# Hepatocellular Carcinoma Pathology Reporting in Academic and Private Practice Settings

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**Becca Battisfore:**

Welcome to the latest edition of the College of American Pathologists' CAPcast. I'm Becca Battisfore, content strategist with the CAP. In this episode, our guest host, Dr. Gladell Paner, will be talking with two GI and liver pathologist about how the hepatocellular carcinoma reporting protocol is used in both academic and private practice settings. Before we get into the questions, let's learn more about our guests, Dr. Paner, we'll start with you.

**Dr. Gladell Paner:**

Thank you, Becca. Good day everyone. My name is Gladell Paner. I am a GU pathologist practicing at the University of Chicago, and in the past six years I had the pleasure of working for the CAP Cancer committee and also for the CAP Pathology Reporting committee. And this year I visit myself on the education side for cap and I'll take this opportunity to promote two of our latest products. One is we have updated the online CAP Gleason course and this new version will be available on November 11. And the second is we will have a CAP webinar on reporting of prostate cancer. This is a two-part course. The pre-work activities will be open on November 18, and the actual webinar will be on January 22. So please check this activities out in the CAP education portal. But today we will be talking about liver cancer reporting.

**Becca Battisfore:**

Great. And Dr. Chopp?

**Dr. William Chopp:**

Yeah, my name is Bill Chop. I'm a pathologist. I've been out in practice for 14 years. I live in the Grand Rapids area of Michigan. I'm part of a Corewell Health System West. Everybody's kind of integrating these days. So I'm the west component of that area. I'm the medical director of eight hospitals in that area, and I'm a part of a lovely group of 30 pathologists and there's three of us that see primarily the gastrointestinal component here. And I've been on the CAP Cancer Committee here for I think maybe five years. I'm rotating off here in December, so I forgot what the timeframe was and my previous life I also did the CAP, I wrote the questionnaires for the PIPs.

**Becca Battisfore:**

Great. And Dr. Hart?

**Dr. John Hart:**

Hi, I'm John Hart. I've been at the University of Chicago for the past 33 years. I'm a GI and liver pathologist and currently serve as the vice chair of anatomic pathology. Have had a lifelong interest in liver pathology in particular, and the University of Chicago is a big liver transplant program, so we see a lot of the specimens that have hepatocellular carcinoma.

**Becca Battisfore:**

Great. Thank you all for joining. And Dr. Paner, I'll let you take it from here.

**Dr. Gladell Paner:**

Thank you, Becca. So my first question is for Dr. Chopp. We know that Dr. Chopp is one of the primary authors of the CAP protocol for hepatocellular carcinoma together with Dr. Lawrence Burgart and Dr. Dhanpat Jain, who incidentally actually was one of our guests in the previous CAPcast. So my question to you, Dr. Chopp, is can you describe to us the background and evolution of the CAP hepatocellular carcinoma reporting protocol?

**Dr. William Chopp:**

Yeah, I'll kind of start off with generalities here. I know our audience is, I look at the protocols like all the protocols is living and breathing documents. And as many of you know, we try to update these every so often based on new literature. And so I really stand on the backs of many other pathologists that have been doing this for a long period of time. And as we get additional information of qualified data, we try to implement that within the protocol. I came on about five years ago, Larry Burgart was there. Great to have people along those lines to help you with this. And what we try to do every time that we do this protocol is review it or not change it based on data. We always try to look at the current data and we all like to sometimes jump to the newest paper or whatnot, but if we don't have solid data here that's reproducible, we try not to implement that.

So quite honestly, sometimes our latest interventions are when we don't change anything at all, we try to look and make sure with that data, we try to look at the SEER data, we try to look at that papers and if there's nothing going on, which actually the last iteration, I think we put it out in 2023, we really didn't make any many changes. I think we had a situation where maybe there was an error in typing or something that we made required that was not supposed to be required, but part of this is what you don't do sometimes is as important as what you do once you do something. It affects obviously national prominence and worldwide prominence as well. So you want to make sure you have the right data. So what we try to do here in this is make sure we vet the data, we go through the experts, and then if we don't think there's a change to be needed, then we don't change it. So quite honestly, the last one, we really didn't do too much. We reviewed it and then we kept it pretty much the same.

