The Role of the Nuclear Radiologist in the Diagnosis and Treatment of Colorectal Cancer: PET/CT

The role of the nuclear radiologist in the detection and therapy of most malignancies is both challenging and rapidly evolving. With new diagnostic and therapeutic radiopharmaceuticals continuously in development and the rapid advancements in imaging hardware and software, nuclear medicine physicians must constantly stay abreast of innovations spanning multiple medical and scientific specialties.

Nowhere in the field of molecular imaging will one find a more direct impact on patient care than with positron emission tomographic (PET) scintigraphy. PET scintigraphy is increasingly becoming a part of the standard of care in staging, re-staging, and occasionally the diagnosis of most of the more common malignancies. Utilizing a radiolabeled analogue of glucose, F-18 fluorodeoxyglucose (FDG), PET imaging can detect an abnormal elevation in metabolic activity such as with most malignant cells. As a result, PET imaging can generally detect primary, metastatic, and recurrent malignant lesions earlier and more accurately than CT alone, which relies on less sensitive and specific anatomic abnormalities. Furthermore, PET can reclassify an anatomic abnormality deemed suspicious on CT as benign, such as a reactive tissue or scar.

As with most malignancies, adding PET to conventional imaging modalities (typically CT), results in a more accurate evaluation of a patient with colorectal carcinoma. For this reason, PET has for some time been approved by the Centers for Medicare and Medicaid Services (CMS) in the diagnosis, staging, and re-staging of colorectal cancer. However, it is better suited for certain types of evaluations than others.

PET can occasionally assist in making the diagnosis of colorectal cancer. There are a number of reports detailing the high degree of sensitivity (generally greater than 90%) with which PET can detect a primary colonic tumor. These lesions may be seen incidentally in patients being staged for other malignancies or be visualized in patients who have recently been diagnosed with a suspicious colonic lesion by another imaging modality, but in whom a definitive pathologic diagnosis has yet to be made. Our experience at the University of Chicago has been typical. A number of undetermined or unsuspected primary colorectal carcinomas were first detected here by PET. Unfortunately, the specificity of PET in this regard is much lower than its sensitivity. Both tubular and focal increased colonic FDG uptake can be seen in many benign findings including physiologic uptake, inflammatory conditions, and even benign polyps. Nevertheless, colonoscopic evaluation of any focal and intense uptake seen on PET should be strongly considered. Recently, some investigators have looked at adding PET to other screening modalities such as CT virtual colonoscopy, but the role of PET in that scenario has yet to be well defined. As a result, PET imaging for colorectal cancer before a tissue diagnosis has been made is uncommon.

The American Joint Committee on Cancer has adopted the TNM classification for staging colorectal cancer, and PET imaging will play an increasingly important role in this regard, although again, is better suited to certain more specific parameters. While harnessing the power of metabolic imaging, PET sacrifices some spatial resolution compared with other modalities. Therefore, PET is not very accurate in determining the T stage, where the exact level of invasion is critical. Determination of N stage depends upon the number of involved regional pericolic and mesenteric lymph nodes. Again, the poorer spatial resolution of PET results in an underestimation of regional disease in positive nodes immediately adjacent to the primary colonic lesion and in those nodes with microscopic metastatic disease. These factors result in a poor sensitivity, on the order of 30%, of PET for N staging of regional lymph nodes (although the specificity for abnormalities in these regions is extremely high, greater than 95%).

It is in the M staging of colorectal cancer that PET truly excels, providing significantly increased accuracy compared with conventional modalities, typically CT, alone. This results in more proper patient management. Extra-regional spread of colorectal cancers can proceed through the lymphatics such as to retroperitoneal or internal iliac nodes or hematogenously, chiefly to the liver and/or lungs. PET provides superior M staging to CT alone with either of these pathways. Recent innovations have expanded the treatment options for patients with hepatic metastatic disease, which commonly occurs. Therapies including radiofrequency ablation, arterial embolization, cryotherapy, and hepatic wedge resection are important additions to the treatment armamentarium, but their success generally depends on accurate delineation of all intra- and extrahepatic lesions to avoid unnecessary and expensive procedures performed on patients with an inappropriate disease burden.

