

Professor Lei Zheng: Multidisciplinary management for pancreatic cancer

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Lei Zheng, MD. (Figure 1), Assistant Professor of Oncology and Surgery in the Johns Hopkins Hospital, trained in the Peking Union Medical College Beijing in 1996 and the University of Texas Medical School at San Antonio in 2000. Dr. Zheng is one of the lead researchers on a project to use immunized sera from vaccinated patients to identify candidate pancreatic cancer associated proteins against which the immune system has been activated. Through this project, he has identified a molecular pathway that underlies the tumor-stroma interaction in the tumor microenvironment of pancreatic cancer. His current research interest is to further explore the roles of the pancreatic tumor microenvironment in developing immune tolerance and in supporting tumor growth, invasion and metastasis. He is also the lead investigator on the development of vaccines and immune based therapies as pre-operative, post-operative, and long-term maintenance treatments for patients with pancreatic cancer. His clinical research interest is focused on developing multidisciplinary therapeutics in the pre-operative/neoadjuvant setting for patients with pancreaticobiliary cancer.

In 2014 International Hepatopancreatobiliary Surgery Forum, Dr. Zheng participated in the International Discussion on Pancreatic Treatment and gave a lecture on Multidisciplinary Management for Pancreatic Cancer. During the forum, he was interviewed by editor of Hepatobiliary Surgery and Nutrition (HBSN) about the treatment of pancreatic cancer.

HBSN: After the international discussion of the treatment of pancreatic cancer, could you conclude the main gaps or differences between Chinese and Western medical development in this field? Do you have any suggestions for Chinese researchers and doctors?

Professor Zheng: One reason we came here is to learn the differences between physicians and surgeons in western countries and in China in their approaches for treating pancreatic cancer. We believe we can learn from each other. Both China and US have distinguished surgeons and wonderful surgical techniques. However, there are differences in the management approaches for pancreatic

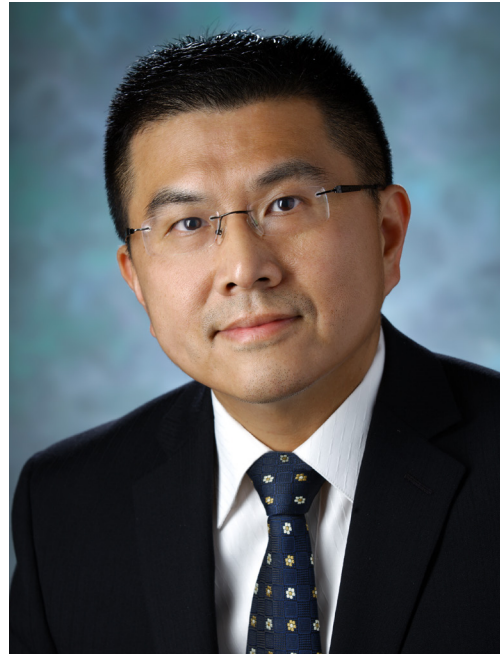


Figure 1 Prof. Lei Zheng, MD.

cancer. Looking into these differences and debating on these differences, we can improve our care for pancreatic cancer patients in both countries. In the last ten years, a huge development happened in western country, practically in US, is in the multidisciplinary approach of the pancreatic cancer management. I am very lucky to be part of the multidisciplinary team at the Johns Hopkins Hospital, where we developed the first multidisciplinary clinic in US. Now, almost every major academic center in US has a multidisciplinary clinic for pancreatic cancer patients. The reason why we have multidisciplinary clinic in US is that, in the past, the patient would come to see the surgeon first, then the surgeon would ask the patient to go to see the medical oncologist; later, it would still be possible the medical oncologist would ask the patient to see the radiation oncologist. Thus it could take a few weeks for the patient to finish seeing all the specialties before a decision on the

management would be made. The treatment could have often been delayed. On another hand if the patient saw a surgeon first, the patient would probably be recommended for surgery even if the surgeon would think the tumor may be better shrunk by being treated with chemotherapy or radiation first. This could simply because the surgeon would worry about the delay of treatment if the patient would have to wait to see other specialists. For the same reason, if the patient saw a radiation oncologist first, the patient would probably be recommended for radiation therapy. Or if the patient saw a medical oncologist first, the patient would be recommended for chemotherapy. The treatment plan would largely depend on who you would see the first. But multidisciplinary cares are different. Patients see the doctors from all different specialties in our multidisciplinary clinic on the same day. Doctors will discuss the patients' cases under the same roof and make a consensus management plan. In this way, the management plan is not determinate by who the patient would see the first. I think, in China, now this concept of multidisciplinary management is getting more and more popular. However, because of traditional influence, cancer patient cares in China are still largely dominated by one specialty or depend on what the patient believes and who is available first to see the patient. Our colleagues in China hope we can help changing the current model of cancer management. In this conference, quite a few presentations given by speakers outside China, with a focus on different stages of diseases, all emphasize on multidisciplinary cares. There are no significant differences in surgical techniques for pancreatic cancer. For example, however, there are still significant differences in treating patients with borderline resectable pancreatic cancer. In US, we start with the chemotherapy first followed by the radiation and then do the surgery. In China, such a patient would have the surgery first.

HBSN: How has the multidisciplinary management for pancreatic cancer evolved over the time in USA?

