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Rectal Cancer Care in the 21st Century

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Rectal cancer afflicts approximately 50,000 Americans each year, making it a common cancer. Despite its commonness, the care of rectal cancer and the results of treatment have remained highly variable across the United States. This variability has been seen in other countries with high incidence of colorectal cancer (mostly Northern European countries) and has been addressed through the use of standardized treatment protocols, designated centers for rectal cancer treatment, and other initiatives. Specific measurable improvements have been noted in the rates of complete total mesorectal excision, the rates of permanent stoma construction, the incidence of local recurrence, and overall survival. For many reasons, American health care has lagged behind in these efforts to improve the standards of rectal cancer care. However, in recent years, much work has been done to demonstrate that there is tremendous variability in the care delivered, and that results are not what we would hope for as compared to other countries in the world. Identifying and proving that there is a problem was the obvious first step. Now we must take appropriate actions to improve the care we deliver.

Over the last decade, a group of rectal cancer specialists has been working within the American College of Surgeons Commission on Cancer® to create a system of standards that will allow institutions to standardize care and therefore improve survival from rectal cancer as well as decrease loss of function (organ preservation) from the therapies performed. These efforts have led to the development of the National Accreditation Program for Rectal Cancer (NAPRC).

The treatment of rectal cancer should involve a multimodality approach. Surgery, radiation oncology, and medical oncology specialists are often involved in the care of these patients. It has been demonstrated that cancer outcomes are better, functional outcomes are better, and patient experience improves with the improved clinical decision making that stems from a multi-disciplinary approach. Historically, surgical-only care of rectal cancer resulted in high rates of permanent colostomy in addition to unacceptably high rates of local recurrence and metastatic disease. The evolution of adjuvant radiation and chemotherapy began to change those results decades ago. Through multiple series of clinical studies, the use of neoadjuvant treatment strategies incorporating chemotherapy and radiation therapy have shown better patient tolerance, improved sphincter

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preservation, and improved local recurrence rates. In addition, response to preoperative therapy can be assessed in the pathologic specimen. We have also discovered that as that response improves, so does the prognosis for the patient. That discovery has led to a desire to improve response to neoadjuvant therapy. These efforts, as well as more reliable ways to judge treatment response clinically rather than pathologically, have led to the concept of Total Neoadjuvant Therapy (TNT); the administration of all non-surgical therapies before any surgical intervention occurs. TNT can be administered in two ways: 1) induction chemotherapy (typically FOLFOX for four to eight cycles) followed by consolidation single agent 5-fluorouracil and long-course radiation therapy (5040GY in 25 cycles) or 2) induction chemo-radiotherapy (CXRT) followed by consolidation FOLFOX. At this point, hard data doesn't exist as to which method is superior and each has its proponents and detractors. The OPRA trial from Memorial Sloan Kettering, due for publication soon, does indicate there may be an advantage in organ preservation (sphincter preservation or non-operative management) with CXRT first.

UPMC has prided itself as a premier oncology hospital system. Dedicated teams of physicians and staff provide state-of-the-art clinical care, engage in both clinical and bench-top research and are leaders in the field of cancer care. Specifically relating to rectal cancer care, UPMC Passavant and UPMC Presbyterian Shadyside have been identified as high-volume centers. The surgeons in the Divisions of Colon & Rectal Surgery and Surgical Oncology along with Radiation Oncology, Medical Oncology, Diagnostic Radiology, and Pathology are collaborating to achieve accreditation by the NAPRC at those two sites. A multi-disciplinary team meets on an every other week basis to discuss pretreatment planning as well as post treatment results for patients who present to our institutions for care of their rectal cancer.

Already we have seen improvement in the standardization of care for these patients. Through the UPMC Hillman Cancer Center Network, patients are receiving best of care practices even if they are not primarily treated at UPMC Passavant or UPMC Presbyterian Shadyside. However, under the guidance of the rectal cancer multidisciplinary team and the surgical decision making and expertise at Passavant and Presbyterian Shadyside, we have seen improvement in clinical response to therapy and better sphincter preservation rates than national averages. In fact, up to 40% of non-metastatic rectal cancer patients who receive TNT are achieving complete clinical response (cCR) and avoiding surgery all together (unpublished internal data). Close follow-up of these patients has yielded a low rate of tumor regrowth and in patients with regrowth, surgical salvage has been achieved in all thus far.

