Podcast Transcript
Intermediate HCC: treatment options and strategies

Brought to you by:
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Dr Rohit Gosain
Welcome back to another episode of Oncology Brothers podcast. I'm Rohit Gosain, alongside with my brother and co-host Rahul Gosain we are on this journey of four-part series of hepatocellular carcinoma (HCC). Today we will be focusing, out of the two discussions, the first discussion on intermediate hepatocellular carcinoma.

In the last two discussions we have focused on advanced HCC where we covered 1st line treatment options with Dr Rachna Shroff and the 2nd line treatment options with Dr Rimassa and Dr Vogel. Today, particularly our focus is on intermediate HCC with an emphasis on multi-modality treatment strategies in this space. We're excited to have two experts with us. Dr Maria Reig, a Hepatologist who's leading efforts for BCLC from Barcelona, and Dr Emil Cohen, Interventional Radiologist with MedStar Georgetown, Maria and Emil welcome.

Dr Maria Reig
Hello.

Dr Emil Cohen
Thanks for having us.

Dr Rohit Gosain
Let's kick this off. So intermediate hepatocellular carcinoma is tricky. Multidisciplinary rather is the key here. Maria we'll start off with you first. Given the background and leading efforts with the Barcelona clinical liver cancer staging system, which is the BCLC. If you don't mind briefly touching on what the BCLC staging system is and how do you exactly go about intermediate stage here?

Dr Maria Reig
The intermediate HCC is the best example of the need for multidisciplinary team because we have all the tumour inside the liver. But the amount of tumour that you have could be completely heterogenic. That's why in the last version of the BCLC, we consider the liver function, the performance status but also what is the amount of tumour that we have? If you remember in the past BCLC-B have only TACE. Now we have some group of patients that could benefit for liver transplantation. Everybody knows that the criteria for liver transplantation are not homogeneous around the world, but we have a specific population that will consider that.

Then on the other side, we have patients who have tumour inside the liver but it's diffuse or it's not feasible to do a loco-regional treatment in this case we think about systemic therapy. But the main group of patients still receives the loco-regional treatment, then we can discuss if we believe in loco-regional treatment, TACE or radioembolization. The evidence-base today is TACE.

So, intermediate HCC is tumour inside the liver without symptoms and the liver function is not anymore an issue. Because if you fit the criteria for liver transplantation you can consider this option. I believe that now is one of the areas that we really have a lot of things to do.

Dr Rohit Gosain
Emil, now would you like to add anything to this HCC staging system, particularly from BCLC standpoint?

Dr Emil Cohen
Well, as usual, I think the oncologists are very well refined in their definitions. In interventional radiology (IR) we try to keep things simple. Obviously like the patients who are going to undergo transplants, depending on the institution's criteria, are easier to handle. Once we have those two other groups, subgroups, I should mention of BCLC-C/B, it gets a little bit harder and a heated discussion about how to treat them. So this is good that we are having this discussion to discuss this issue.

Dr Rahul Gosain
Thank you for touching on that. And it's important to address that BCLC, though is widely used system, of course there are other staging modalities be, it TNM, we also have clip staging. So as a community medical oncologist this can often get complicated. The key here is having these discussions with our radiation oncologist or be it with interventional

radiologists. Okay. Now that we have this foundation, let's take a little deeper dive and view treatment options for intermediate HCC.

Maria, you alluded to this, but Emil coming back to you. Multiple loco-regional treatments be it SBRT, TACE, TARE, Y-90 or are we bridging for a transplant? Can you please walk us through some of these available options here?

Dr Emil Cohen
So the options that we have for loco-regional options are chemoembolization, which is the old school thing that's been around for like 50 plus years. We have modifications of that, radioembolization, which is radioactive beads, as you well know, that's been around for about 20 plus years. And we have microwave ablation but in this category it's a little bit harder to apply. And then you also mentioned the external beam radiation therapy which, again I'm not a radiation oncologist, but based on the guidelines that I've, looked up, it seems like it's mostly confined to cases where we cannot use other curative options. It can be 1st line treatment for HCC confined to the liver if other therapies are not available, or if a consultative therapy, if the patients have incomplete response to liver-directed therapies and salvage therapy as well. That's what I basically gathered.

