Dr. Douglas Evans – Final Edited Transcript from Live Webcast -April 25, 2018

Chapter 1: The Challenge of Pancreatic Cancer

The challenge of pancreas cancer is largely due to its anatomy. And because I know that there are probably many gastroenterologists listening tonight, I'll focus on the anatomy a fair bit. And it's a particular privilege for me to talk about pancreas cancer to gastroenterologists and other physician specialists. And I'd like to especially thank Boston Scientific for allowing me the opportunity to do this.

All of these slides are my own. So please, if you'd like a copy of any of my slides, just send me an email at devans@mcw.edu.

I think if I provide one teaching moment during this presentation, it would be on this slide which I'm going to show you a number of times. And this basically shows our approach to diagnosis and treatment.

Because I started out in surgical oncology as an endocrine surgeon and then moved into pancreatic cancer, we always in endocrine oncology separate diagnosis and treatment. And I think one of the big problems with how pancreas cancer has been managed in the past is that diagnosis and treatment were a continuum. Patients would get a CT scan and then sometimes be brought to the operating room, sometimes the endoscopy suite. There would be various ways in which they could complete their diagnosis and treatment and it would often not be in a clearly defined, well-articulated pathway as illustrated on this slide.

We prefer to completely separate diagnosis and treatments. Here at The Medical College of Wisconsin, it really doesn't matter whether a patient enters through surgery, gastroenterology, internal medicine, radiation oncology, or medical oncology. It can be anywhere.

We start with good cross-sectional imaging, i.e., a CT scan. The patients then, if they do not have a tissue diagnosis, they undergo endoscopic ultrasound guided FNA biopsy. If they are jaundiced or have bile duct obstruction, they have an ERCP with the biliary stent placed.

Beginning when I was on staff at Anderson in Houston, and certainly here in Milwaukee, the endoscopic ultrasound and the ERCP are performed at the same sitting, the EUS done first. If a diagnosis of adenocarcinoma is established, then the first biliary stent that the patient receives would be an expandable metal stent.

The old, historical tradition of trying to match the stent, be it plastic or metal, with how long the physician thought the patient may live, or their stage of disease, I think really makes no sense and is almost an impossible practice to continue with. We obviously place a polyethylene or plastic stent if we do not have a tissue diagnosis because uncovered metal stents will be difficult to retrieve. And the presence of a metal stent may make a subsequent attempt at EUS guided biopsy more challenging.

Once we have accurately staged the patient, obtained a tissue diagnosis and palliated for bile duct obstruction, all patients are presented in a multi-disciplinary conference and their treatment, based on stage, is then delineated, which allows patients to be worked up in a very rapid, efficient fashion and also facilitates clinical trial enrollment.

You can see the problem. Pancreas cancer will soon become the second leading cause of adult cancer death. It already is the second leading cause of adult cancer death in Wisconsin and other pockets within the United States. The reason for that is that it spreads early to other parts of the body. As shown in this laparoscopic view of a patient who was actually quite special to me, who was diagnosed with cancer in the pancreatic body, the presenting symptoms were vague and not yielding a pancreatic cancer diagnosis easily. And as you can see here at the time of diagnosis, the patient had radiographically occult, but laparoscopically visible metastatic disease in the peritoneum even though there were not parenchymal liver metastases.

Like many of our patients, his tumor is now immortalized in our research laboratory. And there are now multiple avenues for a molecular clarification and target identification for patients, especially at larger centers of excellence for this disease.

Chapter 2: Assessing the Surgery-first Approach

Well, the reason why it's so hard to treat pancreas cancer can largely be summarized in the little purple circle that I put here. The pancreas was put in a very difficult position and patients with pancreas cancer have the complications of bile duct obstruction, oftentimes pain and discomfort. They may have gastric outlet obstruction. If not, certainly a lack of appetite, anorexia.

And, oftentimes, as all of you know, most patients present with hyperglycemia. And in fact, the presence of hyperglycemia in the setting of a declining weight is a very sensitive indicator of a pancreatic cancer diagnosis and really in 2018 should mandate a CT scan.

I can't tell you how many patients I see who noticed an increase in glucose, difficult to control blood sugar, while at the same time were losing weight. Very uncommon. Usually for most adults, in the absence of a pancreatic cancer diagnosis, weight and blood sugar will move in the same direction. As weight goes up, blood sugar will go up.