Clearly, these are exciting times for rectal cancer patients and their care not only at UPMC but across the country. As we continue to push the response rates to pre-surgical treatments, we potentially increase the quality of life of these patients without compromising their oncologic results. That sounds like a win-win situation.

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Robotic Liver Surgery: Taking Liver Cancer Surgery to New Levels

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Liver resection, once regarded as an operation with prohibitively high mortality and morbidity, has now become a routine operation in expert hands. As minimally invasive techniques for other major abdominal operations have matured, the interest in applying minimally invasive techniques to liver resection also developed. Technical developments such as more sophisticated energy devices and articulated laparoscopic staplers have enabled surgeons to start tackling liver resection laparoscopically. The UPMC Liver Cancer Center surgeons have pioneered laparoscopic liver surgery and we recently published our experience with more than a 1,000 consecutive cases.[1]

Some of the major technical challenges in liver surgery include the difficult access to the vena cava and major hepatic veins, precision required for dissection at the hilum, and propensity for the liver to bleed. These can be challenging with laparoscopy due to the limitations in depth perception, restricted movement by rigid instruments and fixed fulcrum at the ports, unnatural ergonomics, and difficult suturing particularly in presence of hemorrhage. In addition, there is a steep learning curve, making its practice outside high-volume centers difficult.

Robotic surgery can overcome some of those challenges. Its use in liver surgery has been expanding during the last several years and robotic-assisted surgery has been increasingly described as an alternative to laparoscopy for minimally invasive liver resection. Advantages include improved surgeon ergonomics, a greater range of motion with articulating instruments, improved three-dimensional field of vision, minimization of physiologic tremor, better access to the caudate lobe, posterior and superior liver segments, and ease of using indocyanine green. There may also be a shorter learning curve for use, and there are possibilities for technological assistance with surgery, such as augmented reality and intraoperative navigation, in the near future. Limitations include potential increased cost and loss of tactile feedback.[2,3] Expected increased competition in the marketplace will potentially lead to further improvements of the surgical equipment and probably will decrease costs.

We have recently published a retrospective study to look at the safety and short-term outcomes and long-term oncologic outcomes of robotic versus laparoscopic-assisted liver resection for patients with colorectal liver metastases.[4] Robotic surgery was performed in 115 patients and 514 patients underwent laparoscopic resection at UPMC and five high-volume centers in the United States and Europe. Following propensity matching, perioperative outcomes including mortality, morbidity, reoperation, readmission, intensive care requirement, length-of-stay and margin status were not statistically different between both groups. Analyses demonstrated similar overall survival (OS) and disease-free survival (DFS) between robotic and laparoscopic resections at five years (61 vs. 60% OS, $p = 0.87$, and 38 vs. 31% DFS, $p = 0.25$).

Thus, robotic surgery is feasible and safe, with perioperative and long-term oncologic outcomes and survival that are largely comparable to the time-tested laparoscopic approach.

Current data show that with good patient selection and meticulous technique, robotic hepatectomy is a safe and effective operation that is likely to stay. The goal of robotic assistance is to mimic the techniques of open surgery delivered through a minimally invasive approach. The theoretical advantages of robotic surgery are exciting but the evolution of the technology is ongoing.

To learn more about minimally invasive liver surgery at UPMC, visit our website at: UPMC.com/services/liver-cancer/treatments/surgicalresection/minimally-invasive.

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To refer a patient to the UPMC Liver Cancer Center, please call 412-692-2001

Adoptive Cell Transfer Immunotherapy: Building on a Blueprint Provided by Studies of Metastatic Uveal Melanoma

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Adoptive cell transfer of tumor-infiltrating lymphocytes is a complex, personalized therapy with the potential to generate an immune response against a variety of tumor types. In clinical trials, cutaneous and uveal melanomas responded to this innovative approach, and new trials have been initiated at UPMC to study the utility of adoptive cell transfer of tumor-reactive T cells in other common and uncommon cancers.