While CT has been the standard preoperative modality for evaluating intra- and extrhepatic disease, and is a fairly good one, adding PET has proved superior. CT relies on morphologic abnormalities such as an enlarged lymph node or changes in the enhancement pattern of the liver. It may underestimate disease such as in small nodes involved with tumor or overestimate disease such as with benign reactive lymph nodes. PET assesses these areas directly by detecting an increase in metabolic activity with tumor involvement. A meta-analysis demonstrated PET to be more accurate than CT for a number of sites, including the liver, abdomen, pelvis, and others (sensitivity and specificity for PET was 97% and 76% and for CT 76% and 56%). This superior accuracy for M staging has translated into changes in patient management and better outcomes. In several studies, adding PET to traditional preoperative planning prior to hepatic wedge resection eliminated a significant number of patients with unsuspected extrahepatic disease. This boosted the overall benefits.
3-year survival rate for this patient population to 77% from the more traditionally reported, approximately 40%. One important limitation for PET regarding colorectal staging should be noted, however. For those patients with a purely mucinous cell-type variant, PET sensitivity is significantly reduced given these lesions’ lower metabolic activity.

PET is also extremely accurate in re-staging colorectal cancer, which may recur in the liver, lungs, or other sites. Again, as metabolic abnormalities generally precede morphologic ones, PET yields increased sensitivity to CT alone. Furthermore, following surgery, radiation, and other ablative techniques, there are frequently morphologic changes from scarring that often can be reliably distinguished from active tumor on CT. Once the associated inflammatory activity quickly subsides, PET will demonstrate hypermetabolic activity only in active tumor. In a study which compared CT, serum carcinoembryonic antigen (CEA), and PET, PET was more sensitive than CT or CEA for tumor recurrence and was also more specific than CT (with equal specificity to CEA).

Such results reduce unnecessary invasive procedures and reduce costs—$3000 per patient in this same study.

As superior an imaging tool PET has proven to be, continued advancements in technology promise to make this modality even better. The latest innovation in PET imaging is hybrid PET/CT imaging which fuses the increased lesion detection of molecular imaging PET with the superior anatomic localization capabilities of CT. Precise anatomic localization of a metabolically active lesion can be critical in both intra- and extrahepatic disease and can more reliably classify some uptake as benign, as with occasional physiologic activity. In addition, acquiring a PET/CT study, for technical reasons related to attenuation correction, is significantly faster than PET alone. Furthermore, a number of recent studies have compared PET and CT acquired on separate instruments and read side by side with hybrid PET/CT imaging and found a significant improvement in the accuracy of staging and restaging a number of malignancies, including colorectal cancer. Combined with the fact that most insurers and Medicare cover both procedures, and that both scans can be performed in one sitting, PET/CT imaging has become a more popular choice among referring physicians and patients alike. At the University of Chicago, we are uniquely situated with both advanced equipment and highly trained personnel to perform and interpret these studies, providing superior care to our patients. We are also privileged to be a part of a wonderful team of physicians and other health care professionals who comprise our many talented oncology services.

In summary, most common malignancies, and colorectal cancer is no exception, are more accurately staged and restaged by PET/CT than CT alone. For any patient requiring a CT for staging or re-staging common malignancies, including colorectal cancer, a PET/CT should be strongly considered as it is more accurate, can be performed at a single visit, and is covered by most insurers. At the University of Chicago we are uniquely situated with both advanced equipment and highly trained personnel to perform and interpret these studies, providing superior care to our patients. We are also privileged to be a part of a wonderful team of physicians and other health care professionals who comprise our many talented oncology services.

