Eugene J. Koay: translating promising new radiation technologies to patients with gastrointestinal cancers

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Editor's note

Gastrointestinal (GI) cancer refers to the group of cancers that affect the digestive system. This includes cancers of the oesophagus, stomach, liver, pancreas, gallbladder and biliary tract, small intestine, colon, rectum and anus. GI cancers are regarded as a highly virulent neoplasm with both high morbidity and mortality. Collectively, they are a major cause of morbidity and mortality worldwide (1). Over the past half century, modern radiation therapy has been established and slowly evolved to treat different kinds of GI cancers. However, challenges remain in giving accurate and safe radiation delivery.

This time, *Annals of Pancreatic Cancer* (*APC*) is pleased to invite a well-recognized expert in the field of modern GI radiation therapy, Prof. Eugene J. Koay (*Figure 1*) from Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, for an interview, in which he will share with us his daily routine at MD Anderson Cancer Network, the clinical trials that his team is currently working on, the merits and shortcomings of various radiation therapy techniques, how radiation treatment can be made personalized, and many other interesting facts and stories behind the scene.

Expert's introduction

Eugene J. Koay, MD, PhD, currently serves as an Assistant Professor in the Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. He has served as a Co-Director of Gastrointestinal Radiation Oncology for the MD Anderson Cancer Network and has a joint appointment as an Assistant Member, Department of Department of Nanomedicine, Houston Methodist Research Institute, Houston, TX, USA.

Prof. Koay is well-reputed for his clinical and translational research on pancreatic and hepatobiliary cancers and their physical properties on diagnostic imaging.

Figure 1 Prof. Eugene J. Koay.

He is actively involved in national and international collaborations. He has published over 60 original articles, 10 invited reviews, and a textbook titled *An Introduction to Physical Oncology*. He has given lectures at multiple undergraduate, graduate, medical, health professional and resident courses, and has mentored dozens of students, residents, and fellows over the past decade.

Interview

APC: As a co-director of Gastrointestinal Radiation Oncology for the MD Anderson Cancer Network, what were your daily routine and major duties?

Prof. Koay: While I was the co-director, my roles included helping to establish guidelines for the treatment of GI cancers throughout the network to achieve a common standard of care, reviewing new GI cases on a weekly basis with several of our network partners who wanted regular interaction with the main campus, and being a point person

for any other radiation oncologists in the network for questions regarding radiation therapy for difficult GI cancer cases. I spent about 10% of my time doing all of these things during the week. This was a rewarding experience that I learned a lot from. I got to know many colleagues in our network and feel like we were able to disseminate the MD Anderson approach of multi-disciplinary care for our patients with GI cancers. After about 3 years of service, I recently handed off this role to another colleague so that I could focus more on research. I still maintain some role in network activities, including the establishment of multi-center clinical trials across our network.

APC: Your team strives to improve radiotherapy for GI cancers and minimize its side effects. What are you currently working on? And how have been the efficacy of these methods?

Prof. Koay: We currently have clinical trials for patients with liver and pancreatic cancers that we hope will establish new standards and approaches. For example, one of our trials is NRG-GI003, which is a randomized trial comparing protons and photons for hepatocellular carcinoma (HCC). Many of these patients have cirrhosis and limited liver function. Previous data indicated that protons might result in better survival outcomes. We think this may be due to different dose distributions that can be achieved with protons compared to photons, which affect the cirrhotic liver and the immune system. The randomized comparison will give us the type of data we need to answer whether proton radiation results in a survival advantage for HCC.

Another trial we are doing involves functional image guidance for patients with limited liver function due to advanced cirrhosis, previous radiation, or surgery. Here, we are pushing the limits of what radiation can do in the liver. For example, we are trying to show that the functional imaging can help us safely treat patients who have been traditionally at high risk for developing radiation induced liver disease because of advanced cirrhosis. Our results so far in this group are encouraging. In the same study, we are also testing what dose constraints that we can use to safely treat patients with prior radiation to the liver by external beam radiation or radioembolization with Y90. Here again, we are finding that we can do reirradiation safely when we use our dose constraints and incorporate the functional image guidance. Finally, we have an additional cohort in this study where we are evaluating the safety of using radiation to perform "*in situ* hepatectomies" such as for patients who fail to undergo surgical resection due to lack of compensatory hypertrophy after portal vein embolization. This is especially useful for patients with multiple colorectal liver metastases that are regionally confined. For example, in a few patients with multiple scattered metastases in different segments of the right liver, we have treated the entire right lobe of the liver to ultra-high doses safely. We have achieved good local control of the multiple tumors and have not seen any significant liver toxicities despite treating a very large portion of healthy liver in these patients.