Well this is how pancreas cancer that is localized to the pancreas is managed in many centers across the world. Patients are diagnosed. Now, staging with CT imaging is quite refined. All treatment guidelines use CT or MRI based imaging. If the patient is thought to have an operable tumor, they are then brought to the operating room. Assuming the operation goes well, they're in the hospital one to two weeks. They then have a period of recovery.

Before beginning adjuvant therapy, they typically are restaged. Adjuvant therapy is recommended for all patients with pancreas cancer regardless of stage of disease, unlike other solid tumors. Chemotherapy and surgery are clearly better than surgery alone. The use of radiation therapy remains somewhat controversial, especially outside of the United States. In full disclosure, I still feel that radiation therapy has a critically important role in the management of patients with operable pancreas cancer. And as we see survivals extended, certainly beyond medians of 24-36 months, you will see local recurrence become more of a problem in the absence of radiation therapy being part of the multimodality treatment program.

With the surgery first approach, what we don't know is the biologic impact of this approach. I think all of you have seen patients who have experienced early post-operative cancer recurrence. And certainly surgery is an immune suppressive event. So that the sequencing of treatments-- chemotherapy, surgery, and radiation therapy-- may matter irrespective of the effect of those individual therapies individually.

And what we do know is with a surgery first approach, there really has been no progress in decades. This is a report that was well cited, a huge number of citations on this very well-written paper from Memorial, which showed no change in survival based upon the decade of treatment with a surgery first approach to pancreas cancer. And you can see here the teal line was the most recent experience.

A more updated experience from the same institution shows, once again, a median survival of 24 months. That 24 months with surgery first, with or without adjuvant therapy, is incredibly reproducible. Here's an experience from Hopkins which, once again, shows the same 24 months. And I would suggest that if you spend a little time on PubMed and look at other series of surgery first, the overall survival of operated patients, regardless of their adjuvant therapy, is in that range. It is very hard to move that needle.

Chapter 3: A Neoadjuvant Therapy/Surgery Last Approach

Well, we became interested in a treatment schema other than simply operating upon patients many years ago. And this was actually my Fellow project when I was a Surgical Oncology Fellow at M.D. Anderson and subsequently published after I went on staff. And the reason we did something other than surgery first, the reason we were interested in this, is because of the clinical observation that we would see patients after a successful operation who would come back within a year of surgery and have cancer recurrence. And we said, in retrospect, the operation provided them absolutely no value.

We did a number of clinical trials, certainly refined the infrastructure allowing us to perform neoadjuvant therapy. And this is one of the trials that we published once we entered into the gemcitabine era. And the treatment actually is not that important. These patients received both systemic gemcitabine and external beam radiation therapy.

But I wanted to focus on the overall treatment schema whereby patients were treated for approximately two months, had three to four weeks off, then were restaged. And our hypothesis was that at the time of restaging, those patients who had rapidly progressive disease would not undergo an operation that in retrospect would not benefit them. In fact, when we first began using neoadjuvant therapy, it was really in an effort to advocate for those patients who would have disease unresponsive to a big operation.

It's interesting that now in the contemporary era of today, neoadjuvant therapy has become more appealing because of the survival results that I'll show you for the patients who actually respond to therapy. It's a fascinating lesson in what we may think is important but may not actually be viewed as important by others.

Well, these are the survival curves published in the Journal of Clinical Oncology. We published this trial when the minimum survival of all living patients was actually five years - so a very mature trial. And you can see that the neoadjuvant treatment schema effectively dichotomized the population into those who would benefit from surgery and those who actually would not. Sixty-four out of the 86 patients completed all intended therapy, to include surgery.

Twenty-two patients were found either at restaging, or at the time of laparoscopy-- we always have laparoscope patients at the time of planned laparotomy - and they were found to have disease progression. So 22 patients were found to have disease progression and did not receive an operation which, in retrospect, would not have benefited them.

And you can see the difference in median survival - really quite dramatic. Most importantly, the median survival of almost three years in patients who completed all intended therapy, including surgery, is something that at that time was not previously reported. No survival of patients with operable pancreas cancer had reached that number.

We have since done a number of clinical trials here at the Medical College of Wisconsin. Some of these that have been published are illustrated here. And you can see the median survivals in these patients is anywhere from three extending almost to four years as we have entered the era of FOLFIRINOX, gemcitabine, and nab-paclitaxel, with or without cisplatin. In an era of more effective systemic therapy, median survivals have even increased. If you think about it for a minute, more effective systemic therapy given prior to the introduction of an immune suppressive event such as surgery, treatment sequencing may matter irrespective of the treatment that is actually used.

