ICD-11 Q&A summary

The ICD-11 webinars, which took place during November 2021, discussed the new ICD-11 coding changes and their relevance in the context of cholangiocarcinoma (CCA).

Summarized below is the discussion with our panel: Prof. Shahid Khan (Imperial College London, UK), Prof. John Bridgewater (University College London Cancer Institute, UK), Mr Hassan Malik (Aintree University Hospital, UK), Dr Robert Jakob (World Health Organization, CH), Dr Jesus Bañales (Biodonostia Institute and European Network for the Study of Cholangiocarcinoma, ES), Mr Andrew Murphy (National Disease Registration Service, Public Health England, UK), and Helen Morement (AMMF – The Cholangiocarcinoma Charity, UK).

1. What are the clinical implications for the molecular determination of the CCA subtype?

Prof. John Bridgewater:

The molecular determination of the CCA is really important. About half of the intrahepatic CCAs have a mutational alteration, a target, and sadly half of them do not. For those that do, targeted therapy is an option, for instance, the recently approved pemigatinib tablet. Compared to chemotherapy it has virtually no side effects and works really well. We also know that the group that are able to receive pemigatinib generally do a bit better anyway, so it gives us information about how well people do and it is great to be able to give these people a non-toxic treatment.

Pemigatinib is just one of several targets we have for intrahepatic CCA; there are fewer targets in the other types—distal and hilar. Nevertheless, there are some targets, and we must keep looking for these and keep offering them to our patients.

All patients with CCA must get a molecular profile to inform us about this. That is a step change in the way we manage these and other cancers. That process is gradually working its way through the system. It is not perfect yet, but it is getting there, and most of us oncologists are relishing the prospect of being able to offer non-toxic treatments to our patients. So, the molecular bit is huge, it is really important.

2. How could molecular subtyping improve the clinical management of patients?

Prof. Shahid Khan:

Historically, during cancer trials before the era of personalized medicine, when a new cancer drug would come out, we would give it to people with cancer and about 10–20% might respond and the others would not, and we did not really know why. But now we know that cancers, particularly liver cancers and CCAs are quite heterogenous tumors; they have different driver mutations and if as a patient you have a particular driver mutation that is specifically targeted by the therapy, then you are more likely to respond. So, the idea is, if we can profile people's tumors and give the specific therapy targeted to their driver mutation, then they are more likely to respond and have improved survival and benefit, rather than a blanket systemic treatment for all patients with the same tumor.

3. Do you think this also has an effect on surgical treatment options as well?

Mr Hassan Malik:

I think it is a chicken and egg situation. You know from the data that AMMF and Shahid have worked on, that over half the patients diagnosed over a long period of time in England had no treatment whatsoever. And it is important that all patients (this is really focusing on the clinical aspect rather than coding) are referred to their local center of expertise for an opinion. Certainly, some of the

intrahepatic tumors were misdiagnosed as a CUP (cancer of unknown primary) and treated on that pathway, rather than diagnosed as CCA where the treatment would be fundamentally different.

As a surgeon, about 20% of the patients you come across on the tumor board will be looking at a resection, and we will design that surgery for that particular case; whether it be a left-sided or right-sided liver resection, or liver resection with the bile ducts; every case is fundamentally different. So, we as surgeons in out tertiary center do that, but what I am always amazed at is what I see after we have done our bit on the coding side of things. I have looked at HES (hospital episode statistics) data, and I am shocked to see an operation that has a fingerprint for a CCA surgery, which includes resections of the liver, bile ducts, and biliary reconstruction, which is a unique operation for a hilar CCA, but the diagnosis is colorectal metastasis. It is not even coded as intra/extra or hilar CCA but the wrong cancer; it just amazes me. So, I think it is crucial, and the patients deserve getting the coding right and that is the message I want to pass on today.

4. Why is ICD-11 coding so important for the CCA patient advocacy community?

Helen Morement:

It is absolutely vital in the battle for getting improved treatments and futures for CCA patients. Lack of robust data is a problem that has plagued the CCA arena for many years. We at AMMF see increasing numbers of people getting diagnosed and younger people being diagnosed. However, that is just considered as anecdote and opinion. I have been told many times, without cold, hard data, 'forget it.'

