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Optimizing Biomarker Testing to Guide Treatment Selection for Metastatic Colorectal Cancer

Announcer:
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Dr. Montgomery:
Well, hello colleagues. My name is Elizabeth Montgomery and I'm a Pathologist at the University of Miami in sunny Florida. And I'm working today with my old friend, John Marshall, who's a fabulous Oncologist at Georgetown U. We used to be together there. And as you know, we'll be talking about biomarker testing, some issues with tissue sampling, and then, what happens after all that stuff is done.

So, let's start with a case and let's see where it takes us. So, a 63-year-old woman had a biopsy of a sigmoid colon mass. No MSI testing was done. No BRAF testing was done. But let's go back a little bit and kind of talk about what happens to tissue, because I know in med school now a lot of colleagues aren't taught. So, what you see here is kind of what happens to the tissue. Notice I put a ruler there, and then you can see just beneath the ruler on the right is some green thing. That's a paraffin block. And you can see from the ruler, it's not very big and there's little stuff in that. And then below that, of course, without patient identifiers, you can see slides from several different patients. And of course, the old pink and blue tones, hematoxylin and eosin. Just to give you an idea of how tiny the tissue fragments can be, let me – I've set a slide to the side from today's work, and I'm holding it up to the camera. And you can see that often the tissue fragments – and this is, you know, you got my finger there – can be really teeny tiny. And I know we'll get into this – more of it, often we have to educate our endoscopists about taking plenty of tissue because nowadays, so many ancillary tests are requested.

Of course, you can see those slides at 1X, and then on the right, there's a hematoxylin and eosin stain section of a colon cancer. At the top of the image, there are some benign colon glands, and below is a classic appearance of the old boring, moderately differentiated adenocarcinoma with necrosis inside the lumina of the abnormal glands. The gross appearance actually is what we see if a resection is done. And of course, you can imagine just from the cavitated thing here, that the endoscopist has to choose where to biopsy, and sometimes biopsying that nasty middle part just results in a bunch of necrosis. Sometimes biopsying the edge of that rolled up stuff results in a diagnosis of adenoma, and it's not helpful even if there's a clinical cancer. Obviously, with the resection a diagnosis had already been made.

So, I've got a couple more pictures to kind of remind us. This is a very nice image here that shows an interesting phenomenon, and that is the presence of the so-called orphan artery. So generally, we like to see an artery and a vein, and here we see an artery on the left, and then there's a bump of tumor on the right, and often this kind of thing proves to be venous invasion. So, as we look at the next slide, you can see I've done a very poor man's trick. On the left, you can see the elastic of the artery, and then on the right you can see the residuum of a vein. The black stuff is elastic and there's a malignant gland sitting right inside a vein. This is on the fast track to get you guys a liver metastasis to deal with.

So, that kind of brings us to the point, what are the NCCN guidelines? What do we need to be doing to follow standard of care when a patient walks in the door with an adenocarcinoma of the colon?

I'm going to let you please chime in, John.

Dr. Marshall:
Yeah, let me jump in. You know, I think we forget all of those steps and those processes, and you might get from an endoscopist, say, I don't know, 3, 4, or 5 bites of tissue, some of which are useful, some of which are not. You try and preserve all of those things you can, right, and then keep them in that paraffin block for now and for later. On a gross specimen like that, I always wonder how you decide what ends up in the paraffin block. If you've got, like a 5-, 7-centimeter tumor sometime, you must end up taking a sample of that to save for later. So, what's that decision making like for you guys?

Dr. Montgomery:
So, of course, the surgeons are well familiar with it, but we sample the margins, and of course, that's for the surgeons. We must dissect out lymph nodes. And for the tumor itself, in the past we were kind of sloppy and just took a section or two. Now, we carefully slice the entire thing, look for the deepest point of invasion, make a slide of that, and then we make sure we put in a lot of sections to catch all of the things that are so important when patients are cared for.

Dr. Marshall:
Yeah. So, when we get that first path report, we often get the sort of T&M stage, the moderately differentiated, the number of nodes, and then that nice line across the bottom that says pending additional tests, something like that. And so, we're excited for those additional tests. So, maybe come back and talk a little bit about what your all's SOP is for what those additional tests are.

Dr. Montgomery:
So, happily, in our organization, because we try to communicate with our oncologists, we try to do as many of the things that we can up front in the biopsy. Of course, if there's a high-stage tumor that allows for planning of neoadjuvant treatment, and that's of course, learned on imaging, not at the time of biopsy.

In our institution, everybody who walks in the door who has a biopsy that shows colorectal carcinoma is immediate – or the biopsy, not the patient – the biopsy is immediately subjected to mismatch repair protein, immunohistochemistry and HER2 immunohistochemistry. And that works well because those are done within 24-hours of the biopsy. And yes, you're going to need your BRAFs and your KRAS's and your mutation burden and all that good stuff. But this is what – you know better than I, but this is your branch-point if it's microsatellite unstable, as opposed to stable.

Dr. Marshall:
Yeah, I think it's really important because so many places have not yet adopted that strategy. They might even have a relationship where they wait for the oncologist or some other person to request that additional testing, particularly if there's limited tissue available. But as you say, this can be done in everybody's shop because what, it's immunohistochemistry. Maybe you can sort of walk us through what that looks like.

Dr. Montgomery:
I mean, basically we do immunohistochemical staining on boring paraffin-embedded tissue. We do it quickly. So, let me show you. Let's get back to our lady who's come in and had her biopsy. This is a beautiful image, in my opinion, of course, because I took it. OK, I'm being silly – of a colorectal adenocarcinoma. And hopefully all of you remember from your schooling years – I hope so – that adenocarcinomas are composed of glands with varying degrees of resemblance to normal glands. And you can see some very nice tubules in the center, that's perfect colon cancer. But then you'll notice that there are a lot of these tubules that are distended with mucin and hopefully, we have some nice arrows that you can enjoy. And that's an adenocarcinoma. There's nice mucus.