Well one of the challenges to neoadjuvant treatment sequencing is illustrated here. Obviously, you cannot give effective induction therapy to patients if you do not have durable, biliary decompression and a means to aliment the patient. The patient has to be able to receive adequate nutrition and they can't be developing cholangitis every month or two. And therefore, they have to have a means of durable biliary decompression.

This is probably the only biliary stent that I'm going to show. Number one, because I don't know how to place them into a bile duct. But I think I'm very good now at taking them out of a bile duct, especially with a specimen such as this. But I can't emphasize enough the importance of having adequate biliary decompression, adequate nutrition, supportive care, with chemotherapy, hydration, antiemetics, growth factors. I'd be happy to send anyone through email our technique for giving all of these items here at the Medical College of Wisconsin.

And as mentioned, we completely separate diagnosis and treatment so that all patients after initial EUS-FNA and stent placement are then discussed during our conference and treated. I'm going to review in some detail a clinical trial that Dr. Susan Tsai just presented last week at the American Surgical Association and it will be published in the Annals of Surgery very soon, looking at profiling at a molecular level the EUS-FNA biopsy and then dividing patients into whether their profile was predictive or not predictive of a beneficial chemotherapy program. And I'll review that in a minute.

In order to do clinical trials in operable pancreas cancer, you have to be able to stage them. You have to define the population of patients that you are treating. When we did the first neoadjuvant trial and wrote the first trial, in approximately 1989, at that time staging was determined at the time of operation. If the patient was deemed operable, then the patient had a stage 1 or 2 tumor. If the patient was deemed locally advanced or inoperable, they had a stage 3 tumor.

That has since been changed, fortunately, to an emphasis on cross-sectional imaging. And again, I would emphasize many of the papers that we have published on this for details. But in general, resectable tumors are those that do not extend to the superior mesenteric artery (SMA). Borderline resectable are those that oftentimes extend to the SMA or the hepatic artery. And locally advanced are those that may encase an arterial structure or occlude the superior mesenteric vein.

We have arbitrarily defined encasement as a tumor-vessel relationship of greater than 180 degrees, and abutment as a tumor-vessel relationship of less than 180 degrees. And again I'd refer you to many publications.

This will be a table in the upcoming edition of Mastery of Surgery, which many of you probably have, and is the current staging system that we use here at the Medical College of Wisconsin. Again, it’s tremendously important to accurately stage every patient at diagnosis so that you can then define the goals of treatment.

Patients with resectable and borderline resectable disease are by definition operable. We have since published a segregation of the locally advanced patients into locally advanced A and B based upon the likelihood that they would subsequently be operable. And I'll talk more about that in a minute.

For the surgeons in the audience, the guiding principles that we use for surgery for pancreatic cancer is to look at three fundamental things-- the patient’s morbidities, in other words, their risk for surgery; the oncologic profile-- have they responded to induction therapy? Has their CT scan changed? Has their CA19-9 or CEA declined? What is their oncologic risk; and then lastly, the surgical degree of difficulty. And why those are important is illustrated here.

We do not operate on a high-risk patient based upon age, medical comorbidities, who then may also need a high-risk operation, arterial venous resection reconstruction who also has a high risk oncologic profile. Their 19-9 has not declined, for example. This is critically important. Survival duration is the primary endpoint. Quality of life is the co-primary endpoint.

In my opinion, at least, if the survival duration is less than one year, surgery provided absolutely no clinical benefit. It doesn't mean that the decision to proceed to the operating room was wrong, but it is important to retrospectively review your own experiences and your results and learn from that experience. Survival duration of one to two years is a gray zone; survival duration of greater than two years, there probably was a surgery associated clinical benefit. But it’s important to assess your results with that frame in mind.

And as I'll show you, an intense commitment to multimodality therapy is certainly where we are in 2018. And at least in my opinion, the field is rapidly moving to a surgery last approach.