We now have our own data project, which was touched on by Hassan. But hugely importantly, in ICD-11, CCA is coded in three anatomical types: intrahepatic, perihilar, and extrahepatic or distal. To this point, in ICD-10 and its previous iterations, there was no code at all for perihilar CCA and if you speak to any expert on CCA, they will tell you that this is the most commonly occurring kind; in fact, Shahid illustrated that very well in one of his tables earlier. Because there is no coding to enable the proper recording of CCA, it gets miscoded/misrecorded, and so we do not have that robust data to support what we really should be doing for patients. And because the data is so skewed, and it depends on what you search for, it leads to a lack of interest; it leads to a lack of awareness, and therefore the neglect of a lot of patients who really deserve a lot better.

I am strongly of the opinion that if we can get this improved coding adopted as quickly as possible, so that the disease is recorded more accurately, it will lead to more robust data to actually prove that what we are seeing is really happening, and therefore we can move forward with asking for policies to be changed, asking for better pathways, and asking for better centers of expertise for these patients. Coding is at the root of this, and I think it is going to be extremely helpful throughout the UK, throughout Europe, and throughout the world.

5. How close do you think we are to having centers for excellence for CCA in the UK?

Mr Hassan Malik:

Not very close, I think we are halfway there. All HCCs (hepatocellular carcinomas) that can be resected occur within defined regional centers. I think the difficulty we have, certainly around some of the more complex surgeries, might be the perihilar tumors, where we have a very high-risk operation in a relatively rare type of cancer. Some centers can undertake a handful of those operations a year, among five or six surgeons; in other centers the surgery will be done by one or two individuals who have the expertise. We see that there is variability; going back to the AMMF data, there is surgical variability around the country, but again because of the difficulty with coding, we cannot delve into that much further at this moment in time.

We have had discussions from a commissioning point of view; I think we are halfway there. I think what will have to drive it is the clinical community, Cholangiocarcinoma UK, and the patient charity. I think transplantation for CCA may also support that agenda, because obviously transplantation can only be delivered in a handful of centers across the country. But it is important to have a balance, we need to take the best of what we have and ensure that we bring all centers up to that level, if we can. Obviously, if there are outliers, then we need to have discussions with those places.

It is also important to remember that the majority of patients are not surgical candidates. It is crucial that there is sufficient local expertise maintained to allow that excellent care to be delivered locally, whether that be endoscopic management of the biliary obstruction, or the oncological treatment options. Again, going back to the oncology networks, it is important the oncology community is aware of all the advances in this rare cancer. Get that biopsy, get the sequencing, get the patients into clinical trials; that I think, is a strong message.

6. How would you encourage the uptake of ICD-11 for CCA globally?

Dr Robert Jakob:

The 'encouraging' is essentially a matter of how fast countries adopt ICD-11. ICD-11 comes into effect from January 1, 2022, and countries will take some time to put it into place.

We know in other areas of ICD, some specialties have chosen to use two systems in parallel: the one that is mandated by the national law, and one that delivers the detail, for example, in pain or in dermatology.

Otherwise, we can just say that this (CCA coding/data collection issue) may be an additional incentive to move as fast as possible to ICD-11, so that everybody can take advantage of this particular area, and also the many other aspects that the new classification comes with.

7. With the adoption of the new ICD coding, do you anticipate that different countries will take it up at varying times and how does that work? Is it very variable and how soon before everyone is using it?

Dr Robert Jakob:

The US have taken from 1993 to 2010 to adopt ICD-10, so there are natural delays. Only two years ago, one country switched from ICD-8 to ICD-10. So, the speed is heterogeneous with the move from ICD-9 to ICD-10. Usually within five years after adoption, things move in the countries. We are working closely together with many of the European countries to facilitate the preparations that obviously need to be done before moving to a new coding scheme.

8. What factors determine when countries/national cancer registries take up changes in coding and how they incorporate them?