On our next image, what we can see is a very high magnification, and I'm trying to show you lymphocytes enmeshed within the tumor cells, and of course, they're called tumor-infiltrating lymphocytes. They're usually T-cells, or they are T-cells, and they are a hint that there might be an important phenomenon. So, in this woman's tumor there was loss of MSH2. We did all four mismatch repair proteins, MLH1, PMS2, MSH2, and MSH6. So, of course, since MSH6, as you know, is the little brother of MSH2, that was also lost. But I'm showing you the MSH2 because it's important. You can see that the malignant glands lack MSH2, whereas the surrounding stromal cells have it. It's a mismatch repair protein, you need it in your body. So, it's completely absent, and that sends us down two paths, and I'm going to send it over to Dr. Marshall because he'll remind us of the two paths that we're worrying about in this patient all of a sudden out of nowhere.

Dr. Marshall:

Well, let me come back to the imaging that we were looking at for this patient. So, could you, as a pathologist, distinguish germline from acquired based on MSH2 presence in the normal stroma versus the tumor? And, because my experience has been we've been going ahead and doing genetic testing. But now that you've shown me this, it sort of makes me think maybe we could.

Dr. Montgomery:
You probably still would need to confirm for germline mutations, but the vast majority of the time, if we see loss of MSH2, it is Lynch syndrome. However, these stains aren't perfect, so once in a while there's something that goes wrong. If there's isolated loss of MSH6, that can actually simply be a reflection of mismatch repair deficiency, often from loss of MLH1 by methylation because MSH6 has a lot of – I can't remember if it's poly-A tracts, but a lot of long tracts that are prone to replication errors. So, if your MLH1 isn't working, occasionally you can have, sort of, fake loss of MSH6. But if we see MSH2 loss, it essentially means Lynch, but it's not perfect. And this is a big diagnosis, so to me it makes sense to confirm it. But the best part is that whoever does the sequencing knows what to go after.

Dr. Marshall:
No, I think this is really important. It is a major branch-point for us.

Dr. Montgomery:
It's a huge branch-point, and in this case, we've got two branch-points; MSI high and, oh my gosh, she might have a syndrome.

Dr. Marshall:
Yeah, inherited cancer syndrome. And I think on a very basic level, I think still to this day, many people who are interpreting these reports that we get, when it says present, present, present, present for these four proteins, that's normal. But when you're missing two of them or one of them, that's the abnormal to look out for. So, just a heads up to make sure we know that we're interpreting the results correctly. And as you alluded to, what this is really generated is finally, for us in colorectal cancer, we have some molecular subgroups. And the one we were just pointing out is this first branch-point of MSI, microsatellite instability, versus stable MSS. And we need that because we need immunotherapy to come into play for those MSI patients. There's an entire algorithm, separate algorithm, for those patients. But as you alluded to earlier as well, we also need to know other genes. The HER2, which can be done typically by most folks locally, but then you get into more and more complex genetic testing also can be done locally by local pathologists, but more and more of us are partnering with organizations, companies, that do this testing. So, you need to know all the different RAS mutations, you need to know BRAF mutations.

But what's so wacky about this whole world? The more we dug into this, the more we've begun to see that different locations of the primary predicted for different behavior. And so, as we started to map the colon and the different mutations that we see, the different subgroups, you actually saw a distinction, maybe along the embryological lines of the colon between right and left. Now one theory is it's the embryology, the other theory, it might be microbiome. But clearly, we need to note the location of the primary because it may in fact be driving some of our decision-making.

So, I alluded earlier to the fact that we need more and more tests. So MSI, we talked about, HER2 we talked about, but then then you get into more complex things such as RAS, BRAF, something called tumor mutational burden, the NTRK or ENTREC mutation is actually, an RNA analysis, it's an RNA fusion you're looking for. And then, CT DNA is a blood-based test. So, more and more, this testing has become increasingly complicated, but with it, increasingly important.

Now, we talked a little bit about testing, but why do you care? Well, because different therapies are tied to different results. MSI down the immunotherapy pathway, BRAF, bad prognosis, down a more complex aggressive chemotherapy route. Your HER2, it brings new therapies to the table. If you're RAS mutated, it takes therapies off the table. So, the way I think about it is you need to know all of these in order to map the course for the patient in front of you. What tools do you have as an oncologist in hand, which ones are excluded due to predictions of resistance?

So, Dr. Montgomery, what do you think about this technology? How's it sort of affecting your-all's practice in pathology and sort of the role and the relationship you guys have with the oncologists and with the partnering companies?

Dr. Montgomery:
It's complicated. as you just said. Luckily, the things that we can do just to get the patient plugged in initially are quite easy and available in most pathology labs. We do, as I mentioned, the mismatch repair proteins on teeny tiny biopsies with the HER2. We don't see many HER2-positives, but you guys know that. And then, in our institution, various oncologists prefer various commercial labs, and I don't know what the right answer is with the commercial labs because you know they do such a high volume that they can do it in a more cost-effective manner than individual institutions, and molecular testing is generally a money loser. So, individual hospitals don't want to offer it.

Dr. Marshall:
You mean we care about that? We don't care about that in healthcare, do we? Whether it's – I don't know, we don't.

Dr. Montgomery:
No, we don't care. But it's expensive, and it has to be paid for and it's important. And then, the good news, of course, as you know, is there are some patients who don't need any chemotherapy and it's great if we can get those patients scoped on time. If people can walk in the door before they have a bona fide colon cancer, but that's not really the realm of oncologists except educating patients to do preventative things if they come in with something else. And I think you're the one who ends up funneling things.