Adoptive cell transfer (ACT) has several potential advantages over other immunotherapeutic approaches to treat cancer. Our UPMC team can select tumor-infiltrating lymphocytes (TILs) with significant personalized antitumor reactivity, activate the cells, and grow them to large numbers. Thus, tumor-fighting T cell populations can be directly instilled into the patient without the need for other immune-boosting agents, which may be poorly effective or cause toxicity.

Immunotherapy using ACT was pioneered in patients with cutaneous melanoma, a very immunogenic cancer, and 30 years of research findings support ACT as a feasible approach to kick-start the immune system to fight cancer. The multistep process starts when the patient undergoes metastasectomy to procure tumor tissue. Next, autologous TILs are liberated from the resected tumor metastasis and undergo large-scale ex vivo expansion. The best ways to select cells for expansion is an active area of investigation. The patient then receives lymphodepleting chemotherapy followed by intravenous infusion of the expanded lymphocytes and treatment with interleukin-2 to promote T cell survival. (See Figure 1.) The patient's tumor response is then monitored[1].

Manipulation of the T cells outside of the body conveys several potential benefits. Most cancer patients have dysfunctional immune systems. Tumor-reactive T cells are present but suppressed by other defense mechanisms. Once the T cells are outside of the body, the physician can "recondition" the patient's immune system. During ACT, the recipient's immune system is wiped out for a short time with a nonmyeloablative, mild chemotherapy regimen administered for seven days. Then, the immune system is repopulated with the TILs expanded ex vivo. This is distinct from other types of immunotherapy, which must stimulate the immune system within the confines of the body. The UPMC team is "setting new rules" by manipulating the cells outside of the body.

After ACT was established as a feasible therapy for cutaneous melanoma, our team at the National Institutes of Health (NIH) wanted to demonstrate proof of principle in another cancer[1,2]. We chose to examine uveal melanoma, a rare cancer that did not respond to any known immunotherapies. In work published in 2016 in *Clinical Cancer Research* and 2017 in *Lancet Oncology*, we demonstrated that tumor-reactive TILs could be isolated from metastatic uveal melanoma and that a subset of patients with uveal melanoma responded to ACT immunotherapy with selected TILs[3,4]. This trial was critically important in establishing ACT as a potentially useful immunotherapeutic approach because even a cancer that had not responded to any other immunotherapies could respond to ACT.

In 2017, our team at UPMC began a phase II trial to further improve ACT for patients with metastatic uveal melanoma (NCT03467516). This trial, which is funded by the UPMC Immune Transplant and Therapy Center, is currently ongoing. One goal of the trial is to confirm our initial observations. Other goals are to identify biomarkers that may predict therapeutic response and to isolate the genes responsible for TIL recognition of uveal tumors. Additionally, the trial allowed our team to set up the production facility and clinical infrastructure at UPMC needed for ACT, including improvements to the bioreactors used to grow the cells. The Immunologic Monitoring and Cellular Products Laboratory (IMCPL) at UPMC Hillman Cancer Center was incredibly responsive as we adapted our protocols to grow T lymphocytes using good manufacturing practices (GMP) at a new location. Only a few institutions around the world are using this approach and have these capabilities.

The UPMC team is currently using this experience with ACT in uveal melanoma as a blueprint for treating other cancers. Two new clinical trials using ACT as an antitumor immunotherapy began recruiting patients at UPMC Hillman Cancer Center in 2019. One trial is using ACT to treat biliary tract cancers (NCT03801083), and one is using ACT against a wide array of solid tumors. Biliary tract cancers include cancers of the bile duct (cholangiocarcinoma), gallbladder, and ampulla of Vater, are relatively rare, and carry a poor prognosis, similar to uveal melanoma. We have expanded TILs from metastases of biliary tract tumors and isolated cells with the appropriate reactivity to show proof of concept in the laboratory. We hope to enroll up to 10 patients per year. The trial is designed to evaluate outcomes after the first 15 patients before moving forward to an enrollment goal of 47 patients. Tumor response, duration of tumor response, disease-free survival, and overall survival will be assessed as study outcomes.

