Editorial (Management of Pancreatic Cancer)

# Pancreas cancer, careful improvements and human connections

"Pancreas cancer is a deadly disease." That sentence, or something like it, appears at the beginning of almost every paper on pancreas cancer that I've ever read or written. For decades practitioners have constantly striven to hone their skills and improve outcomes, yet the prognosis remains stubbornly poor.

A review of the major advances in the field reveals a history of incremental improvements rather than major breakthroughs. The first pancreaticoduodenectomy was attempted in 1898 in Italy by Alessandro Codivilla (1) and resulted in a post-operative death. Unfortunately, there was little progress in improving the procedure until Allen Oldfather Whipple developed and refined it, performing it 37 times over the course of his career during the early to mid-20$^{th}$ century (2). Outcomes remained poor but over the years surgical techniques continued to evolve and improve and now confer many months and even years of survival to appropriate patients (3). Meanwhile, systemic treatments have nudged survival upward, but only slightly. In the 1980's the small but randomized GITSG trial showed that adjuvant chemoradiation therapy with 5 FU followed by 2 years of 5-FU improved median survival by 9 months (4). Later trials placed the benefit of adjuvant radiation therapy in doubt (5) but again showed benefit with adjuvant chemotherapy, with Gemcitabine improving median survival by 3 months (6). Trials of chemotherapy for metastatic pancreas cancer have demonstrated that the right regimens—like FOLFIRINOX (7), and nab-paclitaxel plus gemcitabine (8)—can result in improvements in survival on the order of 2–5 months over their comparators. These regimens are being worked into definitive protocols with hopes of similar benefits. Meanwhile, neoadjuvant therapies are properly selecting the right patients for the right local treatments like radiation therapy and surgery, further improving outcomes. But the gains are not enough.

With the advent of the immunotherapy age, advances are being made in many cancer types that were unheard of a few years ago. Disappointingly, immunotherapy advances in pancreas cancer don't seem as immediately forthcoming. This is in part due to pancreas cancer's dense desmoplastic reaction and immunosuppressive microenvironment. In the clinical setting, single agent immune checkpoint inhibitors have not shown acceptable response rates in pancreatic cancer (9). Therefore, our patients have to wait as we evaluate agents still in development and test strategies that engage several points of the cancer-immunity cycle (10). On a hopeful note, pioneering work studying the immune cells present in a select group of long-term survivors of pancreas cancer may help pave the way for new therapies targeting the immune system (11).

All this goes to show that doctors who treat pancreas cancer have had to learn to be patient. More importantly, the patients waiting and hoping for that breakthrough have to be patient. We've had to settle on treatment algorithms that demand a very anxious kind of waiting on their part.

It may be helpful to walk through the process that patients face upon being diagnosed with non-metastatic pancreas cancer. It generally goes something like this: First there is the shock of finding out that a previously unheralded but now definitely advanced cancer is growing in their abdomen. It is a cancer for which there is no effective screening program, and is barely visible before it is practically incurable. Surgery, they learn, is the only definitive therapy, but many patients find they are not candidates for surgery because of high-risk vascular involvement, operative risk, or medical comorbidity. Patients with high-risk vascular involvement enter into a holding pattern. They are told that because surgery is not an option right now, it would be best to start chemotherapy. If it goes well they might be candidates for surgery in a few months. If a trial of chemotherapy doesn't make the tumor resectable, and if things haven't gotten too much worse, they are often referred for radiation therapy for the local control benefit and the chance of getting surgery later on. Despite being told that the odds of progressing to surgery at that point are quite poor, there is little choice but to try.

As a radiation oncologist, I have spent a good amount of time with folks stuck in this phase of the waiting process. Many of them have uprooted themselves from their homes, families, and communities to come receive treatment at our cancer center. After treatment is done, some travel to other faraway places to try alternative therapies, untested treatments, or even healing waters. The stress of being forced into these kinds of decisions must be grueling at times.

How can we best comfort and care for patients stuck in this holding pattern? I don't pretend to be an expert in this but a few thoughts come to mind. Firstly, our patients deserve the respect we pay them by giving them the best care available right now. When a miracle breakthrough is not readily available, our patients deserve every effort we can give to make the available treatments count. This ideal is apparent in the investigations and discussions presented in this issue of the

*Journal of Gastrointestinal Oncology*. For example, giving the best care possible may mean paying extra attention to radiation therapy planning to avoid unnecessary toxicity as exemplified by the analysis of the effect that breathing differences can have on radiation target coverage by Sarkar and colleagues (12). It may mean combing through big data to discover clues as to most successful real world practice patterns (13). Making the treatment count can be enhanced by careful retrospective proof of concept studies showing that a new effective therapy is safe in practice, as demonstrated by Mancini and colleagues in their retrospective analysis of neoadjuvant FOLFIRNOX chemotherapy (14). Finally, it may mean staying current with state of the art techniques as outlined by Acher and colleagues in their review of surgical advances (15). The careful thinking and skillful care of one small advance at a time does make a difference because it shows respect for the patient.

Secondly, in addition to excellent medical care, our patients deserve our respect for their dignity and humanity. Patients and their families certainly appreciate the technical and medical advances outlined in this special issue. But what sticks in their minds and affects them most is undoubtedly the human connection they feel under the care of the nurses, physician assistants, therapists, technicians, receptionists, doctors, and many other excellent staff members that comprise their "team". Any one of these team members has the ability to recast a painful waiting process into a deeply appreciated human connection, even if only for a moment.

Patients and caregivers have done a lot of waiting for meaningful improvement for pancreas cancer. And the battle we're fighting is not easy to win. Therefore, the way we fight it together is paramount to making it count.

## Acknowledgements

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