**Dr. Gladell Paner:**

Thank you Dr. Chopp. And I think to add to that is that the updates also for the CAP protocols are pretty much aligned with the updates that we have for the WHO Blue Book and also the AJCC. And if there's any updates on that, then we kind of also do some updating on the CAP protocol. But I don't think there's any updates also recently for that part.

**Dr. William Chopp:**

That is correct here. And like you said, we try to time this and Gladell probably knows this very well when we know the new WHO is coming out next year, so we kind of hold off on our updates or whatnot to make sure we kind of align. So there's a kind of a big picture thing. We try to do the committee to do this. Do we do it perfect every time? Probably not, but we definitely try to.

**Dr. Gladell Paner:**

Thank you, Dr. Chopp. My next question is for you, Dr. Hart. And this will be on the practice side of things in the application of the protocol. And my question Dr. Hart, is what are the benefits of having a CAP hepatocellular carcinoma reporting protocol in our routine pathology practice? And the follow up question for that is what are your clinician's response to having this synoptic reporting?

**Dr. John Hart:**

Synoptic reporting is key. I don't think in this era we can live without it. Tumor board follows precisely the synoptic reporting parameters and the oncologist and the surgeons want to hear each of those items ticked off and make sure that it just provides a very consistent approach that the oncologists are very comfortable with, the surgeons are comfortable with and allows clinical trial construction and the understanding data from these clinical trials as they come up. So can't live without these. Of course, as a practicing pathologist, you always have little things about each of the protocols that you wish were different or that you recognize is a problematic area, but standardization is just an absolute necessity. So thank goodness for these protocols.

**Dr. Gladell Paner:**

Thank you, Dr. Hart, excellent points. And also I may add to that is that this protocols assures us that the required elements that is needed for inspection are automatically there already. And just to add to that, and I've worked together with Dr. Hart and here we are using the electronic reporting protocol. So once we sign out the reports, all those required elements are automatically checked. So my next question, I'm going to delve into the elements or the content of the hepatocellular reporting protocol. So this question is for both of you and I would start with Dr. Chopp. Dr. Chopp, tell us about the histologic subtypes of hepatocellular carcinoma and what are the subtypes that are relatively challenging to diagnose?

**Dr. William Chopp:**

Okay, I can take that in kind of two paths here. I think the ones that look like normal liver and the ones that don't look like liver are probably the biggest categories here. But I'll step back a little bit here. We're looking at the protocol here. Right now I think we only have four subtypes that we actually classify, and then we have an area underneath it where we have a situation where we allow the pathologist to put whatever subtype. Currently right now we just have traditional cellular carcinoma, filar serous and clear cell type. Obviously there's other ones recognized by the WHO that aren't on there. The ones that are recognized by the WHO that I sometimes have a hard time with is steatohepatitis. I have seen many times where myself or others, when you first look at that liver biopsy or whatever you get, you look at it, you're like, it's just steatohepatitis in the background.

And I've seen a lot of my partners in myself when the first glance you look at that, then you have to go down that pathway as is this lesional tissue? And if it is, is this possibly ahe hepatocellular carcinoma as my bad joke? I said initially before. Also the other ones are the ones that look very normal. There's maybe subtleties in that core biopsy that you look for where you also ask yourself, is this normal liver? Then you start going on and look into the plates and you get reticulate and do other things that maybe help you classify it. But I think that's the other big pathway I kind fall down as well. And then there's the classification of the, Hey, this looks like it's a malignant something or another is this a poorly differentiated or undifferentiated form of the hepatocellular? And then you use your stains to classify that way. So as I said initially, I think it's the ones that maybe look like normal liver or somewhat abnormal liver that are hard to classify. And the ones that you have a hard time towing, it's actually a liver biopsy at all.