Mr Andrew Murphy:

It is really down to the individual medical authorities as to when they want to upgrade to a newer version of a standard classification. I know that within England, for instance, NHS Digital are currently looking at ICD-11, but no decision has been made as to the implementation.

Once a decision has been made, I would guess it would take several years before all organizations for the NHS in England actually move over, but there has been no timescale addressed for that.

However, as you know, working very closely with you and Helen over last few years, we identified that there was this gap in the coding. So, what we have done is we have actually made changes to

the cancer outcome services dataset so that the three specific areas for CCA can now be recorded accurately within it, and we can supplement the ICD-10 and the SNOMED CT coding that is also available.

9. Does the insurance-based system in the U.S. play a role, or is irrelevant in terms of coding uptake?

Mr Andrew Murphy:

I know from when I have been over there and spoken with registrars, that they have a two-tier system within the hospitals: those that are led by the insurance companies, and those that are not. But overall, they bring all the data together through SEER (the Surveillance, Epidemiology, and End Results Program) and they try to standardize that data.

10. Why does it take so long to implement new coding systems? Is it a very huge logistical issue in terms of IT, training, and changing all your software?

Mr Andrew Murphy:

Yes, because they are all so different. If you look at the difference between ICD-9 and ICD-10, they are very different. ICD-10 is easy to remember because they are just three or four digits, but with the way the classification is done, you only have a very small band of potential diagnoses that you can have within each one. For example, if you look at breast cancer which is C50, you can only go from C50.0 to C50.9 and then you are out of classification code; whereas with ICD-11, you have many more, but the whole coding structure is completely different. It will take a while in order to bring that in, not just training within an NHS trust, but also with system suppliers making the difference so that those new codes can actually be recorded accurately.

11. For those living in countries that have not yet planned to start ICD-11, what actions are recommended?

Helen Morement:

I think it is very difficult for people to plan to take on ICD-11 because it is not down to the individual, it is down to the health authorities in whatever country you happen to be in, and these ICD coding changes have been adopted in certain countries sometimes years after other countries. What we would really like to see is that the global uptake of ICD-11 is much more rapid.

12. How do interested medics/interested people persuade a health authority to adopt a new coding system?

Mr Andrew Murphy:

Within the UK, we have NHS Digital and NHSX, and they have already set up a small task group to look at ICD-10 *versus* ICD-11, but also in the mix with that is SNOMED CT. At the moment, there is a huge drive towards collecting more data using SNOMED CT, which is another clinical terminology system. So, you have competing different systems there, and the priorities are set at national level. Once they are agreed and set, then we can start working with system suppliers to make sure that the system suppliers have the necessary ability to make changes to their systems so that you can record the different staging data accurately and without too much burden. Then once you can do that, you can start rolling it out and doing training on it.

There is a difference between ICD-10 and ICD-11. ICD-10 is very easy to understand; a lot of people have been using it now for many years, and most of them know the codes without having to look at

reference codes and tables. With going into a new system, people have to be retrained, and they have to understand how to do that, and that will probably have to happen with an interface, as Jacob showed, whereby you can type in what you are looking for and it will come up with the code that you are going to need. But initially it is not going be easy to remember every single cancer code that is required.

Prof. John Bridgewater:

What Andrew has just described is the way that we would do it in a sort of national health system. The other way of looking at it, and we have a bit of a flavor of this where I work because we have an American electronic patient records system, is 'follow the money.' You do not get paid on this system; there is a bit where you say coding and then charges, and we do not go near that bit. But maybe we should use that to begin to change; to enforce proper coding because it is not really happening at the moment. And perhaps a bit of a stick needs to be applied, for example, your department is punished unless you fill in your coding for the week.

13. Is there anything that the clinical community can do to encourage better, more accurate coding and recording of CCA at the basic diagnostic level?

Mr Andrew Murphy:

Working through the cancer outcome services dataset, which is the largest cancer dataset in England, we have added in a new data item that specifically defines the three subtypes of CCA. Working with the experts within the MDT, you can not only use the ICD coding, but you can also use a separate coding to define the subcategories to make recording much more accurate.