Mr. A was admitted to our service after having had abdominal pain for several weeks. He is a 56-year-old man who has no significant medical history. He is married with two children. His workup in the hospital, including a colonoscopy, showed a tumor located in the left colon. A biopsy revealed adenocarcinoma. An abdominal CT scan showed metastasis in the liver, in the 4th, 7th and 6th segments. Considering the extent of liver involvement, a decision was made to remove the primary tumor. A laparoscopic left colectomy was performed, and a colorectal anastomosis was used to reestablish intestinal continuity. Unfortunately, we hear stories like Mr. A’s too often and as surgeons we are very frustrated knowing that these cancers could have been prevented.

The role of the surgeon clearly goes beyond diagnosis and treatment in colon cancer. As surgeons we should be involved in educating not only our patients and their families, but also the medical community at large. There is compelling evidence that population-based screening programs reduce the mortality from colon cancer. Many expert panels and medical society have recommended screening for average-risk individuals. Despite the current guidelines, only 30% to 40% of individuals over the age of fifty receive any of the recommended screening tests. This is unacceptable considering colon cancer is potentially preventable. Colon cancer develops from polyps. If the polyps are identified and removed endoscopically, cancer progression is prevented. In the twenty-first century, patients like Mr. A should be a memory of the past.

Over the past few years, we have seen several dramatic advances in the surgical and medical treatment of invasive colon cancer. The surgeons have played a key role in furthering our knowledge and understanding of colon cancer treatment. Several studies have suggested that laparoscopy could be safely used in colorectal surgery. The initial experience with laparoscopy in colon cancer was associated with significant complications and recurrences. For this reason, the surgical community at large put laparoscopy on hold for the treatment of colon cancer. Fortunately, several inspired and talented surgeons were convinced that the advantages of laparoscopy could be applied to colon cancer without compromising oncologic results. With this hypothesis in mind, several large prospective randomized trials were designed and recently published. Two of the largest studies are worth mentioning. A prospective and randomized trial from Spain published in Lancet in 2002 clearly showed that the advantages of laparoscopy (i.e. early discharge, less pain, and faster recovery) are still significant after laparoscopic resection of colon cancers. Furthermore, Stage III patients had a survival advantage after laparoscopy. The authors concluded that laparoscopy should be considered the standard of care by surgeons with adequate skills and training. In the U.S., another trial that was published last year in the New England
There is strong evidence that the outcome after surgery for colon cancer is directly related to the surgeon's experience, case volume, and training. Nodal staging remains one of the main prognostic markers in colon cancer in 2005. Meticulous lymphoadenectomy not only eliminates the bulk of the tumor, but more importantly provides adequate staging. A minimum of 13 lymph nodes is required for accurate staging. The presence of nodal disease in colon cancer is one of the main criteria used by the oncologists to recommend further treatment after surgical excision. Adequacy of proximal and distal margins is also critical to prevent local recurrence. A complete preoperative evaluation is mandatory before undergoing any surgical resection for colon cancer. The incidence of synchronous pathology identified in the colon of patients with colon cancer is as high as 20%. The surgeon is also a key player in the multidisciplinary approach to the long-term follow-up of these patients. There are no well-defined guidelines for follow-up of colon cancer patients. The best tool available still remains to be a thorough history and physical exam that should be performed by the surgeon who had performed the operation and knows the anatomy of the patient, and the extent of the disease. An important component of colon cancer follow-up should also include education of the patient and the family. First-degree relatives of patients with a colon cancer are considered high-risk for developing colonic neoplasm themselves, and therefore should be recommended for a stricter screening regimen. Even more important is education and surveillance when patients are found to be affected by hereditary colon cancer syndromes.

Like many other cancers, colorectal cancers should be approached in a multidisciplinary fashion with the surgeons, gastroenterologists, and radiation and medical oncologists working together to provide the best care to the patient and to educate the families and the community at large since colon cancer is potentially preventable.
The Role of Radiation Therapy in the Treatment of Gastrointestinal Cancers

The University of Chicago's Department of Radiation and Cellular Oncology has a comprehensive program for the treatment of patients with gastrointestinal (GI) malignancies.

