

[MUSIC PLAYING]

**MICHELE  
MOLINARI:**

So my topic will be actually to review the complexity of dealing with patients with unresectable colorectal liver metastases, and the reason why-- it's becoming like an overlapping between transplantation and surgical oncology. And it's becoming a little bit of a new frontier of transplantation, although the frontier was already discovered a few years in the past, and we will see their outcomes during that period of time.

So why colorectal cancer is a very important topic is because it's the third most common cancer in the United States, as well as in many other parts of the developed countries. If you look at the distribution of colorectal cancer, it can be divided in two parts, the right part of the colon versus the left part of the colon.

And this is significant clinical information because the right side colon is a part of the midgut while the left side is the hindgut. And patients with colorectal metastases, from the right side of the colon, have an overall poor prognosis than individuals with colorectal metastases on the left side.

So when the individuals are diagnosed with colorectal cancer, the original diagnosis of the primary tumor has a prognostic indicator for survival at five years. If you can read the table, patients with a very early colorectal cancer, currently, on the treatment strategies that we have, have a 97% survival probability at five years.

The probability goes down progressively the more advanced the cancer is at the time of diagnosis. And if you are diagnosed with stage four, that means a colorectal cancer in other parts of the body, their probability of being alive at five years drops to 11%.

So colorectal cancer, in general, affects about 135,000 individuals in the United States per year. Among these individuals, 50,000 will die usually from metastatic disease. The mortality rate for colorectal cancer due to progression is currently at 37%, which has been improved significantly in comparison to, for example, 15 years ago when our chemotherapy medication were not as effective.

So this is a couple of Meier curves of survival of individuals who have a colorectal metastatic disease. So the blue line are representing individuals who are diagnosed with colorectal liver metastases-- able to undergo surgery. And if you can see the five-year survival, it's about 40% to 45%.

The red line represent individuals who have metastatic colorectal cancer in the liver only, but who are not able to undergo surgery. And as you can see, survival rate at five years drops below 10%. And the green line represent individuals, who are diagnosed with metastatic disease, who are not able to undergo chemotherapy and are not able to undergo surgery. And their survival is usually counted in their first two years and a half. Survival at five years is extremely rare.

So after a radical resection for colorectal cancer, about 50% to 60% of the individuals will develop liver metastases during the first five years. Only 20% to 40% of these individuals are able to undergo a liver resection, which is currently their standard of care in combination with the chemotherapy.

Why individuals with colorectal metastases might not be candidate for liver resection, there are several reasons. And we can start from the technical aspect, which is basically the inability to remove the entire burden of the colorectal metastases due to location of the tumors, number of tumors, presence of a vascular invasion, or their inability to leave enough liver behind able to sustain the life of our patients.

And then there is the relatively contraindication. For example, contraindication due to the fact that the tumor might be close to the margins, and we think that the margins are too slim to be able to perform a complete removal of the tumor. And for some of these patients, there is also concerns about their performance status or their ability to undergo a stressful operation such as major hepatic resection.

There are other oncological reasons. So number one can be the burden of the disease outside the liver or the number of liver lesions. And in the original work, a number more than five lesions was considered as a relatively contraindication to surgery. However, these numbers have become a little bit less important, because we know that some strategies are available to us that can actually be dealing with multiple liver lesions.

And then, of course, you know, progression of the tumor even with the best chemotherapy or other treatments is very poor prognostic factors. In combination with performance status, age of the patient might be a contraindications to proceed for a liver resection. This is a typical example of a unresectable liver lesion, so as you can see, the dark spot on MRI represents metastatic disease.

And as you can see, the relative area of involvement of the tumor is small. There is enough liver parenchyma to be able to undergo surgery with a radical resection. This is an example of a possible resectable tumor. So you can see that the tumor metastases has involved already the right and the left lobe of the liver and that there are many segments of the liver which are involved.

For these patients, we can actually consider a very advanced surgical resection which can entail a delayed liver resection or a combination of a liver resection and ablation treatment for the remaining part of the liver. Or currently, there is a more aggressive treatment which is called Alps, which is basically, in a simple way, we divide the liver in two parts.

We usually perform the division of the liver to the point where we divide the left or the right portal vein. It depends on where the tumor is located. And by ligation of the portal vein, we allow the liver on the contralateral aspect to be growing faster.

And then one week later, we can actually go to the operating room and remove the part of the liver, which is more involved by the tumor, and then clean the remaining part of the liver, as we have now an hypertrophic liver that allows us to do more liver resection than what we could have done at the very beginning.

And then this one is another example of what we know from the very beginning, that it's very unlikely that we will be able to downstage the tumor or perform multiple liver resections, because it's involving not only both lobes of the liver, but there are also signs that there are micro metastases in the remaining part of the liver which are not able to be cleaned by any surgical intervention.

So what is the options for individuals who are not resectable? Well, the only options we have currently is a combination of systemic chemotherapy in addition to external beam radiation, or internal local regional treatment.