In addition to that, within the cancer registry world, Professor Khan came out to a large conference, held 18 months ago, to talk to the registrars to make sure that when we are getting data coming in, they understand how to record it. So, we have national data that is far more accurate than what it has been in the past, and we are not relying on incorrect ICD coding.

We not only receive the data from COSD, we also get all the pathology reports, so if it is clearly inaccurately diagnosed, but recorded within pathology, we can then make sure that we are defining that correctly within the cancer registry reports. Also, over the last couple of years, we have been working very closely with all of the molecular centers around the country, so if there is molecular testing being done on patients with CCA, we will get that data directly, which again will allow us to be very accurate in the future with recording CCA within the cancer registries within the UK.

Helen Morement:

That does sound quite hopeful. So, what we really have to do, as John mentioned earlier this morning, is really push for all CCA patients to get molecular profiling, preferably at diagnosis, and if all else fails, during first-line treatment. That way, we will have more accurate numbers and more accurate data.

14. How do you think we can encourage more clinicians to put patients forward for molecular profiling?

Prof. John Bridgewater:

One of the targets that we find in primarily intrahepatic CCA is the *FGFR* gene, and this is altered in about 1 in 10 CCAs. We have very good drugs for that, indeed, one of them, pemigatinib, has recently been NICE (National Institute for Health and Care Excellence) approved. As such, it is now effectively mandatory for every patient with a CCA to have the *FGFR* fusion looked for. There is a bit

of detail here that is quite important; the *FGFR* fusion is looked at using a test called RNAseq, while the other abnormalities that allow targeted therapies within CCA tend to use a different technology. I think it will be a little while before everybody has all the testing that they are required. But it is a question of education, primarily of the doctors and pathologists looking after patients, and just the knowledge of this potentially extremely good treatment working its way through the system. NICE guidance always takes some time to settle in, sometimes years, but for patients, the sooner we can do this the better.

In short, it is a question of education for everybody, patients, doctors, everybody out there. And AMMF has a key role in really waving the flag here and raising awareness of this very important innovation.

15. How can better CCA coding benefit ongoing research?

Dr Jesus M. Bañales:

In terms of research, I truly think that this new classification will be very helpful for both experimental and clinical studies. For instance, this will allow us to better characterize the tumor biology of the different subtypes. We will be able to understand, at least in part, the similarities and differences between each CCA subtype, which has not been done before.

We have different human CCA cell lines available, which are important to understand if the molecular mechanisms altered are general or specific to each subtype. Considering the genomic and genetic profile, we have different animal models of CCA available. It is important to compare the different animal models with the different human subtypes and try to define and see which is the best model that mimics each subtype, because they might have an important relational impact, and we can see if the responses to the new therapies in the different models are general or specific to each subtype. This might have important translational impacts on the design of clinical trials and on potential sub analysis in clinical trials.

Regarding clinical studies, the new coding is very important for the registry databases. In the European database, we have adopted these new coding changes because it is important to understand the similarities and differences on risk factors between the three subtypes, the mutational profile, their incidence, their management, as well as their response to therapies and their prognosis. We are trying to see these potential differences and similarities in studies that are currently ongoing. Also, when we evaluate the design and evaluate the clinical trials, potential sub analysis can be conducted evaluating the response to therapies considering all three subtypes. I think this is a very important point because the biology and the risk factors associated with each type might be different, and the potential response to therapies also could be potentially different in certain cases.

16. How could better coding actually improve the outcomes of patients in the EU?

Helen Morement:

Everything that we have heard during the webinar points towards the difficulties that we had, and we still have, because of the lack of robust data; and this all comes down to the coding problems and the fact that it is so difficult to prove what we at AMMF and many other people actually see. I think it was Shahid who mentioned something like ‘we are seeing 1% of perihilar CCAs actually recorded’ when in fact, most people will tell you it is ‘well over 50%’ and I think Hassan said even ‘60% of CCAs are perihilar.’

What we see at the moment is a disease with an increasing incidence, one of the worst prognoses out there, and that is something that has not changed in decades. We need to improve the situation.