Dr Rahul Gosain
And can I push you a little more on this? In what scenarios would you use Y-90 (TARE) versus TACE? Today if you have a patient in front of you, how are you making that decision based on these three modalities?

Dr Emil Cohen
There has been a lot of evidence coming to the forefront that maybe radioembolization is not only easier for the patients because it's an outpatient procedure for most part, but also because it's been on explant studies and follow up studies showing much more, progression free survival or tumour necrosis, especially with the personal dosimetry options that we have now. So there has been a trend not just in my practice, but I think most people's practice to move away from chemoembolization and move more towards radioembolization because not only with the side effect profile, you get an advantage there, but also because we see better tumour response to it. So we've been moving more and more towards radioembolization for patients for liver-directed therapy.

Dr Maria Reig
Can I make a comment here? Because I believe that nowadays we need to understand, and the audience maybe needs also to hear our discussion about that, it is not white and black. Now it's more grey and there is more and more discussion because the evidence level is different, but also the patient characteristics. So I agree with the previous comment and I will also add to the audience that we need to consider many factors that are completely beyond the liver function and the tumour burden, and it is more related to where we are working on and on other things, who are the specialists that are in the centre and also the reimbursement. So all of these things now are also part of the discussion for selecting the treatment.

Dr Rohit Gosain
Truly so, because sometimes we are limited with the hospital support or one only have TACE available, patients don't want to travel. So there are much more complications that are tied in with just administering the treatment and sometimes how close the tumour is with the vessel and all that sort of stuff ties in as well with the anatomy aspect of it. Now, while we know that, this in general, hepatocellular carcinoma is associated with poor prognosis, as a result, systemic therapies, which have been doing well, at least in metastatic setting, are being put out or brought in earlier stages. We have seen that, whether that's standalone or combined with loco-regional therapies, we've seen that with REPLACE data with regorafenib plus pembrolizumab versus TACE or TARE, and EMERALD data with durvalumab with TACE.

Maria, we'll start off with you here. How are you interpreting that and how are you, sort of, talking about the data here?

Dr Maria Reig
This is also a challenge because today we are talking about intermediate HCC but when you go to the clinical trials, the population that were included are patients candidate for TACE or TARE. That means, for example, the REPLACE trial and also the ABC trial included patients with performance status 0 or 1 and both of them include patients with all the tumour inside the liver. But for example with REPLACE, regorafenib plus pembrolizumab, have patients who are beyond the up to seven criteria. In the ABC trial we have patients who are beyond the Milan criteria. So the key thing here is the stratification factors. But also consider the primary endpoint. The primary endpoint is also different. In one, the ABC is treatment failure, in the other, in the REPLACE, is progression-free survival. How do you interpret all of these data? Maybe we could have another session for that. But to be simple, the key thing is identifying the patients that were included and also the results. We expect to have results in the next year, to know where we are. Maybe we can discuss later the other data. But generally speaking, I'm happy to say that we expect new data, and new information related to treatment failure, for example, and understand better what that means, progression-free survival.

Dr Emil Cohen
Right, I think that's a very good point. I think these therapies, systemic therapies, are showing great promise, especially with combination. And I think, one more thing to add here, every time, I look at a new study, I'm sure you guys all do this too because oncology is much more versed in this, it has to apply to our patient population.

I know that you mentioned, like you know where I am I'm seeing alcohol, MASH and hepatitis C. I'm sure Maria sees a different patient population. And also our listeners in Asia probably see a different patient population hepatitis B etc. So that's always, I know it's probably pretty basic to the oncologists listening to this, but it's just good for my Radiation, Interventional Radiologist friends.

Dr Rohit Gosain
Emil, just to actually harp on some of that stuff that you were talking about, where TARE is better than TACE itself and TACE has fallen out of favour, while EMERALD itself has been utilising TACE. We are waiting on EMERALD TARE, which is rather more TARE focussed. If

this was to get approved, are you going to be relying more on TARE aspect of it versus TACE in this case?