Chapter 4: Borderline Resectable Pancreas Cancer – Case Reviews

To go back to staging, I want to spend a little bit of time on borderline resectable pancreas cancer. First described by Gauri Varadhachary, a medical oncologist, who is still at M.D. Anderson. And you can see here the arbitrary criteria that we used. But, basically, with the understanding-- as I'll show on the next slide-- that borderline resectable patients are at higher risk for systemic recurrence and at the highest possible risk for a positive margin of resection in a local recurrence because, by definition, they have tumor-vessel abutment or encasement. And they are at higher risk for surgery-related complications because the operation is most difficult. So, if you will, this is the most compelling case to segregate the population of patients into those who will and will not benefit from surgery.

And again, certainly my underlying hypothesis is that neoadjuvant therapy would be much more commonly practiced - even though for borderline resectable disease, it's recommended in all treatment guidelines - it would be much more commonly practiced if patients could be adequately stented and cared for during their neoadjuvant therapy by a dedicated team of physicians.

To give you a few examples of borderline resectable patients, especially for those surgeons in the audience, this is an intraoperative photograph of a patient who required a segmental resection of the superior mesenteric vein (SMV). I have, for many years, used the left internal jugular vein as an interposition graft. The veins that are appropriate diameter for the SMV or the portal vein would include the internal jugular vein, the left renal vein, and the superficial femoral vein, as popularized by Dr. Clagett in Dallas for arterial reconstruction.

The internal jugular vein, certainly you can obtain a much longer segment than the left renal vein. And it can be harvested much quicker than the greater saphenous vein, and, of course, is not associated with any form of leg edema. The internal jugular vein takes a little practice to get used to using, but overall is an excellent conduit for use in the SMV or the portal vein. In this case, because the splenic vein was preserved, if you take any significant length of superior mesenteric vein, it is very difficult to approximate the two ends in the absence of an interposition graft.

In this particular patient who required a total pancreatectomy-- and you can see here that the splenic artery is ligated and the common hepatic artery. In this case, despite ligation of the splenic vein, we still needed an interposition graft to bridge the SMV with the portal vein. I typically use interrupted sutures on both the SMV and the portal vein. I think a running suture that is commonly used in transplant surgery with more durable portal vein tissues is very difficult to use in cancer patients who have, oftentimes, received chemotherapy and radiation. The time differences are really not significant. I always use in-flow occlusion on the superior mesenteric artery and systemic heparinization when replacing the SMV or the portal vein.

So we thought we had things figured out until this patient came to see me. And we thought we had the staging segregated into resectable, borderline resectable, and locally advanced. And then this patient came to see me who was actually on the phase 2 trial of gemcitabine and nab-paclitaxel for a locally advanced pancreas cancer. You can see here the celiac artery. And you can see the superior mesenteric artery. So this patient was deemed to have locally advanced disease.

And lo and behold, look what happened. Prior to the advent of FOLFIRINOX and gemcitabine and nab-paclitaxel, one did not see this type of treatment response. It was really quite dramatic. So this patient was then sent to me for surgery. And we said, well, wait a minute. This patient is not supposed to be operable. And therein began our quest to more clearly delineate the locally advanced category of patients.

And this just shows the trial, published by Dr. Dan Von Hoff, of gemcitabine and nab-paclitaxel that the patient was actually treated on. And this is her intraoperative photograph. And you can see here the portal vein. The pancreas has been divided. The transection point of the pancreatic head is there. The superior mesenteric artery. The right and left celiac ganglia have been divided. And you can see the origin of the celiac artery and, here, the common hepatic artery.

The operation first developed by Appleby would have simply divided those vessels, removed the tumor and left the patient with hepatic arterial flow based solely on retrograde flow from the gastroduodenal artery. I have traditionally always returned forward flow to the common hepatic artery, especially when we take the left gastric artery to enhance a gastric perfusion.

You can see that the result, pathologically, was quite dramatic - an excellent pathologic response to induction therapy - which I might also add included chemoradiation after the gem-nab and before surgery. Here is the intraoperative photograph with the tumor removed and then with the reverse saphenous vein graft bridging the celiac and the common hepatic artery.

In this case, we had to remove the proximal left gastric artery. So if you think for a minute, irrespective of returning forward flow, right now the stomach is supplied by the right gastric and the right gastroepiploic. And there certainly is a concern that delayed gastric emptying could be enhanced in this situation by relative hypoperfusion of the more proximal stomach. Returning forward flow from the celiac to the common hepatic will enhance arterial flow in the right gastric and the right gastroepiploic. So we especially want to do this when we have to take the left gastric as part of an Appleby procedure.