Colorectal Cancer

The main treatment for most colon cancers is surgery, typically a hemi-colectomy. In patients with adverse prognostic factors, based on local invasion and lymph node status, adjuvant chemotherapy is administered. Occasionally, radiotherapy is used for tumors adherent to surrounding structures or for residual disease after surgery.

In contrast, rectal cancer is a model site in which tri-modality therapy (surgery, chemotherapy, and radiotherapy) is commonly used. In the past, post-operative chemoradiotherapy was tested extensively, but recent data suggest that pre-operative chemoradiotherapy is both more efficacious and less toxic than post-operative. At the University of Chicago, pre-operative RT with concomitant chemotherapy (typically consisting of 5-fluorouracil [5-FU]) and surgery are performed, with additional chemotherapy following the surgery. We are participating in a Radiotherapy Therapy Oncology Group (RTOG) trial that explores novel pre-operative and post-operative chemotherapy agents. In particular, pre-operative chemotherapy using capecitabine / irinotecan (used in conjunction with standard pelvic radiotherapy) is being compared against capecitabine / oxaliplatin; the post-operative chemotherapy will be FOLFOX, the recently established post-surgery standard chemotherapy regimen for stage III colon cancer.

Anal Cancer

Anal cancer is managed in a radically different way than rectal cancer. Primary chemoradiation, with surgery used for those not achieving a complete response, is the standard of care. Chemotherapy usually consists of 5FU / mitomycin, and radiotherapy is administered daily to the anal tumor and regional – inguinal and pelvic – lymph nodes.

Because 5FU / mitomycin / RT is a regimen not easily tolerated, we are using state-of-the-art RT treatment planning and delivery methods. The most important recent technological development is intensity-modulated radiotherapy (IMRT). IMRT permits the ability to develop highly conformal radiation treatment plans that can deliver a high dose to the targeted tumor and low dose to surrounding normal structures. Our group has presented and published results demonstrating excellent dosimetric and clinical/toxicity outcomes with the use of IMRT for anal cancer.

Stomach Cancer

Stomach cancer is typically managed by surgery and, unless diagnosed at a very early stage, postoperative chemoradiotherapy. Because of dose-limiting toxicities to many of the regional normal structures (small bowel, spinal cord, kidneys, and liver), resulting in the risk of causing nausea/vomiting and other difficulties during RT, we are using state-of-the-art treatment planning and delivery methods. IMRT is an important recent technological development, which lends itself to application at this challenging disease site. Our group has presented and published dosimetric and early toxicity outcomes with the use of IMRT in the management of stomach cancer, and has shown the ability to reduce dose to critical structures and have generally low toxicity rates with the use of IMRT.

Pancreatic and Biliary Duct Cancer

The preferred treatment of pancreatic and biliary duct cancer is surgery and, in selected cases, post-operative chemoradiotherapy. If the cancer is felt to be unrespectable but not metastatic, the standard treatment is chemoradiotherapy alone. In this unrespectable population, at the University of Chicago we are participating in the TNFerade trial, involving the use of gene therapy in addition to standard chemoradiotherapy. Also, we are using state-of-the-art treatment planning and delivery methods with IMRT for the treatment of pancreatic and biliary duct cancer. We have presented and published our IMRT experience at this site, reporting improved dosimetric and clinical outcomes compared to older RT techniques.