The second new trial of ACT examines the effectiveness of this therapeutic strategy against many different solid tumor types. This trial (NCT03935893) is a fascinating trial that will allow us to treat virtually any cancer. The trial has 10 different arms including analysis of common (e.g., stomach, esophageal, colon, pancreas) and uncommon cancers (e.g., Merkel cell, neuroendocrine tumors) and serves as a novel treatment option for patients seen at UPMC Hillman Cancer Center. This ambitious trial is the only one of its kind in the world and is pioneering in its potential to explore ACT as a treatment for many types of cancer. As our team examines tumor response and patient survival, we will also work to define the biologic signature of T cells reactive against each tumor type and determine if they can grow TILs from each unique cancer and use these cells for treatment.

Although our team is excited about the trial, which just began recruitment in May 2019, we anticipate that the majority of the cancers studied will not have triggered the immune response necessary to isolate good T cells for ACT immunotherapy. In anticipation of this outcome and to facilitate further research in the field, all tissue collected during the trial will be banked in a repository for sequencing and translational science efforts.

This sets the stage for an obvious next step: genetically engineering T cells when T cells appropriate for ACT immunotherapy cannot be isolated from cancer patients. In the laboratory, our team is working to isolate single T cells with antitumor reactivity and clone the genes encoding the T cell receptor from each cell. These genes determine the T cell's immunoreactivity. We are isolating a number of these valuable genes to generate a library of tumor-reactive T cell receptors and envision a future where tumor-reactive T cells do not need to be isolated and expanded from each patient. Instead, tumor sequencing and HLA type would guide the clinical team as they "pick a receptor off the shelf," insert it into the patient's T cells, and expand the transformed cells for ACT immunotherapy. This molecular cloning and bioengineering project is a secondary goal of his large trial to use ACT against solid tumors. Working at UPMC provides a tremendous advantage during these efforts, as our team has great access to both primary and metastatic tumor samples.

Although ACT of TILs is a promising immunotherapy, the vast majority of tumor-reactive TILs undergo cell death shortly after infusion, and only a small subset of TILs persists as long-lived memory cells. Animal models of ACT immunotherapies have demonstrated that if the cells are exhausted when they are removed for expansion, they grow poorly in the lab, work poorly when re-implanted, and exhibit telomere shortening and limited ability to produce ATP. Novel strategies are needed to enhance the metabolic fitness of the highly differentiated T cells needed for ACT immunotherapy. We have an active research program exploring ways to bioengineer TILs to reprogram their fate following ACT. Our studies in animal models suggest that metabolic reprogramming can augment the survival of TILs. Our team is continuing these investigations through a funded NIH R01 grant, which began in July 2019, that focuses on reprogramming the mitochondrial metabolism. We are examining whether they can give TILs a metabolic boost using a gene therapy approach. This research will improve our understanding of T cell metabolism and determine whether bioengineering can be used to improve ACT. The long-term goal is to develop clinically relevant approaches that promote the metabolic fitness of human TILs after adoptive transfer.

The paradigm of using selected immune cells as a cancer treatment is very new. The customized therapy goes against the convention of identifying antitumor drugs that might be useful in many patients. We describe this work as "a bit of a Manhattan Project" as our team explores ACT immunotherapy against different tumor types, develop a molecular understanding of the underlying mechanisms, and develop gene therapies and bioengineering approaches to improve adoptive immunotherapy. In February 2018, UPMC announced a $200 million investment in the UPMC Immune Transplant and Therapy Center. Through this initiative, UPMC will promote innovation by fostering novel treatment approaches that harness the body's natural defenses to fight cancer, harmful diseases and infections. ACT is an outstanding example of life-changing medicine through immunotherapy at UPMC.