**Dr. Gladell Paner:**

Thank you, Dr. Chopp. I'm going to loop the same question to Dr. Hart. And Dr. Hart has a big liver consultation service. And so the same question to you Dr. Hart, regarding histologic subtypes and also what subtypes do you think are challenging to diagnosis? And of course we have, as Dr. Chopp mentioned, we also have to consider the specimen not only innate to the tumor, but also especially in a biopsy specimen.

**Dr. John Hart:**

I agree with everything that Dr. Chopp already mentioned. I do feel like we're behind. I'm envious of our GU colleagues with all of their beautiful subtypes of renal cell carcinoma each with its molecular pathway, its characteristic immunohistochemical stains and its clinical impact. I do feel like hepatocellular carcinoma is slowly moving in that direction and it's going to be, and I hope in the next iteration of the CAP synoptic report form, it will capture some of these new emerging subtypes like the steatohepatitic subtype. I think that is deserving of separate recognition and should be coded or captured in our synoptic report. Another one that I think is very important is the macrotrabecular massive subtype of HCC. It has a real clinical relevance. It has a much higher rate of recurrence after RFA or after resection because it is often multifocal and it has a high incidence of vascular invasion.

And there are a couple others that are emerging as well. I know this obviously has to be data driven. There has to be good data for Dr. Chopp and Burgart and Jain to look at to justify inclusion, but I think that hopefully in the next iteration we'll have those additional subtypes included. There's a wonderful paper by Mike Torbenson and talking specifically about subtypes of hepatocellular carcinoma and where it makes sense. Obviously it doesn't make sense to recognize a subtype if it doesn't really have any molecular basis characteristic mutation or fusion and also some clinical impact. If it's no different than ordinary hepatocellular carcinoma, then really is it a value to separate out a subtype? But for those subtypes that do satisfy those criteria, I hope that we can move to recognizing them in our CAP protocols.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. So the way I understand is that subtyping is pretty much on the histologic side of things pretty

**Dr. John Hart:**

Much, yes. Right now it's on the histologic side of things, but molecular is becoming increasingly important as well, and particularly in a non-cirrhotic background. And I would encourage all the listeners to remember that important point when you're talking about liver tumors is that the differential diagnosis is just dramatically different when you have a cirrhotic background versus a non-cirrhotic background. In a non-cirrhotic background, you certainly have to think about benign hepatocellular lesions like focal nodular hyperplasia, adenoma, Dr. Chopp was referencing that, but also metastatic tumors that can very closely resemble hepatocellular carcinoma. And we don't want to make that error in a cirrhotic background. It's very different. You're really, if you think you have a malignant tumor, you're really limited to hepatocellular carcinoma and cholangiocarcinoma.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. And I will have a follow-up question here for you. And this is about molecular testing. And my question is that what are the usual reasons for ordering molecular testings for hepatocellular carcinoma in your practice? Do you order molecular tests for diagnostic purpose or for predictive markers as a response to therapy?

**Dr. John Hart:**

Where we use it sometimes is in the distinction. In a difficult case, particularly in a needle biopsy sample between hepatocellular and adenoma and hepatocellular carcinoma, if you have a terp promoter mutation that is strong evidence that you're dealing with hepatocellular carcinoma, that might be extremely well differentiated and look very much like a hepatocellular adenoma. So there are selected circumstances, it's much more important in cholangiocarcinoma that we won't be discussing during this broadcast. But there the oncologists often ask for next-gen sequencing, whereas in hepatocellular carcinoma, not as often.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. And I'm going to loop on the same question to you, Dr. Chopp. So in the private practice setting in particular in terms of molecular testing for hepatocellular carcinoma, for diagnostic purpose, for predictive reason as well, can you comment on that?

