Discussion of 2021-1759

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR MANAGEMENT OF COLORECTAL CANCER WITH PERITONEAL DISSEMINATION: 30 YEARS OF EXPERIENCE AT A SINGLE INSTITUTION

**DR BRYAN M CLARY** (LaJolla, CA): I want to thank Dr. Levine and his colleagues for their pioneering work in this field over the past 3 decades. We owe their group a debt of gratitude for their disruptive, persistent, and impactful work in this very challenging disease. Wake Forest and a handful of other early adopters in this field have taught us over the years several important lessons regarding the management of patients with colorectal peritoneal metastasis, the most important of which is that there is hope.

This very important lesson was for many years hidden from most of us whose smaller minds had difficulty seeing as failure anything other than cure. This work has never been easy. Nine-hour operations, 2‑week hospital stays, roughly 70% overall complication rate, and the still very challenging survival statistics. The vision and efforts of the group at Wake Forest and others have been clearly validated, as witnessed by the recent explosion of peritoneal malignancy programs across the country. True to form, Dr Levine’s team contributed logistical help to many of these programs.

In today's presentation, we have been given the opportunity to learn from 3 decades of experience. Such a rich experience can help address many questions regarding the application of this treatment to these patients.

Can the authors comment further on the impact on long‑term outcomes of extraperitoneal metastasis, such as low-volume disease in the liver and lungs and how they approach such patients? For example, would they perform minor wedge resection to deliver for parenchymal metastasis in this patient population?

The authors observe, as one might expect, that preoperative performance status is a strong predictor of outcomes. In addition, they found that preoperative systemic therapy has very little impact on overall survival in patients who underwent complete gross resection of their peritoneal metastasis. Interestingly, this latter finding has largely been replicated in patients undergoing resection of isolated hepatic metastasis. In this context, I would ask the authors if it is indeed the right strategy to deliver highly toxic systemic therapy before operation, given the propensity for it to negatively affect preoperative performance status. The authors state in their manuscript that typically, they use preoperative systemic therapy to better select patients, but we all know that the likelihood of progression on current regimens is quite low over modest intervals of times such as 3-6 months on therapy.

To help us better understand this issue, can the authors tell us what proportion of potentially resectable patients treated upfront actually progress such that cytoreduction is not attempted? In addition, is the performance status of the patients with pre‑resection systemic therapy worse compared with patients undergoing resection upfront?

While today's presentation and manuscript focuses on survival, can the authors comment on quality of life issues in resected patients? One of the main concerns that detractors have regarding this form of therapy is that patients with limited life expectancy spend much of their remaining lives with a poor quality of life related to perioperative complication. So, this would be important to address.

My last question lies in the use of staging laparoscopy for operative planning and assessment of resectability. Our group at the University of California, San Diego frequently uses laparoscopy as a standalone procedure in advance of cytoreductive surgery to assess suitability for subsequent cytoreductive surgery.

**DR JOHN H STEWART** (New Orleans, LA): I would like to commend the Wake Forest group for advancing cytoreductive surgery and heated intraperitoneal chemotherapy for the past 30 years. The program is considered the gold standard for the management of peritoneal surface malignancy.

Firstly, they have developed an extensive referral network based on an excellent clinical program.

Secondly, they have conducted early phase clinical trials in the area.

Thirdly, they have reported outcomes in large cohorts of patients. This is made possible by a well‑maintained prospective database.

The role of cytoreductive surgery in intraperitoneal chemotherapy in the management of peritoneal surface malignancy has been hotly contested over the past 30 years. Issues have included the biologic rationale of 120 meta chemoperfusion, its role in the management of appendiceal malignancy, and its place in managing patients with peritoneal surface dissemination from colorectal cancer.

The later issue has been evaluated in several critical studies including PRODIGE 7, which did not show a median survival benefit in patients who underwent heated intraperitoneal chemotherapy in addition to cytoreductive surgery.

I do know, however, that there was in subset analysis a group of patients who were shown to have some benefit in overall survival. The present work by the Wake Forest group adds to this body of literature for a group of patients with limited therapeutic options.

Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status scores of 2 underwent prehabilitation. Can you tell us what constitutes prehabilitation? What proportion of patients had improvement in their performance statuses and subsequently moved on to cytoreductive surgery and heated intraperitoneal chemotherapy?

The use of neoadjuvant therapy in this group of patients did not increase the complete resection rate. What do you believe to be the underlying reason for this finding? Does this data suggest that we abandon neoadjuvant therapy for patients with peritoneal surface dissemination from colorectal cancer? Were you able to determine if the addition of targeted therapy, including Bevacizumab, Cetuximab, Ipilimumab, Nivolumab, improved resectability in this cohort?

Mitomycin C was the perfusate of choice in this study. However, other agents, including Oxaliplatin, have been approved for the systemic management of metastatic colorectal cancer. In fact, a Phase I trial of Oxaliplatin for peritoneal surface dissemination of appendiceal cancer was completed at Wake Forest. Are there plans to consider other perfusates in the future for colorectal cancer?

Finally, your group presented your work on gene expression profiling in appendiceal and colorectal tumors in the 2011 meeting of the Southern Surgical Association, held here at the Homestead. Do you plan to update this work for the colorectal cohort based upon the findings of this paper?

Of note, there were clear disparities in the delivery of heated intraperitoneal chemotherapy cytoreductive surgery in patients with colorectal cancer; 83% of these patients were Caucasian patients. I would like to understand the ability of patients from underrepresented groups to receive this lifesaving therapy.

**DR DAN “TREY” BLAZER** (Durham, NC): I think that the PRODIGE trial has thrown a wrench in the way that our medical oncologists view cytoreduction in hyperthermic intraperitoneal chemotherapy (HIPEC). Will we ever be able to conduct a trial in the US that can help further establish the role of this technique?