In summary, the GI Radiation Oncology program is comprehensive. We offer advanced treatment techniques for all of the major GI disease sites for which RT is administered.
The Role of the Medical Oncologist in the Diagnosis and Treatment of Colorectal Cancer

The medical oncologists at the University of Chicago are dedicated to educating and treating patients with all stages of colorectal cancer. This team of physicians not only focuses on researching new therapies to treat colorectal cancer, but also strives to educate the medical staff, including medical students, residents and fellows, in cutting-edge treatment options. Dr. Hedy Kindler directs the Gastrointestinal Oncology Program. Dr. Deepti Singh and Dr. Gregory Friberg work specifically in clinical research with known and novel combinations of drugs in the treatment of colorectal cancer. Dr. Ursina Teitelbaum is directly involved in patient care. Our team also includes a dedicated research nurse, Pam Lofton and a clinical nurse, Christine Holmstrom. Renelle Salceda, Colleen Smith, and Kuromby Oliver are actively involved in data management of our current clinical trials.

Once a week, our Gastrointestinal Oncology Multidisciplinary Tumor Conference meets to discuss patient diagnoses, stage of disease and possible treatment options. This meeting is attended by medical oncologists, surgeons, radiation oncologists, pathologists, research nurses and genetic counselors whose expertise help develop comprehensive treatment plans for patients with newly diagnosed colon cancer. For patients with colon cancer that have lymph node involvement, chemotherapy may be recommended after surgery to help reduce the risk of the cancer recurrence. In the case where the cancer has spread beyond the colon, chemotherapy can be used not only to reduce tumor growth but also increase survival. In special cases when colon cancer has only spread to the liver, chemotherapy may be given before surgery to help remove cancer and possibly cure some patients with advanced colon cancer.

Within the past ten years, dramatic changes have occurred after the approval of four new drugs for the treatment of colorectal cancer. These new therapies have resulted in significant changes in treatment options for locally advanced and metastatic colorectal cancers. Research related to these new medications has not only led to more treatment combinations, but also improved side-effect profiles. A large area of interest in colorectal research involves new “targeted therapies” or drugs that specifically target tumor cell growth factors to induce apoptosis or cell death. The new addition of targeted drugs like Avastin™ to conventional chemotherapy has increased survival by approximately five months in patients with advanced colorectal cancer.

The University of Chicago Gastrointestinal Oncology Group is very active in colorectal cancer research. Not only do we participate with national groups like the Cancer and Leukemia Group B (CALGB) to further cancer research, but we also conduct trials with the National Cancer Institute (NCI) to test new agents for advanced colorectal cancer. Some handpicked pharmaceutical studies are also available for new drugs that are not yet approved by the FDA, but may show benefit in the treatment of this specific cancer.

With a multidisciplinary team approach, active research program, and the possibility of new drugs on the horizon, we are able to individualize treatment plans for each patient in the fight against colorectal cancer at the University of Chicago Hospitals.

The Role of Nursing in the Diagnosis and Treatment of Colorectal Cancer

The University of Chicago Section of Hematology/Oncology is committed to providing the most current treatments to colorectal cancer patients. The gastrointestinal oncology research nurse is responsible for ensuring that the plan of care is carried out for each patient. The Gastrointestinal Oncology Program participates in a number of clinical trials in which the oncology research nurse assists the oncology clinical research team with regard to patient readiness, patient eligibility to participate in a clinical trial, and the implementation of research activities. The oncology research nurse is also an educational and supportive resource for patients and their families.
The Role of the Gastroenterologist in the Diagnosis and Treatment of Colorectal Cancer

The role of the gastroenterologist in the diagnosis and treatment of colorectal cancer (CRC) is diverse. It can be broken down into three main categories: prevention/early detection, treatment, and palliation. Disease prevention, both primary and secondary, involves modification of factors to reduce the risk for the development of colorectal cancer. Primary prevention includes lifestyle modification, smoking cessation, exercise, and chemoprevention. Secondary prevention involves screening and surveillance for colorectal cancer. This not only includes appropriate endoscopic and/or radiographic screening, but also requires individualized risk assessment and stratification to ensure optimal risk reduction. It is extremely important to identify individuals at high risk for colorectal cancer. These include individuals with a personal or family history of CRC or polyps, a history of inflammatory bowel disease, or inherited cancer syndromes, all requiring individualized colon cancer screening and surveillance programs. Early detection of colorectal cancer can often be curatively treated endoscopically, while polyp removal has been shown to decrease the risk of colorectal cancer development. Newer endoscopic technology allows for the earlier detection of premalignant lesions, and we continue to study the most effective modalities to screen for colorectal cancer. This is especially true in individuals at high risk for colorectal cancer. As with most diseases, effective prevention programs require continued education regarding the risks and benefits of lifestyle decisions and screening programs. Given our increasingly diverse population, it is essential that culturally competent, language specific programs are available to ensure equal access for all populations.