Dr Emil Cohen
My practice has shifted a lot from TACE to TARE in the past five, ten years. I do still do TACE occasionally, but to be completely frank, it's usually when the TARE has not worked or if I think there's a very unique situation. So this is where it has been at and I think most of my partners are doing the same thing. But going by guidelines, if we're just doing bridge to transplant, etc., TACE is perfectly viable still in those situations occasionally.

Dr Maria Reig
To add to this comment, we also need to remember that at the beginning radioembolization would focus on patients with more tumour burden. Now, they are moving more for local localised tumour. And there is no data to support that one is better than the other due to the patient population.

So again, I believe that we can consider it as an alternative option for those who are not candidates for TACE. But if you are in a centre and the interventional radiologists use this technique, we know that it is safe and we have true response. And so that's why the discussion is beyond what is a priority for the physicians and the patient. For sure.

Dr Rahul Gosain
And again Maria, Emil you've touched on this. It's not black and white because the real-world patient in front of us looks very different from what they usually go with in clinical trials. And by the time something is approved, we're looking forward to something else already. One thing in the clinic settings that we often run into is, if you're having side effects, is it more so from the TKI that we're giving? Is a more so from the immunotherapy or the loco-regional therapy that we're getting?

Maria, can you touch on this a little more? How do you often dissect as more and more of these therapies are moving early on and now focusing on intermediate HCC?

Dr Maria Reig
Yes, sure. For combination, loco-regional treatment plus immunotherapy or TKIs, we have experience in the clinical trials and we need to follow the rules for the clinical trials. And then you translate to clinical practice for sure. Systemic therapy depends on the profile of the adverse events, you can induce to things that are more related to one treatment than to the other. Frankly speaking, complications after chemoembolization or radioembolization are really, really rare if the patient has compensated cirrhosis. And so on.

So generally speaking, we focus on the profile of adverse events and depending on that we discontinue or not. If the patient has severe adverse events then regardless of the origin, you have to resolve the complication and then you can decide retrospectively if it’s linked to one or the other. But from a clinical point of view, I believe that the most important thing is to identify the profile of the adverse events that we are talking about.

Dr Rohit Gosain
All this data is convincing but the real world is of course a lot different because there are a lot of factors that are tying in, as we were talking about it earlier, whether that's different practice patterns or different patient profiles, centre capabilities or regional differences, whether one is practicing in Europe versus North America.

Maria, let's start off with you here, in real practice, outside of clinical trials, how are you putting all this together and treating patients with intermediate hepatocellular carcinoma?

Dr Maria Reig
In Barcelona we treat according to the guidelines and we treat with TACE. Having said that, if the patient is failure to the TACE or is not candidate for TACE we could consider radioembolization or systemic therapy. But if you go to the evolution, there are some patients that would also benefit from SBRT. That means, depending on the characteristics of the patient, we go through different options, depending on the data that we have in terms of evidence. For our group the evidence base is overall survival. But we know that in clinical practice some patients are not candidates for that. The only thing that we are not doing, at least up to now, is giving combination therapy, systemic therapy, plus chemoembolization / radioembolization outside the clinical trials because the data we can discuss later on, is not mature enough.

Dr Rahul Gosain
We all are eagerly waiting on overall survival and Emil you had touched on that as well. This is all exciting, but we eagerly await overall survival before all of us jump on the bandwagon. Emil, coming back to you for loco-regional control here. Any pearls around sequencing? Maria touched on this, that if someone got TACE maybe you can still use SBRT. Some of these modalities that you have in hand, be it with IR or radiation colleagues, how are you sequencing that?