So if we look at the most recent advancement in chemotherapy, we had, at the beginning, 5FU, which was the original chemotherapy that was proven to be effective. But during their most recent years we have additional, other chemotherapy, which are Oxaliplatin, Irinotecan, and the addition of antibodies against growth factors such as the epidermal growth factor or the vascular growth factor.

And these additional antibodies have been able to be more effective in decreasing the volume and the size of the tumor, in addition to that growth. So we are able, currently, to obtain a five-year survival if not being able to be resected, which is currently in the 15%, 20%.

So ideally, the combination of multiple treatment strategies can actually improve the ability to aim for cure for individuals with advanced colorectal liver metastases. However, not always these treatments respond to chemotherapy, and not always we are able to transform non-resectable hepatic colorectal metastases in a resectable liver a burden.

So the strategies for conversion to resectability currently are, number one, you have to have a systemic chemotherapy as colorectal cancer already metastatic to the liver should be considered a systemic disease. So you need to have a systemic treatment that covers all the possible foci of metastatic disease.

And these are basically chemotherapy is currently based on genetic profile of the tumor. So for some tumors, there is FOLFIRINOX. Some other tumors are more responsive to FOLFIRI in addition to other antibodies against their growth factors. And the other additional aspect is to be aggressive not only on the chemotherapy but also on the surgical strategies.

And that is the reason why a multidisciplinary approach with the surgeons, intervention radiologist, oncologist, and radiation oncologist is beneficial because their strategy has to be tailor based not only on the performance of the patients, but also on the location of the tumors. So currently, as I mentioned before, we can actually do portal vein occlusion with the idea of making their contralateral liver bigger, so that we can go in-- and possible do a resection or ablation.

Or additional, to do the splitting of the liver, ligation of the portal vein. Go back one week later to do more surgery and then try to perform these over if the patient develops a recurrent disease even after hepatic resection if their patient is able to have enough liver volume.

So for the point of view of the likelihood of resectability, due to the fact that a tumor can progress or not only progress inside the liver, but also develop extrahepatic liver metastases, the likelihood of resectability for individuals with advanced colorectal liver metastases is only about 5%. So we are talking about a very small proportion of individuals who are able to be treated with these kind of advanced and aggressive therapies.

So what are the possibilities for in these individuals who fail all the possible available strategies that we discussed? The next frontier would be liver transplantation. Liver transplantation for individuals with colorectal metastasis is not a new idea. Some patients were transplanted in the early phases of liver transplantation with a kind of dismal outcomes, and the reason for their dismal outcomes was for multiple reasons.

Number one, it was the poor selection, so those are where individuals with very advanced tumors which could not be treated otherwise. The second part was that the chemotherapy regimens was not as effective. But now with the new advances of chemotherapy and a multimodality treatment, we can actually reconsider the idea.

So before 1995, there was a number of individuals who underwent liver transplantation for colorectal metastases. These individuals were in the transplant registry, and now they were kind of reassessed and reanalyzed. And what the analysis shows, you know, for liver transplantation, the one-year survival was 62% and the five-year survival is 30%.

These were selected patients that were transplanted mostly in the north part of the Europe, where they have a significant number of donors. And Norway is a leading-- there's a new revival of transplantation for colorectal metastases. And the reason why is because they have more donors than possible recipients.

So the Norwegian consortium decided that it would be something to consider to use these organs. Instead of shipping these organs to other countries, part of the consortium is to use them inside the Scandinavian countries and to use them for individuals will fail all the treatment options for colorectal metastases.

So from 2006 to 2011, under a significant strict protocol, these individuals were enrolled, and they had to satisfy the inclusion criteria. So they had to have a very good performance status. They had to have at least a minimum of six weeks of chemotherapy, and the chemotherapy had to show some effectiveness. So the tumor was not progressing.

They underwent the radical resection of their primary tumor. And then, of course, you know, they had to prove that there was no other disease outside the liver by CT scan or MRI in addition to that PET CT scan. And these individuals were considered for transplantation if able to tolerate mTOR inhibitors, which are basically a combination of immunosuppression medications that have also an antineoplastic property.

So the exclusion criteria for their protocol was individuals who had ECOG status more than 1 and weight loss more than 10% as a proxy for the possibility of a cachectic neoplastic syndrome, which is an indicator for poor prognosis. And then they had to be having a standard contraindication for liver transplant [INAUDIBLE] usually cardiopulmonary disease or very poor or high comorbidity index.

The day of surgery, these individuals were taken to their radiology department, that they had to do a repeat CT scan of the chest in order to rule out the possibility of small lung cancer that we are not diagnosed originally. They had an exploratory laparotomy to identify if there was no carcinomatosis.

And then they underwent a frozen section of the lymph nodes in the area of the [INAUDIBLE] ligament where the majority of extrahepatic lymphadenopathy is identified in individuals with colorectal liver metastases. And then the follow-up was basically the typical follow-up for oncology patients. So physical examination and then CT scan or chest X-ray to rule out the possibility of recurring disease.