Professor Zheng: We have this in US only for ten years. Ten years ago every specialist saw the patient separately and the patient may receive different recommendations from different specialists. We have gradually developed this multidisciplinary system. Every doctor from different specialties must devote additional time to the multidiscipline care. They need to be very open to the ideas and suggestions provided from different specialties. Through multidiscipline approaches, even our own understanding

of diseases has changed a lot. Now we don't just look at the disease from our own specialty, but also learn to see the disease from other specialist's points. Everyone's clinical skills have been improved. For example, surgeon can talk about chemotherapy, radiation oncologists can talk about surgery, and medical oncologists can talk about radiation. Because we understand the principles, strengths and weaknesses of treatment approaches used by each specialist, we can come up with a consensus of treatment plan after a multidisciplinary discussion. The second advantage of multidisciplinary management is to ensure the implement of personalized treatment. At the multidisciplinary tumor board, the management plan for each individual patient would no longer follow any fixed path, but will be individualized according to the patient's clinicopathologic factors, performance status, family histories, and, hopefully in the near future, molecular markers.

HBSN: What is the biggest challenge for the treatment of pancreatic cancer in western country?

Professor Zheng: Pancreatic cancer in US is still a disease with very poor prognosis. Only 20% patients are suitable for surgery at the time of diagnosis. And 40% patients already have metastasis diseases at the time of diagnosis. The remaining 40% of patients are considered to be locally advanced. This means they have local diseases but have a borderline resectable disease or do not resectable diseases. We are optimizing the treatment for this stage of disease and hope to get more patients down-staged by chemotherapy and radiation therapy to a condition that can be surgically resected. Even among patients with surgical resectable pancreatic cancer, 80% will still have recurrences within five years. For patients with metastasis diseases, we have made significant progress in the treatment in the last few years and newer, combinational chemotherapy is able to prolong the patient's life from six months with the traditional single drug chemotherapy, gemcitabine, to 11 months with the new combinational chemotherapy called FOLFIRINOX. However, none of us wouldn't be satisfied with "11 months". Therefore, we are still lacking effective therapy for pancreatic cancer. Another challenging is, the incidence of pancreatic cancer is still rising in both western countries and China. In either geographic area, the incidence of pancreatic cancer is still not high at this moment, but the mortality rate is high. In US, pancreatic cancer is the fourth leading cause of death from cancer because the majority of patients with pancreatic cancer

unfortunately do not survive beyond a year. It is predicted that in next 5-10 years pancreatic cancer will become the 2nd leading cause of the death from cancer, only secondary to lung cancer.

HBSN: Do we have any improvements in the early diagnosis of pancreatic cancer?

Professor Zheng: I think this is an important area. Tremendous effort has been put into the early diagnosis through identify biomarkers of premalignant conditions. One of the approaches at John Hopkins Hospital is to look into those premalignant lesions of pancreatic cancer which we called pancreatic cysts. Not all the pancreatic cysts will develop into cancer; so it's very important from the early diagnosis' point to distinguish between those pancreatic cysts that will never develop into a cancer from those that will become cancer sooner or later. We would want to resect those pancreatic cysts that have malignant potentials. However, the surgery of pancreatic cyst is as big as the surgery for pancreatic cancer and associated with complications. We still don't have a very good way to distinguish between cysts that can turn to cancer versus those that will never. At this moment, we try to distinguish them based on the radiographical images such as CT scan or MRI and endoscopy-guided ultrasound. Now, we have started to develop molecular diagnosis tools, for example, through detecting mutated DNA within the cyst fluid. We hope to use biomarkers to detect premalignant lesions with malignant potentials by sampling blood or body fluid in a minimal invasive manner.

HBSN: Is there any specific research area that you will be pursuing and you expect to achieve?

Professor Zheng: Certainly, all the specialty fields will continue to evolve. Our surgeons are continuing to improve their surgery technique and incorporate those minimally invasive techniques like laparoscopic pancreatectomy. Patients are interested in new techniques because new techniques will potentially bring new benefit to them. Radiation oncologists are continuing to develop new technique. For example, the stereotactic body radiation, which is one of the newest developments in the pancreatic cancer radiation oncology field, has a more focused treatment field and potentially has a bigger treatment

effect on tumors. At Hopkins, laparoscopic pancreatectomy surgery and stereotactic body radiation are two major developments in the local therapies of pancreatic cancer. Our medical oncologists are continuing to develop systemic therapies such as newer combinations of chemotherapeutic drugs and new targeted therapies for pancreatic cancer. Immunotherapy is a new modality of systemic therapy. Historically, pancreatic cancer is thought to be non-immunogenic. It has been assumed that pancreatic cancer would not respond to immunotherapy because there are very few immune cells in the pancreatic tumor. Such a notion had become a big hurdle for developing immunotherapy for pancreatic cancer or other cancers similar to pancreatic cancer, like colon cancer. At Hopkins, we have developed a pancreatic vaccine. In our most recent study, we gave the vaccine therapy to patients two weeks prior to the surgery, and then examine the tumors obtained from the surgical resection. We found vaccine therapy has turned the tumor from a non-immunogenic one into an immunogenic one. We observed the formation of "lymph node"-like organized lymphoid structures in the tumors. Now, pancreatic cancer is no longer what we thought to be and is not the disease that we should not bother to treat with immunotherapy. Our study has suggested that vaccine therapy may prime pancreatic cancer for immunotherapy and may make it more susceptible for immune-base therapies. Last but not the least, a new focus of pancreatic cancer research is on the personalized treatment. Although overall pancreatic cancer has poor prognosis, different patients have different outcomes; thus, individualized treatment makes a lot of sense. We anticipate, in the future, the treatment of pancreatic cancer will be based on the genetic and epigenetic features of individual patient's tumor or individual tumor's microenvironment.

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