As far as the testing goes, obviously a big issue is, is there sufficient material for sequencing studies? And that's where we come in to educating our colonoscopists and to taking really, way more biopsies than they think because frequently, a colleague can think that he or she has done a really wonderful job sampling, and in fact, only one little, tiny area shows the neoplasm. And it's a bigger issue with gastric biopsies, which is a little off-topic. But probably similar principles apply. I know the gastric societies, or I'm sorry, the upper tract people say you must take at least 10 good pinches in a stomach tumor because the tumor can be patchy. A little less of a problem in colon.

Dr. Marshall:
I was thinking about our relationship with interventional radiology, because they're doing these mini harpoons to get core samples and I think really, gone is the day of the strict FNA, just a quick needle and a quick needle out, for most of these biopsies, because we need multiple core passes in order to have adequate tissue samples, right?

Dr. Montgomery:
That's absolutely right. And really, I mean, the clever kind of top tier interventional radiologists understand this very, very well and really do a fine job of taking a lot of cores and getting good material. Not all of them do, and then re-biopsies have to be planned, which are a royal pain in the well - rectum. So, you know, I guess all we can do is keep gently educating.

Dr. Marshall:
Yeah. As our hospitals have gotten bigger and more spread out. And, of course, I mean, we, as you remember here at Georgetown, we keep our pathologists in the basement. You live in Florida where there are no basements, I guess, so you get a window. But, you know, we need to – we don't run into each other as much and so that communication needs to be bridged somehow. And so, back and forth between, say, oncology and pathology because then it becomes the oncologist's job to communicate that through the patient who's trying to figure out what they've got. They're busily Googling on their side, and the more data we can provide them, the better.

Dr. Montgomery:
So, I have to say, and I'm sure you do it at Georgetown, our tumor boards here are actually very effective in making sure that loops get closed. And you know, we are all imperfect and flawed and human. I'm not going to tell you that I haven't forgotten to tick the HER2 box and then an oncology colleague will say, you know – oh, I am so sorry. I will do that immediately. But, you know, that's the beauty of having close communication and having tumor boards because then these missing things are caught. And I would encourage all colleagues to try to participate in them because they elevate all of us. I'm sure they do at Georgetown as well as here.

Dr. Marshall:
I think one of the pressures you and I both feel is something that gets bundled into turn-around time. How quickly can we go from, you know, a mass is found, a biopsy has been taken to, a pathology read to, a molecular result? And the different tests have different time windows. But it is in the order of a couple of weeks if you're doing full panels and the like, and there are also some barriers with reimbursement and the like about waiting a certain period of time to send out to other things. So, we do have some cultural and socioeconomic barriers beyond just the technology barriers of how long it takes to do certain tests to get that turn-around time as quick as we can, so we can make treatment decisions. But we're all doing it as fast as we can.

Dr. Montgomery:
So, I know that if a biopsy is done in our clinic, you know, today, I will see the slides tomorrow, put out a report, in most cases, and then the ancillary studies will be another day. But there are occasional tumors that haven't read the textbooks and are just weird, or look like they're, oh, this might not really be colorectal cancer, it might be a prostate cancer spreading across the street. And then, that takes longer. But generally, these can be turned around quickly. I hope most people are experiencing that. I guess it depends on the responsiveness of the laboratory.

Dr. Marshall:
Yeah. No, I think it does. And so, you know, to kind of bring this back around, we go from that opening biopsy, the discovery of the mass, the sort of Wham moment for the patient, then the handoff to pathology. We've talked with great review of the processing of that and

then that gets us to the tests that we need to have in order to manage patients with metastatic colorectal cancer, so.

Dr. Montgomery:
So, tell us what's actionable today.

Dr. Marshall:
So actually, all of these on some level factor into treatment decisions, right? So, we talked about the RAS mutation that rules out EGFR drugs, although there is one new drug that targets a specific RAS mutation that's now in play. BRAF matters, HER2 matters. They all matter. Now, you have to remember, as you alluded to, HER2 is not common in tract, or very, very rare. Some are more powerful than others in terms of their clinical impact. But you need to know all of these, in my opinion, before managing a patient.

Dr. Montgomery:
Well, it seems like the summary here is that we need communication, and we need to expeditiously get all this stuff done. The molecular testing, sadly, can take weeks, which is why it's imperative to immediately get the first branch-points taken care of. And obviously, you're going to be doing imaging to make sure there are no liver metastases and whatnot up front, and I'm sure there are all sorts of other fun things that the oncologist has to start dealing with.

So, I'm a pathologist, so I'm not the person who's helping the patients navigate through. I'm kind of a branch-point. But in this module, we're going to discuss some of the patient issues, tissue issues and just systemic issues that are barriers to doing the best job we can for our patients. So, let's start with another case.

A poor man walks into the emergency room with blood coming from his bottom and somebody realizes that, oh my gosh, on rectal exam, this man has a very low rectal mass and takes a biopsy. He has no insurance, and he basically has come in miserable and obstructed. The emergency room biopsy comes to us. So, we've got a problem, Houston. So, Dr. Marshall, this man has no money, he's miserable, he's got a terrible low lesion. What next?