Dr Emil Cohen
So, let me just step back for one second to address that. I think in the United States, we have been trending towards radioembolization a lot more. And there is actually data already in our journals that's showing on explanted livers you're getting a much more complete response, a tumour necrosis from radioembolization (Mosenthal et al., 2024). But of course, those are people who are transplant candidates and we're discussing patients who have more than 1 or 2 diseases so it's a little bit different because we give higher doses. Putting that aside, and we were talking about, we usually generally start out with radioembolization if we can do it again, because it's better tolerated for the patients. Let's just say the side effect profile is better. And we've seen that. And you can do TACE more gently, but if you do it you're going to get less of a response. So I always tell patients who are feeling not so great after a procedure, well at least you know, the treatment is affecting something in your body. Right? But if you don't get any side effects, that could also be a bad sign that maybe we didn't treat you as aggressively as we should have, because there's not just like any one method to do this. I think between my 4 or 5 partners at Georgetown, we have like five different ways of doing things. And we've fortunately discussed those. Once we see one therapy doesn't work, for instance, if the patient hasn't gotten a good response, we move to something else.

For instance, like you mentioned, external beam radiation therapy, just like their guidelines (ASTRO guidelines). If we see that our tumours aren't responding and there's peripheral residual tumour, we might ask our colleagues in radiation therapy to treat them, because frequently there's accessory blood vessels that maybe we can't treat through like phrenic arteries, internal mammary arteries and maybe residual tumour and edge of a tumour. And we ask them for their help to address those issues.

Dr Rohit Gosain
I think this complicated conversation only tends to reiterate that we need to have radiation oncologist, IR, surgeon, pathologist, radiologist, and medical oncologist sitting on the same table when making decisions, especially with intermediate HCC. As we wrap up, Maria, any important studies that are on your radar for intermediate HCC which you're looking forward to and importantly, clinical takeaways from today?

Dr Maria Reig
Sure. In intermediate HCC we have to talk about the EMERALD-1 trial. They showed improved progression-free survival. But I want to emphasise the first point that we discussed at the beginning, 57% of these patients were intermediate HCC. The other 16% was BCLC-C, so advanced stage, or early stage (26%).

Dr Rohit Gosain
In your clinical practice, would the presence of positive data based on EMERALD-1 and LEAP-012, that is combination of loco-regional therapy with immunotherapy, are you utilising these practices currently in your practice at all, or rather waiting for the approval itself?

Dr Maria Reig
In our clinical practice there are different factors. One is the evidence. We have data but is not mature enough. We have a chance to think about new options but we still need to know exactly what is the impact in clinical practice.

Dr Emil Cohen
If I can make one comment, I think Maria alluded to this. I think it would be really nice if we could recruit more of these patients for trials to get a more definitive answer.

Dr Rohit Gosain
Long-term data and recruitment plays a huge role, especially when that's where a community oncologist comes in as well, to help with the accrual process. But again, involving tertiary care centres for multidisciplinary approach is extremely important. Emil, any final thoughts or key takeaways from you Sir?

Dr Emil Cohen
I think you summed it up very nicely. Given the fact that we don't have a flowchart for this category of patients. But if you can reach out to. and as I do too by even calling my colleagues, sometimes in more difficult cases in other institutions to try to get an answer in a difficult patient, it's very useful. And working as a team like you mentioned is extremely important.

Dr Rahul Gosain
Dr Reig and Dr Cohen thank you so much both for your time and insights on this rapidly evolving but complex space of intermediate HCC. For our listeners, let us go over a quick recap.

In today's discussion with Drs Maria Reig and Emil Cohen we focussed on treatment strategies for intermediate HCC, from loco-regional options like TACE, TARE, Y-90, SBRT to systemic approaches and combination strategies.

Dr Rohit Gosain
We also discussed the clinical importance of multimodality approach and the need to personalise treatment based on the patient's specific profile and disease progression. Thanks for joining us. Make sure to check out our other discussions in the HCC series, and stay tuned for the final episode on hepatocellular carcinoma. We are the Oncology Brothers.

Tonke de Jong (COR2ED)
For more details on all the trials mentioned in this podcast, visit the COR2ED website for a complete list with links. If you enjoyed this podcast and want to find out more then please look for the "Oncology Medical Conversation Podcast" under the account of COR2ED Medical Education. Also don’t forget to rate this podcast, subscribe to our channel and share it with your colleagues. Thank you for listening and see you next time.

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