**Dr. William Chopp:**

Yeah, I would say even though we have a great molecular lab, I haven't utilized it much in the community practice setting if I have questions about something I think. But for myself, it's always phone a friend. I think in the pathology community within my own walls and outside the walls, if I don't know what it is, I haven't found it to help me too much. And I found if I find a colleague at another institution to get me another eye on it, I've always found that to help a little bit more right now,

**Dr. John Hart:**

I'll add that sometimes you have a very poorly differentiated tumor and you're considering both cholangiocarcinoma and HCC, and that might also be a circumstance where molecular could be a value because the molecular profile is somewhat different in those two choices. So there's another opportunity in selected cases where molecular can be of value.

**Dr. Gladell Paner:**

So I'm going to move on to another element here, and this is for our audience for clarification of this particular element between multifocality and satellite lesions. So I'm going to ask this question to you, Dr. Chopp. So the question is, describe to us the difference between tumor multifocality and satellite lesions and what is the clinical significance of this findings?

**Dr. William Chopp:**

So looking at this with satellitosis currently for the checklist here, it's a non-required element. There's some different definitions depending on where you look at this at, but based on the international collaboration on cancer reporting, it is recommended that if there's what you see is a larger lesion, if there are smaller lesions, two centimeters or less from that larger lesion and are smaller, they can call that satellitosis. People are believed that's due to the van little metastasis to that area. Like I said, that is one classification in how people use it. That is what we have kind of used and the CAP cancer checklist template from there with tumor multifocality here, I think I look at this and I'd like to see what Dr. Hart thinks is, I don't know if there's always great definitions for all the people trying to define that away from there, but I would then define it further a distance away from that than those satellite lesions that are less than two centimeters away. You can look at this data and I think if you look at some of these situations when people do molecular data comparing some of these things, and I think there's been a mixed bag trying to tell the difference between multifocality or in hepatic metastasis in some of these lesions. I think some papers support it and some don't. I don't know if it's really helped us kind of clarify the situation.

**Dr. Gladell Paner:**

Thank you, Dr. Chopp. Dr. Hart, any comments?

**Dr. John Hart:**

Yeah, I agree completely, and I use the caps synoptic report definition for satellite lesions. We get a lot of native livers, and the larger the resection is, the more likely obviously you're going to find additional tumors. We sample very carefully. We slice our native livers very thinly, and we find lots of dysplastic nodules and small hepatocellular carcinomas at a distance, and we regard those as separate tumors, multiple tumors, even if it is possible that they represent intravascular spread of a primary tumor, we report them out as separate tumors. And it's amazing the number of tumors that we find in these native livers that are below the limit of detection for our radiology colleagues. And so we often have cases with where we use the M designation for multiple tumors. The other area that becomes a little bit difficult to apply is in a tumor that's been treated either by tear or by radiofrequency ablation, you get a very large irregular kill zone where the parenchyma has been extinguished due to the treatment, and then you have little nodules of residual viable tumor. And then again, you get into a definitional issue. Are these independent tumors? Are these satellite tumors? It can be a little bit tricky, but we just apply the criteria that we have in a standardized fashion using the CAP guidelines. That's how we approach those cases.

**Dr. Gladell Paner:**

Thank you, Dr. Hart and Dr. Chopp. Dr. Hart, you mentioned you referred to the staging using the MDE descriptor in multiple primary tumors. Just to clarify, when you have a satellite lesion, would that count as multiple tumors? Would that upstage

**Dr. John Hart:**

No, no, we don't. We don't count that. That's just a satellite tumor. Yeah, if it's less than two centimeters.

**Dr. Gladell Paner:**

Okay, great.