This is our initial editorial which described the division of locally advanced pancreas cancer into Type A and Type B with the hypothesis that Type A may be more likely to achieve a trip to the operating room as opposed to Type B. And again, the importance of knowing the likelihood of resectability based upon the stage of disease at diagnosis is to allow the physician team to have an honest conversation with the patient. While surgery is clearly not a panacea for pancreatic cancer, it usually is a necessary, if not a sufficient, component of the treatment program to achieve a long-term survival and certainly a cure.

Chapter 5: Staging Criteria for Pancreatic Cancer

I don't have time in this presentation to go in to all the criteria that we use in our staging system. And I would refer you to this manuscript, the one by Dr. Christians illustrated here, which was recently published in the Journal of Surgery, to basically determine whether our hypothesis in developing the locally advanced A and B categories was correct. And, in fact, that turned out to be the case.

When we looked at 45 patients with locally advanced Type A disease at diagnosis, 28 of those completed all intended neoadjuvant therapy and surgery as opposed to the 51 patients with locally advanced Type B disease in whom only 12 completed all intended neoadjuvant therapy to include surgery. Importantly, those patients who complete all intended therapy have a very favorable survival, as you can see here. Median survival was over three years in both groups, but a much smaller percentage of the population of locally advanced patients with B as opposed to A actually were operable.

This is the summary slide from our experience here at the Medical College of Wisconsin and shows you the tremendous value of accurately staging patients with cross-sectional imaging at the time of diagnosis so that you can determine goals of therapy, especially with regard to surgery. You can say to a patient with resectable disease: After we complete chemotherapy and radiation therapy, the likelihood of undergoing a successful operation is 90%, with borderline resectable disease, 75%, and locally advanced, Type A and Type B illustrated here.

So the goals of therapy can be accurately articulated to patients. Clinical trials can be accurately performed.

And as I mentioned, surgery appears necessary even if not sufficient for long term survival. Why surgery is such a powerful endpoint is because it's impossible not to be affected by what you see on a CT scan. If the primary tumor is the only measurable disease seen on a CT scan, it is virtually impossible not to use surgical resection as an endpoint. Patients, medical oncologists, probably most physicians like complete responses. And lastly, hope is derived from a clear plan of care.

Here is a locally advanced Type A patient as an example. You can see here really a relatively young man. So certainly stimulating, if you will, a more aggressive approach, although I hate to use that term. At diagnosis, CA 19-9 was approximately 200, the tumor encases the celiac artery and extends down to the superior mesenteric artery.

After four cycles of FOLFIRINOX, we saw a reasonable decline in CA 19-9 with perhaps a little bit of movement on CT imaging. The patient was then treated with SBRT. And one can certainly argue with the use of conformal IMRT versus SBRT. It seems like there is tremendous enthusiasm right now over altered fractionation schedules, schedules for radiation therapy, even if not as part of a clinical trial. But importantly, you can see the decline in CA 19-9 now down into the normal range.

So in this patient, we had a patient of essentially zero comorbidities and young age. So the patient factors were favorable. The oncologic factors were favorable. The 19-9 had normalized. There was no evidence of metastatic disease on follow-up restaging evaluation. And the operation was of an increased degree of difficulty. But having now a fairly large experience with celiac resection and reconstruction, it was one of intermediate grade, if you will.

And you can see here the intraoperative photograph looks very similar to the one I showed previously - an identical technique used in this patient. Once again, the pancreas is divided. The tumor is left attached to the patient just based upon the celiac and the common hepatic artery.

And in this particular patient, you can see once again we had to take the left gastric artery, divided the celiac very close to its origin from the aorta and replaced this with a reversed saphenous vein graft between the celiac and the common hepatic artery. The super celiac diaphragm is illustrated here.

We then accessed this area to allow us to divide the left celiac ganglion and expose the origin of the celiac and the superior mesenteric artery. Again, restoring forward flow in the common hepatic artery is especially important when the left gastric artery is taken.

Chapter 6: MCW Clinical Trial: Utilization of Molecular Profiling to Guide Selection of Neoadjuvant Therapy

So I think I'll talk a little bit about our clinical trial next. And as you can see here, again, there is a complete commitment to separating diagnosis and treatment. So this clinical trial will be published soon in the Annals of Surgery and it was presented last week at the American Surgical Association in Phoenix by Dr. Susan Tsai in our department. Basically, the hypothesis was that all patients will clearly not respond to the selected neoadjuvant treatment and could we further refine that? And all of you have probably seen patients who were treated with FOLFIRINOX and had disease progression. They then received gemcitabine nab-paclitaxel with or without cisplatin and responded or vise-versa, whether it be with metastatic disease or localized disease.