**DR EMMANUEL ZERVOS** (Greenville, NC): I congratulate Dr Levine on 30 years' experience in this challenging disease presentation and thank him for having the courage to perform these operations on patients who we philosophically believe would benefit but do not have the resources or, more likely, the courage to take on in our own institutions. I have personally sent a few such patients to Dr Levine's group, because I knew that they would benefit from this approach but could not offer it at my own institution.

Is there a way to predict Peritoneal Cancer Index (PCI) status preoperatively using imaging? What is the correlation between that preoperative score and your intraoperative findings? More practically, does CT have the precision to identify that subset of patients you alluded to in your presentation with high PCI who might benefit from neoadjuvant therapy?

**DR BRUCE CAIRNS** (Chapel Hill, NC): Who should be receiving this therapy, and who is making the diagnosis or giving the PCI? For example, in the Netherlands, there is a study where all hospitals determine the amount of peritoneal diagnosis, but very few hospitals perform the operation. A total of 340 patients after 30 years is not many and I am curious as to whom should be receiving it.

My second question is regarding the evolution of the incomplete resection and the chemotherapies that are being used. You mentioned the most recent was roughly 15 or 16 years ago. What is the future? Will we be able to perform this procedure, possibly not quite as precisely as you suggest and maybe less dangerously, so that others can expand on this? Or will there be specialized centers that you develop?

**DR EDWARD A LEVINE** (Winston‑Salem, NC): Dr Clary, I think you understand the issues here. What about extra‑abdominal metastasis? It is not part of this manuscript, but we have looked at that in several different settings. All the extrahepatic diseases must be, number 1, very limited, and, number 2, completely resected or controlled. So, leaving unresected, you can get all the peritoneal disease. If you leave behind lung metastasis, you are not really achieving anything. So, you must get it all. And if you can get everything cleared out, the 5‑year survival rate becomes about 5% to 10% worse than you would see. It looks a lot like the R2 A and B type resections, in terms of the outcomes.

In terms of how many cycles of preoperative chemotherapy we use, and should we use it at all, I do believe we still should. Patients who progress through preoperative chemotherapy have a very poor prognosis. That is only about 10% of cases. As you point out, after 6 cycles, performance statistics are going to be degraded. So, I try to limit the medical oncologist to no more than 6 cycles, which is going to show whether the patient is responding. If you do not see a response by the end of 4-6 cycles, you will not get one by giving an additional 10 cycles.

We have done a lot of work on quality of life. It takes between 1 and 6 months to recover from one of these procedures. Most of these are done open. It is a substantial hit, depending on what you should resect. If there are no major complications, which is somewhere in the range of 80-85%, most patients will have a good quality of life going forward. So, you are not leaving patients with gastrointestinal cripples all the time; that is actually unusual.

We use laparoscopy selectively in these cases. Routine laparoscopy is clearly wasteful. Our take‑back rate with no laparoscopy at all in the first 2 decades of this series was 5-10%. If you are doing laparoscopy, you are doing it for nothing 90% of the time. But how do you choose? For patients who have a marginal PCI score, laparoscopy is an excellent tool. For me, it is a tool to choose patients to whom you would not want to offer this procedure. A PCI over 15 on imaging that you can see, you will find is higher later. CT and even MRI notoriously under call the amount of peritoneal disease that may be present when you open these patients up.

For Dr Stewart's questions regarding prehabilitation, it is mostly nutritional status and backing off on the chemotherapy for patients who are marginal candidates. Roughly half of patients are going to make it. If you have a patient who is not a good candidate, you can try. Some will turn around, but the truth is, many of them will not and will never be a candidate for the procedure.

A total of 67% of patients in this study received preoperative chemotherapy. So, that only leaves about 100 patients to judge who had a good response and who did not. We did not stratify by initial response to preoperative therapy. It is notoriously difficult to evaluate responses to peritoneal lesions.

Regarding the perfusate, we use Mitomycin, which has been a default standard for decades. Other agents are clearly useful. I do not think the optimal perfusion agent has been identified yet. I think Oxaliplatin is useful, but not as useful, because the PRODIGE 7 trial used it for only a 30‑minute perfusion time, as opposed to the 120 minutes that we use. It is time to begin looking beyond standard therapy to more innovative therapy, such as the oncolytic virus in the peritoneal cavity.

In terms of genomics and updating our work on gene expression profiling in appendiceal and colorectal tumors, I can say yes. Stay tuned—more is coming in terms of that.

Dr Blazer, what about the PRODIGE 7? Are we ever going to run a prospective trial? I have been taking this platform to cooperative groups for over 20 years, and I do not know that we will get a large cooperative group trial in the US. There are others in the audience who have been trying to do the same thing for a long time. This is a very difficult area, particularly in an era when the systemic chemotherapy is constantly shifting.

Can we do this for everybody? Is there a HIPEC light on the horizon? I do not think so. The one thing that is very clear from this and from anything else that has ever been written about this is, if you cannot achieve a complete resection, you are not doing the patient any favors. To go in and dabble and get the easy stuff is not the solution.

What about disparity? There are disparities here. I will tell you I think we have about 87% Caucasian patients in this study. That is not an equal opportunity event, and I believe most of this relates not to the selection bias when they hit the door, but to the problem in terms of availability and referrals to centers with the ability to do this study. We need more that can, and we should open it up to everyone. When 10% of patients with colorectal cancer are going to wind up with peritoneal disease, and we are doing a few hundred cases over decades, we are clearly not offering enough therapy. The take‑home lesson from the PRODIGE 7 trial, to me, is that cytoreductive surgery should clearly be the standard of care for such patients.