Adoptive Cell Transfer (ACT using TIL)

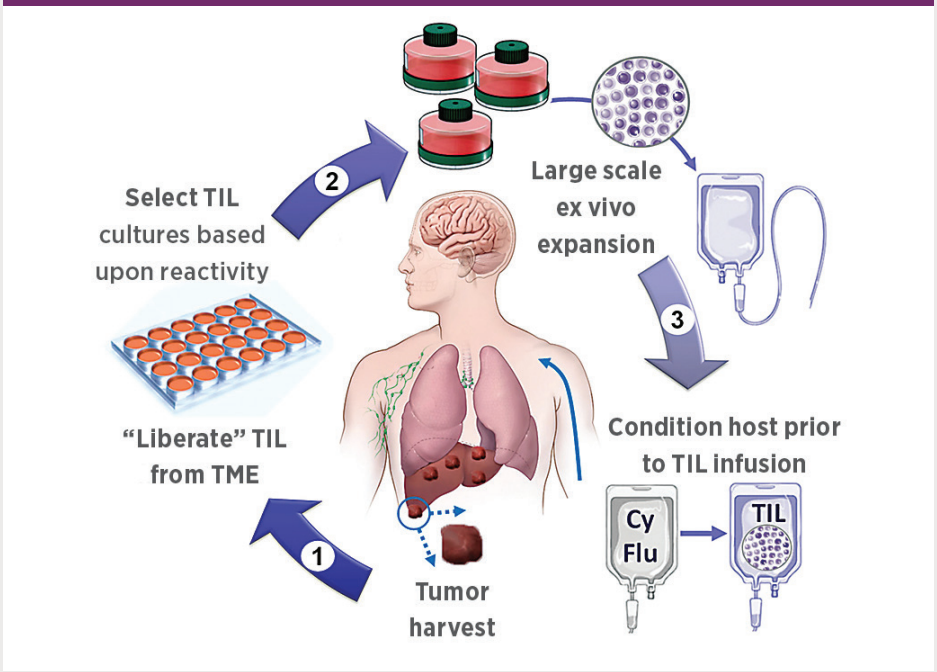

Figure 1: Schematic of the adoptive cell transfer immunotherapy process. Cy Flu, cyclophosphamide/fludarabine chemotherapy; TIL, tumor-infiltrating lymphocytes; TME, tumor microenvironment.

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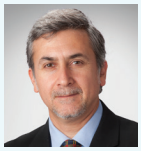
Suggested Reading

1. Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma. ClinicalTrials.gov identifier: NCT03467516. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.
2. Adoptive Transfer of Tumor Infiltrating Lymphocytes for Biliary Tract Cancers. ClinicalTrials.gov identifier: NCT03801083. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.
3. Adoptive Transfer of Tumor Infiltrating Lymphocytes for Advanced Solid Cancers. ClinicalTrials.gov identifier: NCT03935893. Primary Investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.

Paradigm Shift: The Value of Primary Surgery in Metastatic Breast Cancer on Survival



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Breast cancer (BC) is the most common cancer among women. In 2020 the estimated numbers of new cancer cases and deaths in the U.S. are 279,100 and 42,960, respectively.[1] Up to 10% of newly diagnosed BCs are seen at the metastatic stage. Although, metastatic disease defines a heterogeneous group of diseases, traditional therapy for patients with stage IV BC at presentation is systemic therapy (ST), and the goal is to reduce disease progression and support quality of life. Primary breast cancer surgery and radiotherapy (RT) are reserved for palliative purposes such as bleeding and ulceration. However, there has been increasing evidence of a therapeutic benefit of primary site local therapy in several organ sites, including renal cell, ovarian, gastric, and colorectal cancers. Removal of the primary tumor may have an immunomodulatory effect, decrease overall tumor burden, remove a ''seed source'' of new metastases, or decrease the likelihood of potentially resistant cell lines developing.