We now have targeted therapies; it is now mandatory for every patient to be examined to have molecular profiling for the *FGFR* fusion, but it very much depends on the doctors diagnosing it. Will they put that patient forward? Do they know about it? It all comes down to this lack of awareness of CCA, because data show that the incidence is very low, so there is really, very little interest. Actually, the incidence is not low. So, if we can get better coding, which is coming with ICD-11, and therefore better recording, we will then have better data. With that better data, we have the ammunition in Europe, in the UK, in fact globally, to say, look at the incidence of this cancer, look at the mortality which actually parallels incidence, and let's really work together to raise awareness, to raise interest, to boost research, and improve the future for all those unfortunate enough to be diagnosed with this disease.

17. What is the importance in terms of the epidemiology of the different molecular factors that influences the different subtypes of CCA?

Prof. Shahid Khan:

It is important to track diseases; one of the reasons is the importance a disease is given when it comes to resources and funding. When people talk about primary liver cancer globally, people tend to talk about hepatocellular cancer; how it is the second or third most common cause of death in humans from cancer, and how it is so important. A study that was done by HCC UK showed that between the late 1990s and late 2010s, primary liver cancer cases in the UK had tripled, and in that period there were over 60,000 deaths from primary liver cancer. Even specialists in the field assumed that they were all predominantly HCC, but what they found was that 40% were actually intrahepatic CCA.

When you are trying to get funding in an increasingly financially stricken environment to try and do research, it is important that resources are put where there is a significant issue. So, it is important that CCA is not deemed anymore to be an orphan disease and not numerically important. Obviously, it is important to every individual who suffers and their families, but globally as a disease burden, it is significant now, and that message needs to be highlighted, so that appropriate resources are channeled towards it.

18. Jesus, you are chair of ENCR (European Network of Cancer Registries), you have colleagues from all over Europe, you have done a lot of the real-life clinical mapping of what has been going on, so you probably have a lot of experience in how people record the data. Do you see epidemiological differences on perihilar tumors? Do you see more cases of perihilar tumors in the registry?

Dr Jesus Bañales:

Well, there is a bias in the registry in terms of who inputs the data in the registry; we have a significant proportion of professionals/hepatologists, so they are including mostly intrahepatic cases. For 2,200 cases in the registry, more than 1,200 are intrahepatic, with 600 perihilar and 400 distal. The good thing is that all the patients have histological confirmation of the diagnosis, and the location of the tumor is well indicated. What we saw from the preliminary analysis is that indeed the different subtypes have different risk factors associated, so some risk factors are more close to extrahepatic (in this case distal), or perihilar compared to intrahepatic, and *vice versa*.

Regarding management, they obviously have a different management, and the outcomes are also at a certain level different, for example, patients under best supportive care with intrahepatic CCA show worse outcome compared to perihilar and distal, probably due to the underlying chronic liver disease associated. But in terms of surgery, or in this case, a palliative treatment, there are no significant differences at the moment, according to the numbers that we have in the registry. But

again, I think that in terms of incidence of the different subtypes, I think we need to carry out prospective analysis and try to demonstrate this.

19. How can we educate people away from thinking primary liver cancer is only hepatocellular carcinoma, when CCA should also fall under the term?

Prof. Shahid Khan:

I try and do that. I was giving a talk on Monday at the Royal Society of Medicine on HCC, and many of my slides were about CCA, just to emphasize the point that actually, CCA is a huge chunk of primary liver cancers. Traditionally we were taught, and even now people are told, or all the textbooks say, '80–90% of primary liver cancers are HCC, and 10–15% are intrahepatic CCA, and then there are a few percent of very rare primary liver cancers like angiosarcomas or very rare things that one hardly ever sees'; but actually it is more than 10–15% and significantly more as the UK data has shown. How do we get that message across? I do not know.

Prof. John Bridgewater:

Just lots of education. Over the last 10 years, the big thing that we have, which we never really had before, is the MDT; where we can, week after week, just rub it in. Just repeat, just educate, and keep going. From experience, it is not a bad way of passing across information, educating your colleagues about the new stuff that is coming along, and there are huge amounts of it. The business of diagnosis is absolutely critical.