**Dr. John Hart:**

Single tumor. Yep. And we just note the presence of satellite nodules, it actually is important. The size of the lesion is very important and the number of lesions is very important because beyond the CAP protocol reporting for cancer treatment, there's also the liver transplant requirements. Patients either are within the criteria for liver transplantation or outside of it. And so if you have the number of tumors applies in that situation. So we need to have a very accurate count of the number of tumors that are present so that the hepatologist can report back to the liver transplant societies about their adherence to those transplant guidelines outside of the setting of the oncologist reporting and treating the patient for cancer.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. And so my next question is actually related to your answer earlier. So this is about the use of the CAP protocols or elements outside of what is required in the current HCC protocols. So my question to you, Dr. Hart is in your practice, what additional pathology parameters, including experimental or research elements that you include in your pathology report for hepatocellular carcinoma, if any, outside of what is required by cap?

**Dr. John Hart:**

There actually isn't a lot that we add as a comment. We spend a lot of time of course describing the background liver. It has a lot of impact, particularly in the liver transplant, but also in resections for the patients going forward. So I know that get a resection for cancer, you are honing in on the cancer, but don't forget the background liver. Talk about the presence of steatohepatitis or steatosis treatment effects, chemotherapy induced occlusive disease or chemotherapy induced steatohepatitis that needs to be mentioned. The degree of steatosis turns out to be a really important parameter that should always be included in the report for the specimen, and it has this impact. The more steatatic the liver is, the lower its regenerative capacity. And so if they're considering another large liver resection, they may not be able to do that if the surrounding parenchyma is highly steato. So it's really important for the pathologist to mention that they may decide, okay, this patient, unless they lose weight or get their diabetes under control, reduce their steatosis, isn't going to be a resection candidate, but instead might have to have radiofrequency ablation or tear therapy because your removing a large volume of tumor, you don't want to tip the patient into liver failure because their non-tumor parenchyma is diseased.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. It is interesting. Also do the same approach for our resection of kidney cancer. We also make a comment on the status of the nanoplastic. Renal parenchyma is very important and actually some of the renal cell carcinoma potentially have favorable prognosis. And actually what findings on that non neoplastic kidney will be much more important actually than the tumor. I just have a follow up question for that, Dr. Hart. For us in GU, we usually don't comment on the non neoplastic kidney. In the biopsy setting, we have a biopsy for a mass lesion. How about in liver biopsy when you have a tumor and then you have a non neoplastic parenchyma? Do you put a comment on there?

**Dr. John Hart:**

Yes, we do. We always do. Recognizing with a disclaimer that says that the amount of surrounding parenchyma insufficient for evaluation, we often say that, but if there is sufficient and we think we're away, it's not just mass effect. One of our most common comments are the surrounding parenchyma exhibits features consistent with mass effect. But if we do have a sizable amount, even in a biopsy, we'll talk about the degree of fibrosis in the degree of steatosis getting a little away from the hepatocellular carcinoma arena for metastatic colon cancer. Those patients will all be treated with chemotherapy. And so veno-occlusive disease and steatohepatitis related to the chemotherapy given routinely for metastatic colon cancer, you're going to want to report on those two elements in every biopsy.

**Dr. Gladell Paner:**

So what is on the horizon for CAP protocols of hepatocellular carcinoma that may be considered in the near term?

**Dr. William Chopp:**

Well, I think Dr. Hart kind of gave you a preview of some of the things that we've been looking at. Obviously as you alluded to, a lot of it's by histologic type Right now things are moving past that. We have some great work by Dr. Hart and Torbenson and Sanjay Kakar and all that wonderful group there. That's kind of given us a little bit more that we could actually apply to this. And as you said, as I alluded to before, we want to find ones that are clinically meaningful, not just to have a descriptive thing, but things that mean something to the patient. So I think Dr. Hart kind of alluded to a couple there, and I think the next time we come through, I wouldn't be surprised if a couple of those are in there.

**Dr. Gladell Paner:**

Thank you, Dr. Chopp. And I'm going to look the same question to you Dr. Hart. Do you think there's any additional parameters that probably there in the horizon?