For pancreatic cancer, we are establishing the first platform clinical trial for patients with localized disease. This builds on the experience at MD Anderson of using preoperative (or neoadjuvant) therapy. This platform will allow us to test new drugs and combination therapies in patients with resectable, borderline resectable, or locally advanced disease and compare the experimental treatments to controls arms specific for each disease stage. We are collecting imaging, blood, and tissue data to help us understand who these new therapies will be effective for. We expect this trial to open in the coming months and are hoping to partner with multiple institutions and pharmaceutical companies to make this successful.

APC: Modern radiotherapy techniques such as stereotactic, intensity modulated and particle radiotherapy are some emerging strategies to treat GI cancers. What are the advantages and limitations of these techniques?

Prof. Koay: Having such a wide array of radiation tools at our disposal helps us personalize the treatment for the patient and address the needs specific to the individual cancer, taking into account anatomy, tumor-related characteristics, normal tissue toxicity concerns, and previous oncologic treatment history (including prior radiation). Each of these technologies should be used with the patient in mind. For example, the use of stereotactic body radiation therapy (SBRT) for pancreatic cancer has been a great option for many patients. It has been shown to be safe and effective in modern series. Some of the appealing aspects of SBRT include that it can be finished within a week, it does not significantly disrupt systemic therapy (the mainstay of treatment for most patients), and it has low rates of toxicity. However, the maximum doses that can be safely achieved with SBRT for pancreatic cancer are unknown, so for patients with unresectable locally advanced disease, doses have been confined to more conservative levels that have

been proven safe (33–40 Gy in 5 fractions). These doses may not be high enough to ablate the tumors, and one of my colleagues (Dr. Cullen Taniguchi) is investigating ways to safely increase the radiation dose with SBRT. Also, some physicians are hesitant to give SBRT when the pancreatic tumors invade the bowel, as there is concern for ulceration and bleeding after SBRT. This is a topic of debate in the radiation community. At MD Anderson, we tend to use intensity modulated radiation therapy to conventional doses (50 Gy in 25 fractions) in that situation. For most patients, 50 Gy in 25 fractions can be done safely with good outcomes, but it does take a long time to complete radiation therapy. Further, our data indicate the longer treatment is associated with more acute GI toxicity compared to SBRT. Ultimately, we need to understand the biology of the disease better. This knowledge could be used to guide the design of clinical trials that will provide the evidence we really need to decide which patients are appropriate candidates for one type of radiation regimen or another. Currently, our approach is based on clinical judgment and limited data, which are imperfect.

Particle radiotherapy is an emerging area for pancreatic cancer. One advantage of this approach to radiation is that the particles exhibit a physical phenomenon of stopping after going through a prescribed depth of tissue. This helps to minimize radiation dose to normal tissues. There is also some preclinical data to suggest that the biological effects of particle therapy on cancer cells is different compared to conventional photon radiation. There was encouraging data from Asia with carbon therapy, and an ongoing trial will help us understand whether there is a role for carbon therapy in this disease. Proton therapy is another form of particle radiation, and this has been done in trials for borderline resectable disease showing some promising results. More clinical trials will be needed to understand how we can best use particle therapy for pancreatic cancer, considering its generally higher cost compared to conventional radiation techniques.

APC: What are the points of attention when a patient is given personalized radiation treatment?

Prof. Koay: For GI cancers, the points of attention include what type of cancer the patient has, what the anatomy is around the tumor (this determines how much dose we can give safely), whether the tumor is radiation sensitive or resistant (also helps us decide what dose to use), the previous treatment history (such as with chemo, immunotherapy, or radiation), the sequencing of radiation with surgery (if applicable), and other medical conditions (such as whether the patient has collagen vascular disease, active inflammatory bowel disease, previous exposure to radiation sources). Personalizing the treatment takes on many dimensions these days, and each radiation plan is customized to the individual. This is one of the things that makes radiation oncology such an enjoyable medical practice. As new targeted therapies emerge, we may find that radiation sensitization with small molecule inhibitors and immunotherapy may add another dimension to the idea of personalized radiation treatments. There is also new data to show that aggressive local therapy with SBRT or other local therapies (cryoablation, radiofrequency ablation, surgery) can significantly prolong progression free survival and perhaps overall survival in certain situations for patients with metastatic disease. As systemic treatments get better, we may find new ways to incorporate radiation to render patients without evidence of disease.