What we did was we looked at the time at possible potential biomarkers that we could analyze based upon the EUS FNA specimen. Patients who underwent EUS FNA biopsy consented to a couple of extra passes. Those passes were placed in formalin. A cell block was created. Slides were then created from the cell block.

And then we stained those slides for the peptides you can see here. And the biomarkers that we used-- SPARC, TOPO1, RRM1, ENT1, ERCC1, thymidylate synthetase-- provided a window of whether or not those patients, based upon the staining characteristics, would benefit from abraxane, irinotecan, gemcitabine, platinum analogs, and 5-FU.

And this is the trial design. Patients with resectable and borderline resectable disease then underwent EUS FNA. Their biopsy was evaluated for cellularity, be it adequate or inadequate. And then they were treated based upon the profile from immunocytochemistry.

And this is, if you will, an example. Patients were largely dichotomized initially into whether or not they were thought to be sensitive to fluoropyrimidine-based therapy or gemcitabine-based therapy. And then the flow diagram would follow as to abraxane, topoisomerase, and so on. And you can see here the possible treatments that patients would receive based upon immunocytochemistry from the FNA biopsy.

This is an example of an individual patient who, in this case based upon their FNA biopsy, was thought to be sensitive to either gemcitabine or 5-FU based upon low thymidylate synthase, low RRM1, and positive staying for ENT1. So sensitive to either gem or flouropyrimidine. They had no SPARC expression. And therefore, it went down to ERCC1, which suggested sensitivity to irinotecan. The patient was then treated with FOLFIRINOX.

Another patient who had a similar, but slightly different immunocytochemistry profile and actually received FOLFIRI - something a drug regimen that probably would not be used in pancreatic cancer and certainly not first line therapy for pancreas cancer. This patient was actually one of two patients in this 130patient clinical trial who had a complete response to induction therapy, and actually to a drug regimen that would not normally be used.

And this is the CT scan and actually the PET scan on this patient. This is at the time of diagnosis. And this is after FOLFIRI. And you can see a nice CT response and a really quite impressive PET response. CA 19-9 went from 346 down to 79.

Molecular profiling was successful in approximately 3/4 of patients irrespective of whether they had resectable or borderline resectable disease. And many of the patients who did not have an adequate cell block for molecular profiling did not have an adequate cell block because they could not undergo a repeat biopsy.

So for example, if a patient was referred to us after a previous EUS FNA which secured a diagnosis of adenocarcinoma, but there was not adequate cellularity in the cell block, we would reevaluate them for a repeat biopsy. Unfortunately, many of those patients actually had an expandable, uncovered metal stent placed at the time of initial FNA, oftentimes performed in a setting where a cytologist was not present. And with an expandable, uncovered metal stent in place, it is much more difficult to perform an EUS FNA.

Again, I'm going on the experience of Dr. Kulwinder Dua and Dr. Abdul Khan, two of the world's most talented interventional endoscopists that I'm lucky enough to work with here. But for those patients who underwent their initial biopsy without any form of biliary stent, without a metal stent in place, the likelihood of obtaining adequate cellularity from a 22-gauge needle was really extremely high.

This just shows that the patients, their tumors, would be reprofiled at the time of operation. Obviously, we would have a much larger sample. And they would then get profile directed adjuvant therapy. This patient received preoperative therapy, surgery and then profiled to capecitabine and nab-paclitaxel or abraxane; again, a regimen that would not normally be used in operable pancreas cancer.

The overall survival by completion of neoadjuvant therapy and surgery is illustrated here. So 107 of the 130 patients completed all intended therapy, to include surgery, and look at the survival. Really dramatic. And these were 130 patients enrolled in a prospective clinical trial monitored extensively by our clinical trials office. And the median survival, as expected, in patients who progressed and did not undergo an operation was 11 months, which has been relatively reproducible in patients who do not complete all intended therapy to include surgery, identical to the survival we have received in a number of clinical trials beginning in the 1990s.