**Dr. John Hart:**

Yes. I think the subtypes are the main thing. We're going to have some molecularly defined subtypes of hepatocellular carcinoma down the road that will need to be included when there's sufficient data for the powers to be, to feel that they're absolutely necessary. There's one thing that I'm hoping for in the next, and that is to get away from the microvascular invasion up staging the patient. This puts an incredible amount of pressure on the pathologist. I think we're all practicing pathologists and we know how difficult it is to reproducibly recognize microvascular invasion. And it's something that when I'm looking with our fellows, they're trying to make a decision. Is this because it does upstage the patient? Whether microvascular invasion is important or not to recognize is really difficult. So I am hoping that maybe that can be dropped. Certainly macro invasion of a vessel is obviously very important, but it becomes an issue also in these treated cases and how much sampling that you're going to do in the area. I always feel a little uneasy when we have a large area of killed parenchyma, a lot of parenchymal extinction. Trying to submit all of that tissue. Looking for things like microvascular invasion can be quite difficult.

**Dr. Gladell Paner:**

Thank you, Dr. Hart. I'd just like to go back to Dr. Chopp just in case you have additional comments on that.

**Dr. William Chopp:**

No, I'd like to say I think there's a lot to that. All of us have that consternation. Whatever system you look at, it's in the endometrium. Or if it's the thyroid looking in the capsule for the vascular invasion, we could all ask ourselves, there's pathology of sometimes not a precise science in some of that lymphovascular stuff. And there's always papers that try to give you a kind of a hold. But I do think you make a good point when something's not very reproducible. Sometimes we have some criteria, is that something we can hang our hat on? And that's what I want to bring up, how these protocols are leaving and breathing documents and they change over time. And with that, as people give suggestions like Dr. Hart and for the pathology community, they don't know, you can submit your questions about things that you have questions about to the committee.

And we look at those very seriously and things like that are things we look at. Try to review the data and see if we can come up with changes that are better based on that newer literature. Like I said, we are a brethren, we're a community here working together, trying to do the best we can. And we have experts along the lines with Dr. Hart and crew, but we also have general community pathologists that are going through things every day and that send us questions just like this that we look at and try to answer. And sometimes we scratch our head as like, why have we done this for the last 10 years and made people do this? Does it really make sense anymore? And with the newer data. So as I say that, I think the biggest thing is we're a community. We want the experts that are doing the research, but we also need the community people that are practicing day-to-day saying, Hey, is this really something that we need to do? And is this something that's really bringing value? If it's not bringing value or reproducibility, are we really doing anybody any benefit?

**Dr. John Hart:**

Yeah. Well, here in the HCC, it's T one versus T two solely on finding a micro. I don't know if any other cap protocol has a microvascular invasion changing the T stage that dramatically. But anyhow, just something I needed to get off my chest.

**Dr. William Chopp:**

No, no. Hey, I think that's well taken. And these are the type of discourses I think people have. We want to make things better, and I think all of us want to make things better. And like I said, sometimes you look at something you're like, why have we made people do this? And what's the actual literature behind this? And that's what we want to look. Let's go to that primary literature that made somebody do that to see is it really there or not? We try to base a lot of the things on the AJCC, but let's look at their primary literature of why they place in there as well. Like I said, living and breathing documents. So that always can be improved.

**Dr. Gladell Paner:**

Thank you, Dr. Chopp. Yeah, so Lymphovascular Invasion equity is also being looked at into the staging of testicular cancer. So there's something similarity there, similar there for testicular cancer and also liver cancer. So unfortunately that's all the time that we have. So I would like to thank Dr. Chopp, Dr. Hart for your expertise and insights regarding the diagnosis and reporting of liver cancer. And I will go back to you, Becca.

**Becca Battisfore:**

Thank you, Dr. Paner for leading the conversation. And I'd also like to thank Dr. Chopp and Dr. Hart for your insights on this topic. And I want to thank you all for listening to this CAPcast. You can find the cap's hepatocellular carcinoma protocol, along with over 100 other protocols designed to assist pathologists in case reporting on our website. If you have questions or comments about any of the protocols, please email cancerprotocols@cap.org. And for more information about the CAP, visit cap.org.