Prof. Shahid Khan:

Historically, for a decade or so, we have been happy to treat HCCs without a biopsy. It is the only cancer apart from the odd pancreatic cancer where you are allowed to treat without histology based on imaging; the imaging being that if there is contrast which enhances in a triple phase contrast, and there is arterial enhancement and portal-venous wash up, you are allowed to call it a HCC. That would be fine, except that many of those things that are then diagnosed as HCC purely based on imaging, without histology, are then ablated—a needle is put in it and then burnt—so you never get histology. Only a minority of these tumors are actually resected or transplanted, where you can get the histology, but that is less than 10% of all HCCs in the western world. The majority of small tumors are ablated, or treated with transarterial embolization (TACE or bland TAE), and again, if you ablate, or you do embolization, or intra-arterial therapy, you do not get a biopsy. So, you will never know if all those tumors that have been treated in that way were really HCCs or if they were mixed HCCs with CCA—which is another subgroup—or if they were CCAs. There are data showing that in people who have been transplanted for presumed HCC, the explanted liver actually had CCAs in it. This lack of biopsies is one of the reasons why our knowledge of the molecular pathogenesis of HCC and CCA is a bit behind other cancers, although we are making speed rapidly with that.

One of the positive things that has happened, and I am pleased to see it with the trials that are being done now, is that biopsy is mandated in most trials of advanced cancer. Our practice seems to be more and more to biopsy because we have an understanding that we need to get histology.

Then there is the issue of cancer of unknown primary as well, where people have had liver lesions, where we are not sure where the primary tumor is. Again, it is probably a heterogeneous group of cancers of which some are probably CCAs. But there is a trend to biopsy more, which is good.

Dr Jesus Bañales:

I fully agree that there is significant work to do in education on the different subtypes and also on the fact that CCA is a primary liver cancer. But I want to also highlight that a significant effort has

been done in the last few years and also that the specialists in the field are very sensitive about this; for example, during the last few years, there was a 'Hepatocellular Carcinoma Summit', an annual meeting dedicated to hepatocellular carcinoma organized by the European Association for the Study of the Liver, and the title of these meetings changed three or four years ago to 'Liver Cancer Summit' to involve other kind of cancers, including CCA and it has an important slot in this meeting. I think this will help to give visibility to this disease.

20. If both CCA and Klatskin carcinomas are mentioned in the documentation, how do I decide which code to use? Do I have to consult the physician for further detailing in each file? Do I have to code it as both as it describes different sites?

Prof. Shahid Khan:

This is a historic problem. Really it should not be called 'Klatskin.' Klatskin is a term to describe perihilar cancers based on an American pathologist called Gerald Klatskin, who first published a case series of these cancers in the 1950's and then the Klatskin name was attached to perihilar cancers without really strict anatomical definitions. Then the issue was that some people were calling perihilar cancers 'Klatskin' and there was no code for either perihilar or Klatskin. If it was called Klatskin, it was usually incorrectly coded to intrahepatic.

My answer would always be that if you are unsure, please talk to a senior member of the tumor board or the MTD to clarify the anatomical location of what it should be coded as. We should avoid the word 'Klatskin,' and if it is a perihilar, as anatomically defined, then with the new coding system it should be defined as perihilar. But, if there is any doubt as to which of the subtypes it is, please talk to a senior clinical member of the MDT; the radiologist, surgeon, or hepatologist.

21. How do you code when patients have more than one lesion at different locations?

Prof. Shahid Khan:

I think the question is saying 'what if you have a tumor in the perihilar lesion and not so far away, you have an intrahepatic tumor as well? Are we going to assume that is a perihilar that has led to intrahepatic metastasis?' or 'if you have a tumor that is embedding into the gall bladder and also breaching the liver parenchyma; is that a primary intrahepatic or is it a primary gall bladder?'—I think that is what the question is getting at.