Dr. Marshall:
Well, if he was almost in any other wealthy country but ours, they would be solved because he would have access to healthcare, and the like. But of course, that's another module unto itself about how do we deal with taking care of each other in this setting. But we've now uncovered and made a new diagnosis of somebody with a rectal cancer, and we want to be providing the best care we can for this patient. But as all of you know who are listening in, cancer care is very complicated. It requires multidisciplinary care, appointments, rides to get to those appointments. You need to have medicines that supplement your nausea, for example, pain medicines, etcetera. All of these things require, if you will, a village on behalf of the patient supporting that patient. We have our own multidisciplinary village that we bring to try and deliver optimum care, and we know in the United States that there's actually a fairly wide range in outcomes depending on your zip code. Honestly, the best predictor of survival with many cancers is in fact, what zip code you live in, which is sort of a shocking statistic.

Even within here in Washington, DC, between a couple of hospitals that I work at, the survival of colon cancer is one year different. And it's not about how smart the people are who work there, it's about can that patient receive the healthcare that's required and navigate that. So really, to me it comes down a lot to not only the health literacy part, do you understand what it is that we've just told you or made recommendations for, etcetera, do you understand the urgency and the like, but do you also have the ability to comply with that? And I think this is a barrier for all of us everywhere, frankly, not just here in the United States. And it's not just a city problem, because we know that this is also a major issue in rural communities where you need this multidisciplinary team to be available for patients. You need to have all the bells and whistles, the outstanding pathology, radiology, oncology, surgery. But communities of 50,000? Yes, they're fabulous physicians, but do they have a GI cancer multidisciplinary team at the local hospital? Maybe not. And so, there you've got issues of just where you live. Again, back to ZIP code, not necessarily around economy or economics, but access due to distance and geography.

So, we have this explosion of knowledge, right, that's happening, and not everybody's keeping up as well. Face it, if you're a general physician, a general oncologist, a general pathologist, there's a lot to keep up with in terms of what's the proper testing, and the like. And, you know, how do you find the result? Our electronic medical records are not that friendly in terms of where these things sit. Is it a lab? Is it pathology? Was it done somewhere else and is scanned into some folder? And then, I want to kind of point out one problem that we've uncovered. As we've gotten better and better about the genetics on things, what used to be, let's say, a non-important mutation, let's say a bracca of unknown significance, but I did the test 2 or 3 years ago. That test in the back of your EMR doesn't know that there was some paper in nature medicine that now says that that bracca matters, and so we have to be aware enough of what we've done in the past and managing that going forward, so our knowledge and the patients knowledge is keeping up with all of this.

Dr. Montgomery:

So, Dr. Marshall, sorry to interrupt, but is it your practice habit to periodically go through old molecular tests from your patients to see if, wait a minute, maybe we can reframe this?

Dr. Marshall:
If they're sitting in front of me, yes. If I'm not thinking about them and I've stopped following them, no, I'm not going back prior to check in. Where we are seeing some progress is that some of our partner companies are, you know, where they know in their systems that a patient's, you know, result has changed in importance. We are getting notifications, and the like. But that's not consistent. Not consistent across the board. So, I'm not arguing to be paranoid about this, it's more about being aware of it. Think about that poor radiologist, for example, who read a scan from 3 years ago and there was a little tiny dot on the lung that you wave off and say that's almost certainly nothing, and 3 years later it's now a mass, so you get nervous about missing almost anything. Well, that's now true for genetic reports because they evolve overtime as well.

So, we've had to really reestablish workflows and SOP's and the like to account for this additional information for all of our patients. You know, we're charged with addressing these cultural barriers as best we can so that we identify those patients who can benefit from treatments, get them in, get them the support they need. But let's kind of go back to the patient you presented and that biopsy that was done where it was done in the emergency room, I think you said, and maybe talk us through some of the testing on this patient.

Dr. Montgomery:
That's fantastic. So, this is the biopsy. This is all there is. This is blown up way, way, way bigger than the biopsy was. It was probably the size of the gnat's wing. But they're two fragments. The one on the left really doesn't have much going on. At the top of it, there is normal colonic mucosa. At the bottom of that piece on the left, there is a tiny bit of cancer. On the right is cancer. It's a beautiful adenocarcinoma, or to me, it's beautiful. Not for the patient. It's ulcerated. All that pink stuff at the left part is just ulcer debris. So, that is all the tissue there is. How far can we stretch it? And of course, as I mentioned, at our institution, all these biopsies get HER2 immunohistochemistry and MMR protein immunohistochemistry. This uses five sections from the paraffin block, and they're each 5 microns, or 4 microns. So, there's still plenty left for some testing in this case.

So, remember, this poor man has no insurance, and here's the result, which is a good thing, but in a way, it's sort of a double-edged sword. So, his tumor was microsatellite stable. All-form is metric. Pair markers were intact. And this is the only really strong HER2 I've seen since we started doing it. Usually, they're less strong and then we have to send for a FISH confirmation. And you're looking for this strong membranous staining around the malignant cells, how that's being shown. And so, this is targetable. This is actionable.

Now what, Dr. Marshall?

Dr. Marshall:
Yeah. So, this is the issue because you know, even standard chemotherapy and treatment for these cancers is not easy to navigate. The medicines, even basic old-time medicines, 5 FU, oxaliplatin, these drugs, you know, they're expensive and they're hard to navigate for patients. So, now we found something of a new medicine, new approaches to the treatment of HER2-positive colorectal cancer that will be an option for this patient. And no one of us would be able to manage this without our health insurance infrastructure. So, in many ways, we're not only sending this biopsy for pathology and waiting on analysis of that, our social work team and others are immediately in charge of trying to establish some social options for these, some social support options for this patient so that we can offer treatment. And included in that for this patient, will be HER2-targeted therapies. Only about 4 or 5% of all colon cancer patients have HER2-positive, and we'll talk a little bit more about that in a minute. But – so it is a rare finding. It's typically right now, not the initial treatment you would give. It would be something you would do second. But it is something that's teed up for that.