If you look at overall survival by clinical stage for all 130 patients operated and non-operated, you will see here for patients with resectable disease, 41 months; 33 months for those with borderline resectable disease. The overall median survival for the entire cohort of 138 patients was 38 months. That's for all comers signed up at the time of diagnosis suggesting that treatment sequencing may matter.

Importantly, we have a robust pancreatic cancer biorepository. And this is really a key to translational research, as all of you know. We're one of a small number of academic centers in the United States that also has a rapid autopsy program for patients with advanced disease who wish to donate their tumors to science, allowing us to have access to the primary tumor and metastases in those very generous patients.

Chapter 7: Summary Comments and MCW Resources

I wanted to just conclude with a comment that, for those of you certainly in surgery who are watching, surgery as a component of surgical oncology, will become even more complex as systemic therapies improve and as there is greater consensus over something other than surgery first for patients with operable pancreas cancer, be it resectable, borderline resectable, or locally advanced Type A disease. And that's because at many institutions there is not consensus on how to stage the disease using the criteria that I have, albeit briefly, tried to review this evening. Having consensus within your own institution on what is operable and what is inoperable is simply invaluable.

What is happening around the country in the United States right now is that patients who have tumors that are thought not to be immediately operable are incompletely staged. It is unclear what their stage is. And therefore, they receive chemotherapy. They may receive radiation therapy. They may still be thought to be inoperable. They may then receive additional chemotherapy. And essentially, they're still standing and their physicians are confused because they have essentially passed multiple stress tests which they did not expect to happen.

The only remaining site of disease is therefore in the primary tumor in the pancreas. The patient, then, is confused and will oftentimes seek second opinions.

For those of you who are not in surgery who are watching, the optimal time to operate on a patient, especially after radiation therapy, is typically within four to six weeks of the completion of radiation therapy. You can see how this becomes a problem for patients who receive chemotherapy, are then transitioned to radiation therapy, are then deemed not to be operable locally, and then perhaps, receive additional chemotherapy. And then the patient and their referring physicians seek an additional opinion about a surgery.

If the patient, in fact, has an operable tumor, they present an increased risk because of the time duration between radiation therapy and surgery, the multiple treatments in series. And oftentimes, radiation therapy has been given to a degree that is felt to be definitive because the patient is thought to be non-operable.

So this new category of patients – i.e., they're still standing and should not be -- they usually were not accurately staged at diagnosis. The goals of therapy were not clearly addressed or defined. They complete all intended therapy and they're still standing. The only measurable disease is what can be seen on imaging.

And if the patient is doing well and the CT is abnormal, the patient is anxious. They typically make the medical oncologist anxious. The medical oncologist then sends the patient to a surgeon. All of this could be avoided if there was consensus on what is and is not operable.

This is an example in my practice within the last year. The patient received very high dose radiation therapy. We knew that we were going to need to replace the internal jugular vein. I did not anticipate replacing the common hepatic artery, which when I ligated the gastroduodenal artery, essentially the intima-media and adventitia completely fell apart, necessitating a reverse saphenous vein graft from the right renal artery. Again, largely due to high dose low fraction radiation therapy given in a definitive fashion because there was no consensus on the patient's stage of disease at initial diagnosis.

I think we have the first slide up there right now – is that – is that right – so everyone can see live on the computer screen that I can see. And I just want to bring your attention to a few information items which you may find helpful. The We Care Fund is a fund here in Milwaukee supported by the Department of Surgery and a tremendous number of people in Milwaukee that supports much of the innovation that I'll talk about this evening.

Destroy Pancreatic Cancer is a 501(c)(3) company in support of pancreatic cancer research founded by John Couvillon who I was fortunate enough to treat, based out of Atlanta. And there are some very informative patient related videos on there that you may want to see.

The Word On Medicine is our Department of Surgery radio show which airs on iHeart Media every other Saturday afternoon. And there have been a couple very informative programs on pancreatic cancer. We also have a number of YouTube videos entitled MCW Medical Moments which you may find interesting and helpful, especially for your patients.

So with that, I'll conclude. I think I have about 10 minutes for questions. I would like to give a tremendous shout out to my colleagues here at the Medical College of Wisconsin who have made all of this possible and have an unusual, unique commitment to the pancreatic cancer patient. I'd also like to thank Boston Scientific for supporting this educational activity.

And if any of you would like individual slides or manuscripts, please send me an email at devans@mcw.edu and Wendy will forward that information to you. Thank you again for your kind attention and for joining us this evening.