It is not that rare, I would agree. I think that is why the MDT is the place to discuss it, because that is where you have all the expertise. At a proper MDT you have more than one radiologist, at least a couple of surgeons, if not more, gastroenterologists, liver specialists, oncologists, radiation oncologists, medical oncologists; and if between them, they cannot come to a conclusion because it is a case-by-case thing, you have to look at the clinical features, maybe how the patient presented. And that is the best chance of coming up with the most likely original site. Only if it is impossible to conclude, it should be called 'other' or 'indeterminate,' which there is an option for.

Prof. John Bridgewater:

The only other fallback that I know of, and it is not very frequent because normally the MDT is pretty good at calling it, is when you do the profiling, and you find the patient has something that is generally speaking thought to be unique to the intrahepatics, then you can be a bit more sure it is intrahepatic.

Helen Morement:

Thinking of some of the presentations that we've seen at AMMF's conference and from Professor Robert Goldin, who is a pathologist, he has said that when he is looking down his microscope, he can see the difference between the different types of CCAs. So, if something was biopsied, which was in the common bile duct, but it was down near the cystic duct, near the gallbladder, would it not show that actually it had moved its way down, and was actually an intrahepatic CCA?

Prof. Shahid Khan:

So that is a very good point, and I agree as we learn more about the molecular pathogenesis of the different subtypes of CCA and hopefully biopsy more. And as John has pointed out in his talk, in cases where you have multifocal malignancy, we will in the future be relying on the molecular profiling based on histology to determine where we think that cancer originated and also to guide us on the relevant systemic therapies.

Helen Morement:

The more we are learning about the different anatomical types of CCA, the differences that are showing up on molecular profiling, the different mutations in the different types; this is going to become more and more important, because the same treatment does not work for each different type, as we have seen. One size does not fit all.

Prof. John Bridgewater:

Taking that argument even further, in a couple of years-time, or 4 years-time, all you need to know is the molecular subtype in order to treat it.

Helen Morement:

But in the meantime, we need people to know; without robust coding, we are not seeing the true number of people affected, we are not seeing how this is increasing year on year, we are not seeing the numbers of younger people; so, we do not have the 'cold hard data.' Well actually that is not quite right because we are getting data now from AMMF's data work, but of course, that is only in England. But data is still essential to actually change policy and to improve situations.

Dr Jesus Bañales:

Also, it is important to point out that not everything is in the mutational profile. With targeted therapies, we do not cure patients; we are prolonging the life expectancy. So, we need to consider all of the other aspects in order to find a common and hopefully good treatment for most of the cases.

I think it is important to highlight that cholangiocytes, which are the cells that form the biliary tree, are really heterogeneous along the biliary tree. So, cholangiocytes in the liver are different to cholangiocytes in the distal part of the biliary tree; they originate from different embryological tissues; they have different markers, different biology, and they are connected to different cell types. In the liver, obviously, the microenvironment is not the same as that in the distal biliary tree. So, in principle and by definition, CCA tumors that arise in the liver are different than CCAs that arise in the distal part of the biliary tree.

Also, we need to consider that the origin of CCA tumors can be different. The definition of CCA is this the expression of markers of biliary differentiation only, but these tumors can generate from differentiated cholangiocytes, from hepatic progenitor cells, from progenitor cells in peribiliary glands, and even from hepatocytes under transdifferentiation. The only thing that defines CCA is the

anatomical location and expression of markers of biliary differentiation at the histological level, so all these aspects definitely impact on the tumor itself and on the features of the tumor.

So, CCA tumors should definitely be coded differently. This new coding is of tremendous help, but hopefully in the future we will provide additional coding related to the biology of the tumor. We are on the way, this is the first part, the starting point, and we are looking forward to the use.

22. The new ICD-11 changes do not need a certified professional, which means anyone could pick up the diagnosis easily through the website and software. Do you foresee any problems with that?