So, as I mentioned, our workflows are in place. That includes, if you will, a precision medicine test of the patient's medical knowledge, their own village and their level of support, their ability to receive and maintain a cancer therapy approach to get your optimum outcomes. And then of course, once you then have all of this information, you can put together the plan for this patient. So, I think this is a great case that adds a layer of complexity that the patient brings to the table in addition to the complexity that the cancer brings to the table. Great case, Dr. Montgomery.

Dr. Montgomery:
It is a great case. Actually, he was – so, I'm in a health system that has essentially two places, one where the folks have insurance and the other one where you can walk in the door and not have a dime in your pocket, and you will be looked after. It might take a little while, but you will be looked after. And there is some mechanism in this charity hospital where this man presented to see to his care. But it ends up being an uphill battle for the things that are expensive. People are determined and caring, but it's still really hard, as you know better than I.

Dr. Marshall:

Yeah, that's great. Well, it's not great. It's great that you have the support.

This is Module 3, where we're really going to drill down on some of the main clinical trials that establishes the biomarkers and the therapeutic interventions that one uses when one uncovers those biomarkers. And we're going to start as we have been starting, with a case. This is a 56-year-old man. He's married, he has two grown children. He basically has some abdominal pain, which is not uncommon how these present. And he gets a CT scan, and the CT scan is dramatic with a bunch of liver lesions and ascending, so right-sided colon mass, and some small lung lesions. And in this case, this patient would have what we call unresectable metastatic disease. Sometimes with one or two lesions we might go in and remove the metastatic – the oligo metastatic disease, but in this case, there are too many here to treat. He gets a colonoscopy, and if you will, the lone biopsy is this adenocarcinoma with a couple of alligator clip biopsies from the gastroenterologist.

And so, from my perspective, here's a patient with symptomatic widespread metastatic disease and pretty clearly systemic chemotherapy is the choice. Now, one of the things that goes through our heads, is should we get more tissue because of the – so, the answer is yes.

Dr. Montgomery:
Yeah!

Dr. Marshall:
From the pathologist. So, tell me a little bit more about what I can learn from that colonoscopic biopsy. When I was trained, which was 1,000 years ago, the rule was you had the biopsy-prove metastatic disease. But we don't do that as much anymore. But I think maybe the fact comes back because of tissue acquisition.

Dr. Montgomery:
Yeah, it was a different ballgame, as you know, you just needed confirmation for uni-type therapy, and then obviously, in some ways by idiot logic, it makes more sense to be biopsying the thing that's already spread to get your molecular testing. Probably, it would have been better if the gastroenterologist had taken more biopsies, but these things happen. And I think many of us old-timers are kind of thinking in an old-timer mentality instead of a, we need to target things. We need the tissue to do the targeting.

Dr. Marshall:
Can you tell me a little bit about if I – let's say, I get wildly successful with the chemotherapy here and there's nice tumor shrinkage, but there's still residual disease, have I in some way made it harder to do molecular testing on that tumor if I went back and got a biopsy of responded cancer?

Dr. Montgomery:
Well, the biopsy of responded cancer won't have any cells in it, if it's really well responded. But of course, those little filler cells can still be tested, but it can be hard because you need a certain percentage of cellularity to be able to amplify your DNA and RNA to test properly. So, it's nice to have gotten it up-front. Do we do it later? Of course, all the time. And I suppose that will get whatever mutations have been introduced over time after you whack it once with chemotherapy. Feel free to use technical terms, by the way.

Dr. Marshall:
But so, a lot of times now, we have these new blood-based tests, these liquid biopsies.

Dr. Montgomery:
Great.

Dr. Marshall:
And those, just to caution everybody here, can be very useful, but they are looking for just sort of generic cancer mutations. And the way that next gen sequencing works is if you're not really shedding a lot of, if there's not a lot of cell turnover, that can be negative or even misleading. So, there are plenty of times where we'll do that because we can't get access, the tissue's too small or it's in a difficult place and use that as a substitute. But in my opinion, I think Dr. Montgomery might agree with me, tissue is still the gold standard for molecular profiling?

Dr. Montgomery:
I would strongly agree with that. And I mean, I'm sure you've had the situations, for example, anytime I, you know, cough sideways, I probably get a little RAS mutation somewhere and then it just sort of takes care of itself over time. And so, you can have – you can find these RAS mutations in somebody who's walking around healthy as a horse. So, you really do kind of want at least some point have a real piece of tumor. We're not quite at the point where liquid biopsy is ready for absolute confidence, but it's great. I think you guys do a great job using it to follow, right?

Dr. Marshall:
Yeah, yeah, that's exactly right. So, you think well, why do you care? Well, you care because there's a lot of different things you can uncover. That 45% there at the top of RAS mutations means if you have one of those, you're not going to be giving one of the classes of drugs because it predicts for resistance. BRAF at 8%, or HER2s, and others are less common, but very important because of the medical impact of those treatments. And honestly, we've shifted away from big Phase 3 studies where A is compared to A plus B to, you have the right molecular profile, we have the drug we think fits. And more and more, approvals are based on even single-arm Phase 2 studies. So, we're dependent upon these tests in order to both do clinical trials, but also to designate which treatment? So, if you look at the only reason oncologists have not yet been replaced by AI or robots, is because we have to integrate all of these different features.

