Discussion of 2021-1722

NEOADJUVANT THERAPY FOR PANCREATIC CANCER: INCREASED USE AND IMPROVED OPTIMAL OUTCOMES

**DR KEITH D LILLEMOE** (Boston, MA): I would like to congratulate the authors for a well-presented, polished presentation and a very nice paper based on a thorough analysis of the hepatopancreaticobiliary (HPB) NSQIP database. I think it is worth acknowledging the role that Dr Pitt has played for over a decade in initiating, developing, and using this important tool, HPB NSQIP, to improve quality of care and pancreatic surgery. He has been a pioneer in this area, and this is another important contribution.

 I would like to say that, in my mind, this paper adds to the evidence supporting neoadjuvant therapy (NAT) for patients with pancreatic cancer. Look at the history of NAT, I would like to credit John Hoffman from Fox Chase Cancer Center in Philadelphia and Doug Evans and his colleagues at MD Anderson for being pioneers in this work, long before most of us were willing to accept the potential value. We were all non‑believers, feeling that even though the survival rate was not good and almost a third of our patients were never able to get adjuvant therapy, we stayed away from NAT, thinking it would hurt our surgical outcomes, delay surgery, and increase complication. But, as this and other studies have shown, that is no longer a question.

 Ten years ago, when I arrived at Massachusetts General Hospital, I was introduced to FOLFIRINOX therapy combined with external beam radiation in patients with borderline resectable and locally advanced cancer. In 2015, our group, led by Cristina Ferrone, presented our initial (and one of the first large) experiences with this treatment regimen for patients with borderline resectable and locally advanced cancer to the Society of Surgical Oncology, and subsequently published it in *Annals of Surgery*. We compared the results in a non‑randomized fashion with concurrent patients with upfront resectable pancreatic cancer.

 Our single-center results were essentially the same as this paper has reported today: improved perioperative outcomes, better pathology, and improved overall short‑term survival. That report has been reproduced by many others, and there is currently a randomized controlled trial underway supported by Stand Up to Cancer investigating this possibility.

 The result has been a paradigm shift. Previously, NAT was limited to patients with advanced or borderline cancer. Now, NAT is being considered for patients with upfront resectable cancer, which is, again, being investigated by a prospective multicenter randomized trial sponsored by the Alliance.

 Today's paper adds to the conclusions of these single-institution reports, using the national data from HPB NSQIP. The large numbers generate a lot of impressive p values, with clinical differences of just 2 to 3 percent. But really, the main point is the lowering of clinically significant pancreatic leak, cutting the incidence by almost 50 percent. This point alone probably accounts for most of the favorable outcomes reported, and leaves little doubt in my mind that these operations can be performed safely after NAT.

 For more advanced tumors at our institution, we found that operations take longer and result in more blood loss. You show in this analysis that the operations do take longer and have increased incidence of vascular bypass, but have fewer perioperative transfusions. Did you measure estimated blood loss in the operating room, and does “perioperative transfusion” include interoperative transfusion? Because that data does not really seem to agree with what we have seen.

 Finally, and I think most importantly, your study showed dramatic and both statistically and clinically significant improved results with respect to T‑stage and N‑stage after resection in patients with NAT. Those patients receiving NAT had a T‑stage of T‑1 or less in almost a quarter of patients, and an N‑stage of N‑0 in almost 50 percent, whereas those not receiving NAT had less than 10 percent and less than 30 percent, respectively.

 I know you do not have access to the preoperative staging, but we can assume that in most cases, NAT was offered to patients with more advanced tumors than those who were taken for upfront operation during this time. Thus, I believe these results are the most important findings of this study and provide convincing evidence that NAT is rapidly becoming the standard of care for all patients with potentially resectable pancreatic cancer. I believe the next question to be addressed is, what is the role of NAT in patients with metastatic disease?

**DR WILLIAM G HAWKINS** (St Louis, MO): Many of us who perform pancreas surgery every week are quite surprised by this paper, and by earlier publications that revisit current standard of care. Only about half of patients are receiving NAT today. Your paper builds on a body of evidence demonstrating that NAT is both safe and effective. I concur with Dr Lillemoe's conclusion that this comparison is valid. What you cannot say in your paper when comparing these 2 groups (because the patients are not randomized, and they are evaluated by different metrics that correlate with outcomes, like tumor size), but what Dr Lillemoe and I can say in the discussion, is that we believe these data. Why do we believe these data? We are going to have one group of physicians who give neoadjuvant chemotherapy to everybody, and we are going to have another group of physicians who do not give chemotherapy to anybody before operation. The validity of the comparison comes into question if there is a group of physicians who give chemotherapy selectively. When someone is selective about giving chemotherapy, human nature suggests that they are going to be biased towards including patients with more advanced disease in the chemotherapy group. And then, when you look at your data and compare, you see that T‑stage is down and N‑stage is down, which is consistent with the literature, and critics might say the groups are different. However, experts can say that these data are different because chemotherapy likely works to downstage the treatment group, making these data very believable.

 While this paper demonstrates how pancreatic surgery is moving forward from an outcomes perspective, I do think it remains humbling to be a pancreatic surgeon, in that only 50 percent of our patients have optimal perioperative outcomes. Considering this data and all the preceding data, and considering the fact that the first discussion I had with Dr Pitt about whether to use NAT occurred during my board examination in 2002, why has our community been so slow to widely adopt NAT?