Prof. Shahid Khan:

Well, I think that the system seems a bit easier, but we will not know until people start using it widely. I have always felt that senior clinicians should have a more proactive role in the coding when it comes to patients being discharged from hospital for whatever reason, because if you do not accurately code all the things that have been done for that patient and all their diagnoses: firstly, it is not good for data collection; and secondly, your hospital does not get appropriately remunerated. I think when it comes to the MDT, it is not routine practice for a senior member of the MDT or the MDT lead to sit with the MDT coordinator at the end and go through the coding. He or she may go through with the MDT coordinator and say this is the plan, just to recap that we have got the right plan, but in my experience, they do not sit and say, 'the diagnosis here was neuroendocrine tumor, code it as this' or 'the diagnosis was perihilar, code it as this'.

Does this happen at your MDT meetings, John?

Prof. John Bridgewater:

It does not happen at the moment. The closest MDTs get to that now is TNM, because TNM is now mandated. There is the 'wringing of hands' when they have to put down the TNM at the MDT, but I think that the MDT is probably the only place where correct coding is ever going to happen, because as you say, once the patient is out of there, there is no process for doing this. Also, the people who are doing it, are not sufficiently senior and so not sufficiently able to get it absolutely right. I think you will get a bit of flak from your colleagues for suggesting this, but maybe we should start recording the coding at the MDT. These discussions are very important, and quite frankly, the first MDT to do it and to produce a real genome staging pool, a real ICD code for every single patient, that would be quite an accomplishment.

Mr Andrew Murphy:

The cancer outcome services dataset, which is the largest cancer dataset we have in the UK, records all information about the diagnosis, all the way through to treatment. We have a series of fail-safes within it to try and get the best quality data coming through. We have a team of people around the country, liaison officers, who go into hospitals and work with MDTs. One of the things we recommend people do within the MDT is to allocate a clinical champion, it does not have to be the clinical lead, or the consultant, it could be a junior doctor, who can work with the MDT coordinators so that if they have any queries, or they did not understand the complex discussions that were happening, they could sit down with them and go through each case. Then they could make sure that the performance status, the TNM stage, or any other clinical coding is actually entered correctly at that time.

Prof. Shahid Khan:

So, we need a coding system that is accurate, but you also need the right people, putting the right codes in.

General comments

Prof. Shahid Khan:

I want to end on a positive note, and I am optimistic because I gave a talk last week at London's Royal Society of Medicine; I think it was an update on hepatocellular cancer; I was going through all the updates and I reflected on my own experience. When I became a consultant and senior lecturer in London in 2007, there was no real standard treatment for HCC; there was nothing on the horizon, and then a year later, the SHARP trial came out and then we had sorafenib. I set up a HCC clinic with my colleagues and in that time, in the last 7 or 8 years, we have gone from nothing really proven to standard treatment with sorafenib, a second agent lenvatinib, the third agent is a combination of ATEZO-BEV with a VEGF and a PDL1 inhibitor, and two options for second-line agents (regorafenib and cabozantinib). We did not have SIRT, we now have SIRT, we did not have IRE, we now have IRE; we were using radiofrequency ablation, we are now using microwave ablation. So, all these things have happened in HCC in the last few years. For CCA, there was again nothing; there was no standard treatment until GemCis in the ABC trials; and now we can do molecular profiling; now we have pemigatinib. So, I do feel that it is a bit slow, but I am optimistic when I think of how many new treatments we have at our disposal in HCC just in the last few years.

Dr Jesus Bañales:

Also, one of the reasons why some trials failed was because of the number of patients included and also the lack of potential sub analysis in clinical trials, potentially according to the location. I think this new coding is something of a benefit for the design of clinical trials, for future sub analysis.

Prof. John Bridgewater:

This comes to the core of what Helen has been going on about for years; when you get the numbers, when you do the studies, actually, the numbers are there to do proper clinical trials. All the trials before ABC-02 were without exception, less than 50 patients; I think the biggest one was 55, and everybody thought, ‘oh we can never do this, there are not enough patients in the world to do this.’ Actually, when you added up all the studies, there were thousands of patients around and all you needed to do was to be bold and actually do the study. I think subsequent to this now, pharma are doing many 100-patient studies globally, really very rapidly. So, we need to know the numbers and believe in what you want to do; you have to go and do it.

I completely agree with Shahid, CCA probably lags behind HCC by a few years, but it's catching up fast.