So, what does the patient bring to the table? Their comorbidities, their age? What is the tumor burden? In our case patient that we're showing, a lot of tumor burden. So, we're looking for a good response. He's symptomatic from that, where some patients present with very small tumor burdens and much less symptomatic. So, maybe I don't need to push as hard. Then, I've got to know what chess pieces I've got on the board by knowing the genetic abnormalities and immunohistochemistry abnormalities, and then I got to know what the patient wants. What are the patient desires. And it takes all of this and chat GPT is not quite ready to deliver that for us. And just to remind everybody, if I look at what drugs we do have, what does the chess board look like? That group on the left doesn't require molecular profiling, so we do not have a certain gene or molecular expression which predicts for group – the isatuximab/panitumumab group, that's the group that's required to have RAS testing, and BRAF testing, and her two testing. I'll come back to that in a minute.

Before you give that, you even need to know where the primary was. If you remember, our patient's tumor was on the right side. Really, the data says only left-sided tumors respond to these treatments for unclear reasons. And then you have the BRAF, about 9%, because we have therapies. And then, what I will call the rare tumors, where just a few patients have those. And so, I always like to think when I'm opening a pathology report to Dr. Montgomery, this is for you to reflect on, is I almost feel like a kid opening a Willy Wonka chocolate bar and wondering if I'm going to get a golden ticket inside? Am I going to find something that you've uncovered, that's going to make a big difference for this patient. I don't know if you feel that way when they become positive for you.

Dr. Montgomery:
Oh, I don't get the joy that you do because I'm not directly talking to the patient, but when I see that there's a mismatch repair deficient tumor, I feel like I'm on the upfront test. I feel like the oncologist has hit the lotto and I'm really happy. Obviously, the HER2 is a little bit of a more slippery slope. And John, here's how dumb I am. What is puquitinib?

Dr. Marshall:
Puquitinib's the newest medicine that's going to hit the ground at the end of 2023, where it's predicted any day now to have FDA approval. An oral VEGF inhibitor that looks very good in Phase 3.

Dr. Montgomery:
Awesome.

Dr. Marshall:
So, it's a sort of oral cousin of the bevacizumab gang.

Dr. Montgomery:
Wonderful.

Dr. Marshall:
So, once you know this, think about those folks out there who take care of breast cancer. You don't start without knowing HER2, ERPR, etcetera. The same is now increasingly true for colon. So, I've organized this slide. It's lines of therapy, depending on what gene mutation you started with. And so, your algorithm, your pathway varies based on this. And this is why, yes, you can start with, sort of, generic, if you will, chemo and maybe bevacizumab without molecular profiling, but you need to know pretty quickly what the other markers are, particularly MSI, particularly BRAF and HER2, because you're going to need to know very quickly. And we talked a little bit already about turn-around time, and sometimes we feel, like, obligated to start before we have all these tests, but reiterate again, Dr. Montgomery, about the timing on HER2 and MSI. That's quick, isn't it?

Dr. Montgomery:
All right, well, that's easy. The initial turn-around time just for the proteins, remember we talked about the proteins, we're not talking about the molecular test for microsatellite instability. We're talking about proteins. That's like 24-hours from the time that we actually see the slide that shows the cancer, and same with the HER2. However, if the HER2 is equivocal, then it has to be sent for FISH to see whether it goes one way or the other, and that's often another week or so, which is very stressful. I have a question for you. As your patients come in the door and all they've had is a biopsy, how do you sort of balance this staging against talking about chemo? Because

obviously with the biopsy, you have no idea what the stage is. So, how do you kind of get them into the flow?

Dr. Marshall:
Almost always, by the time they make it to the oncologist, somebody has done a CT scan. It's rare that you haven't had some imaging, but that does happen. Sometimes we move quickly enough that we go right from the gastroenterologist office to our office, and then we begin the discussion of we need to know where it all is.

Dr. Montgomery:
I see.

Dr. Marshall:
So, you map out the process, and it's all part of the subsequent testing. There's a lot to be done between first visit with oncologist and first treatment, including as you mentioned earlier, multidisciplinary tumor boards and reflection on the pathology molecular testing. So, there's a lot to learn before you can refine it to the level that we have on this slide.

Dr. Montgomery:
Got it. And then, is rectal change the algorithm that you were just presenting or is it all still the same idea?

Dr. Marshall:
So, in a localized disease it clearly does, because that's when radiation and different drugs come into play. But in metastatic disease, that's couched in the left-sided colon cancers versus the right. But biologically, your question is very smart because it probably is a different subgroup, but we haven't yet really figured out how it's different or how it should influence our practice.

So, let me just kind of highlight a couple of studies that I think are important to understanding strategy. This is a study out of Japan and this sort of kitchen sink one versus kitchen sink two. So, this is 3 or 4 chemo drugs plus the only variable here is a different biologic, cetuximab targets the EGFR pathway. You remember, we learned that you have to be RAS wild-type, BRAF wild-type, HER2-negative, and left-sided. And when you do that and compare it to the same chemo backbone with bevacizumab, you actually see very nice positive results. A concept that we have called depth of response. So, if you have right patient right drug, you drive the cancer back much, much further than if you don't. So, knowing this, even at the front line, one could justify using cetuximab as the initial treatment to get your best shrinkage for that patient.

Dr. Montgomery:
And you're talking about all-comers, correct?

Dr. Marshall:
All comers, if you have a – but all-comers in this subset of RAS wild-type, BRAF wild-type for metastatic disease. But we've alluded many times to the microsatellite instability subgroup of patients, and the first study that was quite dramatically positive was in metastatic microsatellite-high colon cancer. So, remember a lot of these patients are indeed inherited cancer syndrome. Some of them have acquired MSI, so ultimately you need to distinguish that. But what this study compared was single-agent pembrolizumab. So, this is an IO therapy, versus traditional chemotherapy in the MSI-high patient. And what you see is the response rate of the pembrolizumab was much higher than the chemotherapy. The toxicity was much less. But to me the most dramatic part of this is that 83% of the responders are still responding. So, if this worked, it worked for a long time. Flashback to, you know, Jimmy Carter, or former President Carter with his brain metastases from melanoma.

