

Professor Timothy Pawlik: what have we achieved in hilar cholangiocarcinoma over the past decade?



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Timothy M. Pawlik (Figure 1) is currently the Program Director of Hepatobiliary Surgery, and Director of the Johns Hopkins Medicine Liver Tumor Center. He is a Fellow of the American College of Surgeons. Dr. Pawlik serves as the Co-Director of the Center for Surgical Trials and Outcomes Research within the Department of Surgery. The Center helps facilitate surgical investigators in the design and implementation of clinical trials. Dr. Pawlik also serves as Associate Program Director of the Johns Hopkins Clinical Research Network with a focus in facilitating surgical clinical trials for the JHCRN.

HBSN: *Can you give us a brief description of hilar cholangiocarcinoma in terms of its development, possible early diagnosis, and treatment principle?*

Dr. Pawlik: Hilar cholangiocarcinoma is a very important cancer worldwide including in the United States. In most patients, we don't know what factors are associated with the risk for getting hilar cholangiocarcinoma, although we do know that patients with Primary Sclerosis Cholangitis (PSC) are at a higher risk. In patients with PSC, these patients should be followed very closely and make sure that they don't develop a stricture or potential cholangiocarcinoma. Unfortunately, most patients do not have any specific risk factor and often present with symptoms of jaundice before any stricture or cancer is suspected. As such, early detection is definitely a big problem in the general population. When patients with present jaundice and a high bilirubin level, we would typically work those patients up with MRI and MRCP. MRCP can be very helpful to define the extent of the disease and the relation of the tumor to surrounding structures, specifically the vascular structures, such as the portal vein and hepatic arteries. After we have obtained imaging, in those patients with a high bilirubin, we typically drain the biliary tree. This is especially important if the surgeon is considering a major liver resection. Biliary drainage can be achieved either endoscopically or if that's unsuccessful, percutaneously. In general, before doing a

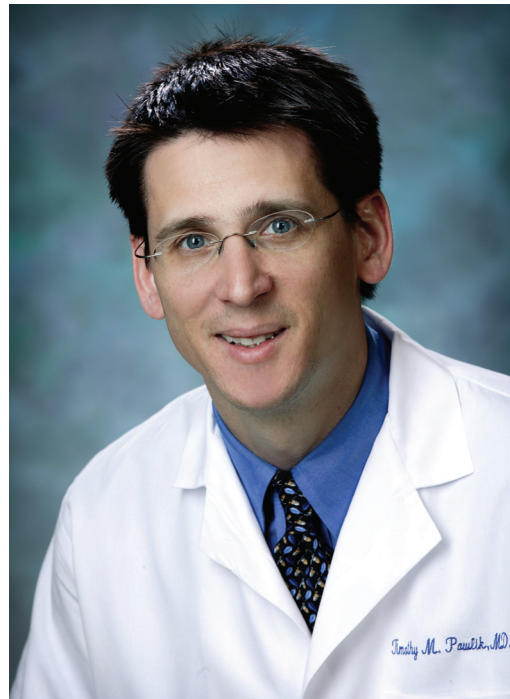


Figure 1 Timothy M. Pawlik

major hepatectomy, we like the bilirubin to be less than about 7.

HBSN: *How has the treatment of cholangiocarcinoma evolved over time?*

Dr. Pawlik: The treatment and surgical approach for hilar cholangiocarcinoma has changed over the last 20 years. In the past, some individuals thought the resection of the extra hepatic biliary tree was sufficient to remove the disease. However, now all experienced liver surgeons generally agree that you almost always need to do a liver resection in conjunction with resection of the extrahepatic biliary tree when treating patients with a hilar cholangiocarcinoma. By doing the liver resection, the ability to achieve a negative

surgical margin is significantly increased. And we know that achieving a negative surgical margin surgically is one of the most critical factors to help ensure a patient has a better long term prognosis.

HBSN: What are your own experiences with hilar cholangiocarcinoma?

Dr. Pawlik: Hilar cholangiocarcinoma is unlike some other HPB tumors that we often deal with as surgeons. For instance, with pancreatic cancer, now with excellent cross-sectional imaging, we almost always have a very good idea of whether the tumor is resectable or not before the time of surgery. In contrast, with hilar cholangiocarcinoma, even with the best imaging of CT, MRI, and endoscopy, there will still be a subset of patients who are unresectable at the time of surgery, due to either an involvement of the main portal vein or more commonly, involvement of the contralateral arterial vasculature. The finding of inoperability at the time of surgery may be even as high as 15 or 20 percent of patients. In the other approximately 80 percent of patients who are candidates for resection, the majority of those patients typically will end up getting an extended right hemihepatectomy with resection of extra hepatic biliary tree. This is because right sided hilar cholangiocarcinoma often involves the base of segment 4B and the surgeon needs to remove the right liver as well as the entire extrahepatic biliary tree. For those individuals who have a hilar cholangiocarcinoma and invasion of the left bile duct, the surgeon performs a left hemihepatectomy. In general, at the time of surgery not only should you do a formal liver resection, but you also need to remove the caudate lobe. If one does not resect the caudate lobe, especially on left side hilar lesions, the incidence of local recurrence can be higher. So the principles of operation involve resecting the extra hepatic biliary tree, as well as typically a major liver resection with the inclusion of caudate lobe, a portal lymphadenectomy and then restoration of biliary continuity with the GI tract.