 You were very careful to conclude that there is no association between better outcomes and use of NAT. You (appropriately) did not conclude that NAT is the driver. Did you analyze other factors that you and others have shown to be associated with improved outcomes in pancreatic cancer? For example, did you look at the distribution by hospital volume or surgeon volume or academic vs nonacademic centers, because I think much of the improvement in survival, without looking at those, could be associated with increased centralization or increased hospital volume and experience.

**DR JOHN L CAMERON** (Baltimore, MD): Do you know what percentage of patients who received NAT had a complete response? In our series of about 300 patients who underwent NAT, 15 percent had a complete response. There was no residual lymph node disease. There was no residual primary. And in that group, with an actuarial look at long‑term survival, they have a survival rate of between 60 and 70 percent. And I think that group of patients who has a complete response are the primary reason that NAT is going to improve the overall care and response of these patients.

**DR PETER J ALLEN** (Durham, NC): Were there any trends with respect to the systemic therapy vs radiation therapy given to patients over time? I think that, given the lack of benefit in prospective randomized data, many groups are erring away from the routine use of radiation therapy. Why do we think that patients who undergo NAT have better operative outcomes? We recognize the importance of NAT in terms of disease‑related outcomes, but with respect to operative outcomes, what is the hypothesis? If the patients are in better physical shape, and if they are not undergoing treatment at higher-volume centers, is there something else that can be gleaned from the data that improved outcomes with respect to operative variables?

**DR RICHARD A LYNN** (Palm Beach, FL): With this large HPB NSQIP database that you have available, where you can look at so many variables, for those patients who undergo a vascular reconstruction or resection, how many of those would be performed by the HPB team and how many by the vascular surgery team? Did which team handled it affect morbidity?

**DR SYED A AHMAD** (Cincinnati, OH): I think Dr Pitt mentioned that the improvement in overall outcomes was driven by decreased clinically relevant pancreatic fistula, and I wonder how much of that is due to the radiation. We have known for a long time that radiation hardens the pancreas texture and decreases leak rate. Regarding fistula rate, did the authors look at patients who underwent neoadjuvant chemotherapy only vs patients who underwent chemotherapy and radiation?

**DR CATHERINE H DAVIS** (New Brunswick, NJ): Dr Lillemoe’s comment is absolutely correct, that his group at Massachusetts General Hospital was ahead of the curve with respect to the adoption of NAT for pancreatic adenocarcinoma. However, what is unique about this paper is the demonstration that this strategy has been widely adopted on a national level and that the percentages have more than tripled since 2019.

 Thank you for addressing that there is a low complication rate after NAT–this observation is important and will hopefully further encourage adoption.

 Clinically relevant postoperative pancreatic fistula (CR‑POPF) is one of the most troublesome complications after Whipple procedures; this dramatic improvement in CR‑POPF rates is a game changer. The CR‑POPF rate was half in the NAT group as compared with the upfront surgery group and improved over time in the study.

 Your observation about the lower transfusion rate is an astute one, and a challenging question to answer. One possible explanation has to do with planned vascular reconstruction vs an unplanned vascular injury. Now, with borderline resectable patients, surgeons are prepared in advance when they need to perform vascular resection or reconstruction–they control the vessels, have the appropriate tools and team members present, and the result is minimal blood loss. However, blood loss may occur when there is an inadvertent vein injury leading to major blood loss and transfusion. Unfortunately, we do not have information on estimated blood loss.

 When we first saw the T+N stage data, we were also impressed. However, when we scoured the literature, we found that pathologic downstaging with NAT was well-reported.

 To address Dr Hawkins, 2020 data published last week shows that NAT is up to 48 percent. Compared with other national databases such as the National Cancer Database or the National Inpatient Sample, these data are the most current. We anticipate, given this observed trend, that 2021 will likely bring us over 50 percent. Additionally, clear data suggest benefit of NAT for borderline resectable and locally advanced patients. However, the jury is still out on patients with resectable tumors. An ongoing Alliance trial out of the Massachusetts General Hospital led by Cristina Ferrone will address this question.

 Of course, you are right that pancreatic surgery is humbling. However, optimal pancreatic surgery is now up to 54 percent in the 2020 data and 60 percent in those who received NAT. We demonstrate increasing trends in optimal pancreatic surgery over time. Clear trends demonstrate increasing optimal pancreatic surgery in all pancreatectomies, including Whipple, distal, and all pathologies in a paper by Joal Beane recently published in the *Annals of Surgery*.

 Regarding the comment on slow adoption, we would argue that an increase from 13% to 48% over an 8-year period is dramatic–NAT was used in <10% of patients for decades. Again, a large subset of patients with resectable tumors exists for which the role of NAT is still unknown.

 With respect to your question regarding other factors, NSQIP does not report hospital- or surgeon-specific data. However, we were able to see that broad spectrum antibiotics, wound protectors, collecting day 1 drain fluid, amylase levels, and early drain removal in addition to NAT, have improved outcomes.

 Dr Cameron, you are absolutely correct that pathologic response drives oncologic outcomes. Unfortunately, we do not have any more data regarding pathology in the NSQIP database other than T+N status.

 Dr Allen, both an increase in neoadjuvant chemotherapy and neoadjuvant radiation therapy was observed, though the increase in radiation therapy was more modest. To address your question as to what is driving improved perioperative outcomes, we believe the decrease in CR‑POPF rate is largely responsible.

 Dr Lynn, thank you for your question; however, who performed the vascular reconstructions is not reported in this database. The HPB team, the vascular team, or the transplant team may be involved, depending on institutional practices.

 Dr Ahmad, thank you for your question. We did not examine radiation alone in this analysis, but the association with neoadjuvant radiation was reported by Amanda Cooper in her study of the 2012 Pancreatic Demonstration Project.