Dr. Montgomery:
Yeah.

Dr. Marshall:
He's, of course, still with us and this was 20 years ago, and that was maybe 15 years ago when he was treated. This is the same sort of what we call tail-on-the-curve. So, you don't want to miss this, right? This is an opportunity for single-agent treatment with a dramatic impact

Dr. Montgomery:
Right. I mean, how many people walk in who are on immunotherapy with these awful gastrointestinal symptoms, and then I see a biopsy. What percent?

Dr. Marshall:
Let me back that up. So, you know, the immunotherapy for all of its charms is in fact got some significant side effects.

Dr. Montgomery:

Awful side effects.

Dr. Marshall:
So, about one out of five patients who gets immunotherapy gets one of these autoimmune reactions, and that could be skin, it could be lung, it could be GI tract. We see a lot of endocrine abnormalities in this place. So, we have to monitor. Hey, immunotherapy has made us all better internists because we have to remember back to all of those different systems that can be affected by the immunotherapy. So, it's a really strong point.

But with that, has become what we call sort of immunotherapy fever. All patients know about these drugs. They too want to be that tail-on-the-curve, but we have to remember that most of our colon cancer patients don't have that MSI biomarker, and so there is a lot of work in this space looking at new immunotherapies. This is just an example of a clinical trial of two novel immunotherapies given at the same time where we weren't seeing dramatic responses, but we were seeing responses. And so, if this kind of data can be replicated for a larger patient population, then we will be seeing more and more immune therapy interventions even in the MSS patient.

So, let me drill down on something that we didn't do very well, or at least we didn't do very efficiently, and that is figure out for cetuximab and panitumumab who are the right patients at the right time. Now, the initial approval of cetuximab was in 2004. I was young then, and if you gave it to all colon cancer patients, we had a 10% response rate. Well, if you're thirsty in the desert, this is water, right? So, this was worth trying in everybody. But as you look down this table, you see first, RAS mutations, then BRAF, then left-sided. You can see that the percent of patients who are candidates is falling to the current level where it's only 15%. But then, look at the response rates. So, in the right patient at the right time you get much better benefit. Now, it's a smaller market, if you will, from a development perspective, but it's a much more effective therapy when you give it. So, it's eliminating waste and making us more efficient.

Same is true for BRAF. Now, this was first uncovered in other cancers, melanomas, other cancers. But we looked, and about 9% of colon cancers have a BRAF V600E mutation. So, it's a very specific mutation. But unlike melanoma where you can give one, maybe two drugs, blocking this needed more than one drug. So, you had to come at it from more than one angle because our pathways are not as crisp, it's not as dominant as some of the other cancer pathways. So, in this clinical trial, the BEACON study, it was a two drugs versus 3 drugs versus traditional chemotherapy. Very well-done study. And it actually showed that three drugs – so, if you hit the pathway three times, you get a better response rate, but it didn't translate into a better survival. And with that, there was a higher toxicity rate. So, the FDA, and I think appropriately, approved the 2-drug cocktail based on this critical BEACON clinical trial. And so, all patients need to know their BRAF, and we think even at frontline, because we're taking this second-line data I'm showing you here and moving it into initial chemotherapy. And ultimately, we'll move into the adjuvant setting for patients with that.

Now, the really big problem for GI cancers is this gene, the RAS gene. It's mutated in nearly half of all colon cancers, almost 90% of pancreas cancers, and other GI cancers. And the problem is, is that we can't really develop drugs. It's what we call untargetable right now. It predicts for resistance. OK, that's useful. But what we'd really like is to take advantage of it. And right now, there's only one G12C, which is only one that has a targetable agent for it on guidelines, etcetera. First approved for lung cancer and the like. But this is an area where we really need new drug development.

So, to kind of closeout this targetable therapies, the newest kid on the block is HER2. And we talked about this a little bit earlier, but if you look at all colon cancers, you'll get frustrated because it's only a couple of 3%. But if you look at that patient with the left-sided, so that rectal lesion. Patient whose already RAS wild-type, BRAF wild-type, etcetera, that's where they are. So, what I always coach the oncologists around me, is that that patient you're about to give the EGFR drug to that I just talked about, make sure you've also looked for HER2, because this also predicts for resistance to the EGFR, and yet, you've got therapies to provide that patient.

And the first demonstration of this was actually a Phase 2 open-label clinical trial – so no control arm – in HER2-positive colorectal cancers with a response rate, as you see there, approaching 40%, a progression-free survival of 8 months, and tolerable toxicity. So, this combination of trastuzumab and tucatinib together in the MOUNTAINEER clinical trial was a positive hit.

Now, one of the coolest new areas of therapy in all of cancer is this targeted smart-bomb antibody. And in this case, we're using trastuzumab, which targets HER2. Everybody knows about this. But instead of just blocking the receptor, why don't we stick some poison on it? And so, when it sticks to the cancer, it's delivering the chemotherapy to the cell that needs it. Of course, there's also bystander effect. So maybe the cell next door has really strong HER2 expression, but the one right here doesn't. Well, the drug's being delivered locally to both cells. And so, you get this sort of bystander effectiveness. The chemo in this case is a drug called deruxtecan. It's a topo-inhibitor. And these drugs have been highly effective at breast cancer and other cancers. Would they work in colorectal cancer? And the answer was, yeah, they work.

HER2 expression? And, Dr. Montgomery, I want to talk to you a little bit about different cancers having, sort of, different perspectives or guidelines on what is HER2-positive or negative. Maybe because their breast has very strict rules, gastric sort of follows, colon may be a

bit different. What's your take on this?