HBSN: Are there any controversial aspects on the resection during surgery for cholangiocarcinoma?

Dr. Pawlik: The more controversial aspects of surgery for hilar cholangiocarcinoma involve vessel resection. In our data from the papers we have published, as well as the other published papers, have also shown that among those patients who have involvement of the portal vein the

surgeon should precede with the resection of the portal vein and reconstruction. This can be done safely, although there does seem to be a slightly higher risk of perioperative morbidity and mortality. For patients who need arterial reconstruction of the hepatic artery, there is much less data on that. It would seem that peri-operative mortality risk is even higher for resection and reconstruction of the artery. Therefore, in general, we believe that this is as a relative contraindication to resection. Routine resection of the portal vein using the so-called “no-touch” technique is more controversial.

HBSN: Can you please describe the ‘no-touch’ technique?

Dr. Pawlik: This concept of routine resection of the portal vein, the so called no-touch technique, is very interesting and potentially should be adopted in the future although the data right now is still somewhat preliminary. Some investigators have shown that in patients undergoing extended right hemihepatectomy, the routine resection of the main portal vein may provide a survival benefit to individuals, because it avoids dissection of the bile duct along its the dorsal aspects adjacent to the portal vein, and therefore theoretically prevents disruption of the tumor during the dissection which may lead to a better oncological outcomes. However, the data have only been reproduced in a couple of medical centers. Whether universally adoption of this technique will provide better outcomes for patients is still to be determined.

HBSN: How about the future treatment of hilar cholangiocarcinoma?

Dr. Pawlik: For hilar cholangiocarcinoma, three things are going to be very important in the future. First, additional data on this no-touch technique may provide more compelling data and evidence to fundamentally change how we technically approach these patients in the operating room, who we are resecting and that may lead to improve long-term survival. Second, we need to develop more effective systemic agents for these patients. Although hilar cholangiocarcinoma tends to be a local regional disease, still many patients will recur and we have to develop better systemic agents to treat those patients. The third is to better define the role of transplantation for hilar cholangiocarcinoma. Liver transplantation is the ultimate no-touch technique because you are completely removing the liver and the hepatic hilum. The data are compelling for

patients who have PSC related hilar cholangiocarcinoma, as the outcomes after transplantation appear to be much better than resection. Many of us would favor transplantation as the primary approach to treat PSC patients with hilar cholangiocarcinoma. Whether transplantation will become the preferred approach for patients who have none PSC related hilar cholangiocarcinoma remains to be seen.

HBSN: *Can you tell us some insights of how to decide a resection surgery for those with metastatic neuroendocrine tumor and where are we in the treatment?*

Dr. Pawlik: It's a very exciting time for the treatment of patients with neuroendocrine tumors. Unlike 10 or 20 years ago where there were not many therapeutic options, there are now significantly more treatments to choose from for patients who have advanced disease. For those patients who have neuroendocrine liver metastases, I think two of the most important aspects to decide whether to operate on these patients is (I) whether the patient is symptomatic or functional and (II) what is the amount of disease in the liver. I tell patients there are two reasons to operate on you: help your symptoms and prolong your life. If patients don't have symptoms, then it really comes down to whether the operation will prolong their life. And I think that is tied to how adequately we can completely remove all sites of disease. So those patients who have low volume disease, whether they are symptomatic or asymptomatic, if I believe I can completely remove all the visible sites of

disease then I would offer them an operation. If the patient is asymptomatic and has a large volume of disease in their liver, the data from our institution and others suggest that maybe the survival benefit associated with the surgery isn't as great. As such, I refer patients with large volume liver disease who are asymptomatic for some type of intra-arterial therapy and/or systemic therapy with a new targeted agent.

HBSN: *Can you give us some insights into the future development of neuroendocrine cancer?*

Dr. Pawlik: In the future, it's going to be very interesting to see how we incorporate these new targeted agents into the overall therapeutic plan. There are some very exciting data about using mTOR inhibitors, such as everolimus, as well as other agents such as sunitinib to treat patients with advanced disease. The combination of surgery with targeted systemic agents, or combining intra-arterial therapy with these targeted systemic agents, may provide us with many more tools to treat these patients with advanced neuroendocrine liver metastases.

HBSN: *Thank you very much.*

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