In patients with a relapse, so identification of extrahepatic disease or intrahepatic disease were treated individually. That means that they were treated with ablation resection or a combination of the both. And if they had the lung metastases, they were considered for a lung resection in combination with the thoracic oncological team.

So the results are that, among the 25 patients who were eligible for this protocol, one patient was removed because of the presence of ascites which was considered a negative prognostic factor for a possible malignancy and lung metastases. Two patients had positive lymph nodes. And then 21 patients were transplanted.

So if you look at the intent of treatment analysis, 84% of these individuals were treated according to their protocol. And in oncological aspect 84% of intention to treat analysis is significantly high in comparison to more like chemotherapy or other radiation therapies where the intention to treat analysis sometimes falls below the 70%.

So for the point of view, the tumor characteristics, as you can see, there were individuals with even up to 30 lesions. But what is more important, if you look at the five-year overall survival of all these individuals, 55% were alive after five years. Although if you look at the disease-free survival, unfortunately, it was zero. So these individuals had very early recurrent disease in a median six months. That was the time of disease-free survival.

And after the disease was diagnosed, then underwent an aggressive protocol for possible surgical treatment or chemotherapy treatment. However, when you look at the overall disease-free survival, no one after two years was completely free from the recurrent disease.

Which were the predictors for survival after undergoing liver transplantation for colorectal mets? Well, the smaller the tumor, the better is the overall survival, as we know for many other solid organs. The second part is the tumor markers as a proxy of the ability of differentiation of the cancer cells. So CEA level less than 80 was a good prognostic factor.

And then the time interval from the diagnosis of the original cancer to the diagnosis of colorectal metastasis. So the longer they were out from their primary diagnosis, the better was their prognosis. And then the partial response to chemotherapy or a stable disease on chemotherapy, as you can see, if they were responding, they had a significant stable disease-free and overall survival in comparison to individuals with progression of cancer on chemotherapy.

So at the end of their analysis, they perform a predictive score. And as you can see, the red line is represent patients with a very low risk scores. So zero to one. And then you can see that individuals with a number of factors more than four were basically having the worst prognosis, with the majority of them dying in the first three years.

So going back after the Norwegian study revolutionized, a little bit, our concept of colorectal metastasis and liver transplantation, another study came out. And what they did was to look back and then reassess every single transplant that was done with the pathology showing that there was a metastatic disease in the liver.

So they found 12 individuals with this particular diagnosis. And because these individuals were transplanted in the modern era, they went back, and they assessed their survival and disease-free survival. And what they found was, in those 12 individuals treated with modern chemotherapy and other modalities, their overall survival reach about 40% and the disease free survival was 35%. So they concluded that there is a possibility of curing unresectable colorectal metastases by using liver transplantation as an option.

So after the study and after these results were made available, we decided to consider liver transplantation in populations of individuals who satisfy strict inclusion criteria with the idea that-- at the University of Pittsburgh, we have the largest live donor program, and therefore we can actually perform at these kind of operations in the optimal settings.

So we can actually plan the liver transplantation after the patient is treated with chemotherapy. After they undergo CT scan, PET CT scan. After we review all the tumors with the multidisciplinary team. And we decided to perform the possibility of liver transplantation for individuals with adenocarcinoma of the colon and the rectum with negative resection margins.

They have to be considered non-resectable by surgical definitions, and this has to be a consensus. They have to be on chemotherapy for at least six to 12 weeks and showing stability on a chemotherapy regimen. And then a CEA level less than 100. They have to be, of course, having good performance status, and they have to have a live donor.

And the reason for the live donation, as I mentioned before, it allows you to be planning these operations, number one. And number two is that, unfortunately at this point, cadaveric liver transplantation for colorectal metastasis is not still accepted as a standard of care.

So the exclusion criteria are poor performance status, previous or current extrahepatic metastases or local recurrence and any general contraindications for liver transplantation. Usually, these individuals are in that younger group of patients. And then if they have a BRAF mutation which is a mutation of the oncogenes that are associated with a very poor prognosis. These individuals are not considered at this point for this treatment.

And then after they undergo the operation, number one, we induce them with the interleukin-2 receptor antagonist. Then we use the FK tacrolimus plus MMF for the first four weeks. And then we will switch them to mTOR inhibitors. As I mentioned before, mTOR have been associated with an antineoplastic effect. And so the patient will be switched to Everolimus after their four weeks to prevent possible thrombosis of the hepatic arteries or portal vein.

For the post-operative chemotherapy, this is a very typical question. So what happens to these individuals after they undergo transplantation? Is there a role for post-operative chemotherapy?

So there is no data enough to say that these individuals have a benefit to undergo chemotherapy after the operation. So at this point, we leave it up to the primary medical oncologist or surgical oncologist referring the patients to decide if the candidate is able to undergo systemic chemotherapy, as there is no guidelines that can help us to say which patients will benefit and which patients might not be a very good candidate for extra chemotherapy in addition to the immunosuppression medications.

I thank you for your attention. And if you want to have the protocol or any information about this protocol, I put my email. And I can email you the protocol if you are interested in it. Thank you so much.