Dr. Montgomery:
So actually, as you allude to, there are some differences. For example, in breast cancer, this is getting very nerdy and technical, you want to see the HER2 on the entire membrane circling the cell for that to be a legit positive. We back off a little bit in the stomach. And you can see the, standing just on the sides of the cell, with the surface not having the staining, that's kosher. Colon, we've kind of parroted the GE junction and adenocarcinomas at the esophagus, so it's pretty close to that one, but it's different from the breast one. And then, you've alluded to something super important and what that is, is there is HER2 expression heterogeneity in tumors. And in fact, you can have a biopsy that's HER2-negative, and then when there's a resection, holy moly, a bunch of other stuff has it. So, the cool idea of starting with your HER2 as your anchor and having poison, if you will, attached to it, is awesome, because often we do see tremendous heterogeneity. And that's a perfect way to ZAP some of that. So, very clever technology that's coming up. But it's a big problem because there's very patchy expression sometimes and sampling error can be a big issue.

I know with colorectal cancer, sometimes we repeat the testing when we have a larger sample to see if we get lucky. I can't say it happens a lot, but it happens, and it certainly happens in GE Junction and esophagus adenocarcinoma. So, very good point.

Dr. Marshall:
Well, and also with these drugs, these targetable drugs, there's data in breast cancer that you don't have to have that full expression in order to benefit.

Dr. Montgomery:
Right.

Dr. Marshall:
So, we've taken some of the triple-negative breast cancer, moved over into a new category. We're not quite there yet in GI cancers. There is data to support that, but it's not as strong as it is, say, for example, in breast cancer. Can I ask you, sort of – I've admitted to lots of slowness in uptake in the oncology world about some of these. Is this true in pathology? So, are all pathologists kind of up to speed that they need to know where this tumor came from, what cancer we're talking about for the HER2-positive or negative?

Dr. Montgomery:
I don't think so. I think probably in those of us who have the advantage of having these tumor boards and being able to discuss things with our oncology colleagues, and then sometimes an oncology colleague will ask for something. It's like, huh, why you want that? Oh, because of this article. Oh gosh. OK, thanks. That's interesting.

So, unfortunately, yes, it's not all oncologists are created alike. Not all pathologists are created alike. We all know this. And I guess we all just do our best to elevate ourselves and elevate our colleagues.

Dr. Marshall:
And each other, right? So, it's a good open communication that's important to make sure everybody's on the same page. You mentioned earlier about, do we need to go back and test lung cancer? It's a standard to look for resistance. For example, breast cancer. It's a standard to look through new tissue through lines of therapy. With some of ours, I would say the answer is, yes. HER2 might be one of them. MSI is MSI, so we don't tend to repeat that, or RAS. They're very truncal mutations. But what I really do is go back and test the quality. How long ago was the test done? Was the breadth of the test good? Did we do it on good tissue? And so, sometimes I'll make the argument to re-biopsy and retest, simply because the test changes.

Dr. Montgomery:
I could not agree with you more. The technology has exploded and gotten so much better. Just not that many years back, you couldn't look for the RNA fusions. Now it's much easier because the technology is better. It's not like you're going to get every case with an NTRK alteration or rearrangement, but now we can test for it nicely.

Dr. Marshall:
And so, I just, to wrap us up here a little bit, I think what these precision medicine progress has given us is in fact, a way to be more effective. We want to not just pound on patients till they can't take it anymore; we want to use our medicines as wisely as we can. And each one of these different medicines, both the standard chemos and the targeted therapies, as you brought up earlier, have issues with different side effects and the like, so we have to be aware of how best to manage those when we're choosing to bring them to the table.

So, I hope this has really been a useful program for you all, and I know I always enjoy working with and learning from Dr. Montgomery, and the perspective of our pathology partners. And I just want to summarize that the high-level heterogeneous disease, molecular profiling and anatomic location matter a lot in decision-making. We pretty much think every patient needs biomarker testing. You would

second that, Dr. Montgomery, would you not?

Dr. Montgomery:
I would, I mean obviously not an early cancer in a polyp, but yes, for somebody who has a targetable cancer and an actionable cancer, absolutely.

Dr. Marshall:
And then, talk a little bit one more time, high-level, about what you need in terms of a sample size and quality in order to do good molecular testing.

Dr. Montgomery:
So, it can't be necrotic, and it should be abundant. And it can be really hard if you're taking needle biopsies and pinch biopsies. But as you mentioned earlier, our interventional radiologists are learning to take way more pokes, way more cores than they thought they needed. And then of course, our endoscopists are learning to take way more biopsies in case some of them are rubbish. Sometimes with our best efforts, we still get a bunch of rubbish, and we keep trying.

Dr. Marshall:
The two of us agree that liquid biopsy is useful, but tissue still is the gold standard as that technology evolves, so go there first if you can. We've reviewed for you already, that RAS and BRAF, HER2, MSI, etcetera, it must be done for colon cancers. We talked in Module 2 a lot about the barriers that exist both on the medical team side and on the patient team side, that we have to work extra hard in order to overcome that. I was thinking just last night that our new RVU model of medicine has sort of taken the career-ness out of our work. And so, this is where we have to remember that we went into this as a career, not as a line-worker at a factory. So, maintain your career-ness as best you can. And with that, in partnership with multidisciplinary team members, do the best you can to use all of these tools in the toolbox to optimize treatment for all of your patients with metastatic colon cancer.

Closing remarks, Dr. Montgomery.

Dr. Montgomery:
No, I think the key point is working together as a team to the extent that we can. Our complete objective amongst all of us is to do the best job we can for our patients.

Dr. Marshall:
Thanks everybody for listening in. We hope it's been useful.

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