While the majority of colorectal cancer treatment requires surgical intervention, gastroenterologists are increasingly involved in treatment of early cancers. Endoscopic mucosal resection of stage I cancers can often be achieved, while carcinoma in situ can be resected in most situations, avoiding the need for surgical intervention. As individuals adhere to screening programs, our role as gastroenterologists in the treatment of CRC continues to expand.

Our role in palliative care for advanced colorectal cancers in nonsurgical patients includes endoscopic stenting across lesions for relief of obstruction, and the treatment of bleeding. An extremely important role in these unfortunate patients is to offer education and counseling regarding screening of family members, which can often provide comfort during end of life issues.

At the University of Chicago, we have a multidisciplinary approach to individuals with CRC, which includes gastroenterology, oncologic surgery, oncology, radiology, pathology as well as radiation oncology to ensure optimal risk reduction, counseling, genetic counseling when indicated, and to provide both education regarding treatment options and future disease prevention for patients and their families. In addition, we have a very active High Risk Program, which is staffed by gastroenterology, gynecology, oncology and genetic counselors to address those individuals with a hereditary predisposition for colorectal cancer.

There are many important research programs underway in the Section of Gastroenterology at the University of Chicago addressing colorectal cancer. As a leading center on inflammatory bowel disease, we are studying colonic carcinogenesis in ulcerative colitis, using an animal model of colon cancer induced by azoxymethane. Most recently, research is now being translated from bench to bedside. This involves studying gene expression changes in aberrant crypt foci (ACF), the earliest detectable mucosal abnormalities in pre-malignancy and putative precursors of colon cancer, in patients with ulcerative colitis. We are also studying targets of (UDCA), a putative chemopreventive agent in ulcerative colitis-associated colon cancer and have identified Ras and cyclooxygenase-2 (Cox-2) as major targets for the chemopreventive actions of UDCA in AOM colonic carcinogenesis. Along these lines, we have also been involved in studying the chemopreventive effects of COX-2 inhibitors on sporadic adenomas in average and high-risk individuals.

Most recently, we are studying the mechanisms that maintain genomic integrity and the genetic and molecular associations between genomic integrity and cancer susceptibility. In addition, we are investigating new methodologies and strategies for the identification and characterization of low-penetrance mutations that cause susceptibility to colon cancer and to breast cancer. Projects include both candidate-gene and whole-genome genetic analyses of susceptibility alleles.

We have numerous active clinical research programs studying colorectal cancer, addressing a wide range of clinical interests. Topics include: chemoprevention for sporadic adenomas and ulcerative colitis; barriers to colorectal cancer screening in diverse populations; effective communication for colorectal cancer screening and surveillance; endoscopic techniques for polyp identification and removal; novel preparations for colonoscopy; early endoscopic treatment for colorectal cancer; CT colonography; stool based markers for colon cancer; genetic predisposition syndromes; cultural competency and colorectal cancer education; community based participatory programs for effective CRC outreach; and health disparities in colorectal cancer.

We continue to work to translate our research efforts to deliver cutting edge treatment and management for CRC. As gastroenterologists, we work together with a multidisciplinary team to provide optimal risk assessment and reduction, prevention and early detection, in the hopes of eliminating this often preventable disease in all populations.