APC: How does technological improvement enhance the "personalized level" of radiation treatment?

Prof. Koay: The advances in technology can be generally summarized by grouping them into conformal radiation treatment techniques, image guidance, and immobilization methods. Conformal radiation techniques include SBRT, particle therapy, and intensity modulated radiation, like we discussed earlier. By controlling the radiation dose distribution, we are able to squeeze high doses into the tumor while maintaining safe doses for surrounding healthy tissues. To achieve this type of radiation dose distribution, we need to be able to verify that the patient is in the right position before each high dose treatment. This is how image guidance has made a major impact on our field. New imaging methods include computed tomography (CT) guidance, magnetic resonance imaging (MRI) guidance, and functional imaging guidance (like positron emission tomography with radiotracers). To achieve a reproducible setup, we need to immobilize patients in the same position from one treatment to the next. Technological advancements in external and internal immobilization have opened new avenues for us to deliver radiation. Our setups are accurate within 1–2 millimeters for stereotactic treatments, and this level of accuracy is expected to achieve better oncologic and toxicity outcomes. As these technologies become widely adopted, we will need clinical trials to reevaluate the role of radiation in specific contexts, such as for localized

pancreatic cancer. Older radiation techniques did not seem to support a role for radiation in pancreatic cancer, but with more accurate and precise delivery, it is something we as a field should consider, especially given the improved outcomes with systemic therapies. I see this being similar to what was achieved with breast cancer a couple of decades ago. As the systemic therapy improved for breast cancer, local control with radiation and surgery became a more important consideration.

APC: Several research of yours are receiving funding support from NIH. Would you introduce us to one of these projects?

Prof. Koay: A project that I am helping to lead focuses on the immune microenvironment of pancreatic cancer and how the physical attributes of the disease make this cancer "immunologically cold," meaning that few anti-tumor immune cells can infiltrate into the tumor. We have identified different subtypes of pancreatic cancer based on their physical attributes on diagnostic CT scans, and have found that the immune microenvironment in these imaging-based subtypes differs considerably. We are studying how nutrient gradients and physical forces make this cancer toxic to immune cells like lymphocytes. Through these basic investigations, we are developing therapeutic approaches that may help us overcome this immune-privileged state of pancreatic cancer. This may open the door to new combination approaches that help bring immunotherapy to patients with pancreatic cancer. This work is sponsored by the NIH's Physical Sciences in Oncology Network.

APC: What are the major challenges in your research area? And what have been driving you to move forward and make progress in it?

Prof. Koay: The major challenges in research with pancreatic and hepatobiliary cancers include the high mortality rates of these diseases, the lack of methods to detect these cancers early, and the lack of effective treatment options for patients with advanced disease. As a physician scientist, I see the personal toll these diseases take on patients and their caregivers, while being aware of the biological and physical underpinnings that make these cancers so tough to treat. Seeing it from these different perspectives motivates me to think of solutions that are practical so that we can make an impact on patient care. Our lab is trying to develop new ways to treat these cancers through therapeutic clinical trials with radiation, creating new imaging algorithms to increase the sensitivity to detect small liver and pancreas lesions early, and identifying subtypes of hepatobiliary and pancreatic cancers to match patients to therapies that have a higher chance of working.

APC: What do you think are the key factors of successful research?

Prof. Koay: There are many paths to success. My approach has been to pursue investigations that I am passionate about. I like to brainstorm and bounce ideas off people constantly. I try to share this passion for research with my lab members, and mentorship of the next generation of scientists and clinicians is something I have taken a lot of pride in. I teach my students how to generate focused questions that are driven by a clinical dilemma and perform studies to support or refute their ideas. Additionally, all of our projects in the lab are collaborative and multidisciplinary. Internally, our lab works well together. Externally, we collaborate effectively with groups inside and outside of our institution because we establish strong lines of communication and are clear and open about what each team member will do. So far, this approach has led to some decent successes. I am also trying to improve my approach constantly, as I am a student of leadership and management. I enjoy reading books about these topics. One thing I've come to realize about research is that its success depends not only on the ability to do good science, but also manage time and resources. Reading books on leadership and management as well as biographies of successful individuals has helped me a lot as my lab matures. I imagine my approach will continue to evolve over time, but I think the main pillars of the approach will always be there—passion for research, scientific curiosity, and mentorship.

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