably foolishly, volunteered to try. My role was to take responsibility for the guidelines, to get together a team of authors who I thought would be able to contribute and then drafting and planning out the sections, sending it out to various authors for their input, and coordinating their responses and that of the reviewers. Guidelines such as these are reviewed extensively; locally, nationally and internationally, and as such it is a really difficult coordinating process. With a disease like cholangiocarcinoma there are little data in some areas and little in the way of large randomized controlled trials and, as such, international reviewers will disagree with one another due to personal experience.

Q What are the biggest challenges we face in managing cholangiocarcinoma at present?

In HCC, we at least know the population that is at risk of developing the disease; 80–90% of patients with HCC have cirrhosis or chronic hepatitis. With cholangiocarcinoma we do not have such a well-defined at-risk group. We know that in patients from the Western world, primary sclerosing cholangitis (PSC) is the most common known predisposing factor, but 70% of all patients in the Western world with cholangiocarcinoma have no known predisposing risk factor. This, in turn, means that there is no population group to screen. And even for the group that we know is at risk of cholangiocarcinoma, those with PSC, there is no proven screening strategy.

Another big challenge is diagnosing cholangiocarcinoma and being able to tell whether a biliary stricture is benign or

malignant. This is very difficult to do with imaging, and the pick-up rate is low. This is a big challenge because if it is missed it can kill the patient; and if it is wrongly diagnosed as a cancer then the patient can undergo a huge operation for no reason. Current tumor markers, CA 19-9 and CA 125, are not very effective. There is a real need for better, more accurate positive and negative predictive markers to differentiate biliary strictures as benign or malignant.

A third issue is that even after diagnosis, only a minority of tumors is amenable to resection, and as such the patient is likely to die. The only cure is an R0 resection, but only a minority of patients present with a tumor of that size. In most patients surgical resection is not feasible because the tumor is too widespread, and then there is really very little in the way of effective treatments. Radiotherapy has not significantly improved mortality, and chemotherapy agents such as gemcitabine and cisplatin are not cures, although they do slightly improve survival. There is a real lack of curative options other than surgery that make a significant difference.

Q What do you think will be the direction of hepatic cancer research in the UK over the next few years?

Molecular profiling of cancer is going to become more and more important. One thing I fear is that for 10 or more years it has been deemed unnecessary to biopsy a liver lesion to diagnose cancer, and instead we have relied on imaging. If someone has cirrhosis and they have a characteristic lesion that on contrast arterially enhances and then undergoes portal venous wash-out, it is diagnosed as an HCC. So liver cancer is one of the few, perhaps only, cancers where histology is not required to make a diagnosis. This is not necessarily a bad thing, but the downside is that we have lost many years in which we have not been examining the molecular profile of HCC. I am convinced that these are heterogeneous tumors. We know that some patients will have a small HCC that is resected or ablated and they are fine, while others experience recurrence very quickly. Some patients are more chemosensitive to sorafenib, and this is similar with cholangiocarcinoma as well.

I believe this is the way cancer management is going in general, with breast cancer management leading the way. The future of cancer management may well be that we molecularly profile the cancer and then tailor the specific type of chemotherapy, adjuvant or neoadjuvant, to whatever the tumor's molecular profile is. Various studies have been carried out on liver cancer, as with other cancers, investigating the knock-out of tumor suppressors, over-expression of oncogenes and so on. But there is no consistency, and I believe we are dealing with a heterogeneous group of cancers.

Q What role will prevention play?

The role of prevention is very important. For cholangiocarcinoma it is difficult because, as mentioned, we do not know who is at risk of developing the disease in most cases. But for the biggest primary liver cancer, HCC, prevention is really important because we know who the at-risk population is (at least 90% of the at-risk population), and there is good evidence, although it is debated, that ultrasound surveillance in patients with cirrhosis will lead to early detection of HCC when tumors are at a size that is amenable to curative therapy. The criticism of the studies demonstrating this is, for example, that they are studies from Asia, or were carried out in HCC populations, and do not necessarily translate to other demographic populations. But there are some other studies out there that suggest they do. I personally believe, and I think most hepatologists believe, in surveillance. The problem is that in the UK, Europe and the rest of the world, studies show that only approximately 30–40% of patients with cirrhosis are undergoing surveillance, even those that are under the care of a gastroenterologist. Therefore, improving surveillance on its own could potentially have a big impact in terms of those who have cirrhosis. And of course liver disease generally is increasing. In the UK, liver disease is the fifth most common cause of death, but is the only one of the top five that is increasing; all the other are either stable or going down. So preventing liver disease generally and

preventing cirrhosis is really vital, because if we prevent cirrhosis and chronic liver disease we decrease cancer rates.

This comes down to government public health policies, for example those relating to obesity. The most common cause of abnormal liver function tests in the clinic in the West is fatty liver disease. Clearly policies that address the increase in obesity are important not just for cardiology, diabetes, and general health and well-being, but also liver disease. In addition, policies related to alcohol planning and minimal unit pricing, which has been a political hot potato in the UK recently, are important. More can also be done related to infectious causes of liver disease: universal vaccination for hepatitis B and screening for viral hepatitis in communities, among others. Only a fraction of patients with hepatitis C are known about and most are probably under the radar. So there is a huge amount that can be done at a national level in terms of preventing liver disease progressing to the stage where liver failure, liver decompensation and liver cancer can occur. I think this is crucial and probably more cost effective than spending millions of pounds developing a new cancer drug.

Q Finally, where will you be focusing your own time and research over the next 5 years?

I love clinical work and that is not something that I would want to reduce. However, I do enjoy teaching and research comes as part of that. My own focus over the next few years is to try and help set up collaborative national studies. I really think this is the way forward; in a place like the UK where HCC and cholangiocarcinoma are important but relatively rare, it is very hard to conduct high-quality studies because of the low numbers of patients. The only way around this is to be part of consortia and to get together with groups of like-minded people at other centers. There is a real understanding in the UK clinical scientific community that to deliver high-quality trials and studies collaboration is the only way forward. The hepatology community in the UK is really getting its act together in terms of centers

collaborating, agreeing to share samples and apply for large grants involving lots of people to pool resources. I am hoping that I can help be part of that with liver cancer research in the UK.

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