The classical treatment options in patients stage IV BC does not consider the number of metastases. However, more than 20% of these patients have a limited number of organ metastases known as oligometastatic disease (<5 lesions). In patients with limited organ metastasis, there is a lower malignant potential of the tumor to spread to other organs. Because of this decreased potential, patients with oligometastatic BC should be classified separately from other metastatic groups. In general, metastatic tumors are biologically aggressive and have poor prognostic features. Contrary to this finding, tumors such as isolated bone metastases are mostly hormone receptors positive, with low or moderate histologic grade and low mitotic activity.[2,3] Better understanding of tumor biology and advances in adjuvant therapies led to improved survival in stage IV BC patients. In addition, new technological advancements with sensitive imaging modalities now enable detection of tiny metastatic tumors that would not have been captured years ago. This begs a question: does limited metastasis staged as metastatic BC represent a different cohort than those staged a decade ago with multiple organ metastases? Limited metastatic lesions are assumed to represent all the metastatic foci a patient has and will have in their lifetime. Furthermore, this opens the discussion to the possibility of local therapy to primary tumor and metastatic foci to curing or, better said, giving a chance for remission for a lifetime.

Studies showed that complete clinical and pathological remission is possible in stage IV BC at presentation when a treatment protocol includes locoregional therapy (LRT) of intact primary tumor. In published study where 13% achieved no evidence of disease (NED), progression-free survival, and overall survival rates were 100% and 98%, respectively at five years and remained the same at 10 years. NED patients more frequently had solitary metastasis (79%) and surgery to resect cancer (59%). In multivariate analysis, NED status and estrogen receptor positive status were associated with prolonged overall survival. This study demonstrates that attaining NED status significantly impacts overall survival in patients with de novo metastatic breast cancer and that LRT plays an important role in attaining that NED status and its associated improved survival.[4,5] Several retrospective series and meta-analysis have demonstrated that primary tumor surgery in metastatic disease prolongs disease-free and overall survival and prevents locoregional progression.[6-15]

In June, the results of the multicenter, phase III, ECOG 2108 study were presented earlier than expected at the ASCO 2020 meeting by Khan et al. In this study, patients with stage IV BC at presentation were given ST and patients whose distant metastases remained stable or regressed were divided into ST and LRT groups. There was no difference in overall survival between the two groups at three years (68.4% vs 67.9%) (HR, 1.09; 90% CI, 0.80-1.49; P = .63). However, the three-year locoregional recurrence (or progression rate) of the LRT group was lower than the ST group (10.2% vs 25.6%; HR, 0.37; 95% CI, 0.19-0.73). This study presentation is criticized for the failure to obtain negative surgical margins in 20% of patients in the LRT group; this is an important because previous studies showed that failure to reach negative margin is associated with worse survival. Another criticism of this study is its significant portion of the patients with high tumor burden; 44% of patients had fascia and skin invasion with nodules and 48% had T4 and/or N2/3 disease.[16]

However, long-term results of the multicenter, phase III, randomized controlled MF07-01 study showed that LRT reduced the risk of death by 34% compared to ST alone. In subgroup analysis, the risk of death was lower in patients with solitary bone metastases. Median survival was found to be 14 months longer in the LRT arm among patients with solitary bone metastases.[17] A recent retrospective analysis of stage IV breast cancer using the National Cancer Database evaluated the impact of primary breast surgery or metastasectomy on survival. Around 55,000 stage IV BC patients were included in this analysis. Survival analysis showed primary breast surgery (lumpectomy; median OS: 45 months, and mastectomy: median OS: 44 months) was associated with better OS when compared to no surgery (median OS: 22 months). The statistical effect was larger in the subgroup with metastasis to one site, but still significant in the subgroup with multiple metastatic sites. Metastasectomy also yielded a survival benefit. Overall, analysis suggests the potential utility of surgery in stage IV patients, which has been inconsistent in clinical practice and often underestimated.[18]

Conclusion

The current National Comprehensive Cancer Network (NCCN) guidelines state, "The role and timing of surgical removal of the primary tumor in patients presenting with de novo stage IV (M1) is the subject of ongoing investigations and must be individualized. Performance of local breast surgery and/or radiation therapy is reasonable in select patients responding to initial systemic therapy."[19]

Surgical resection of the primary tumor can have a beneficial effect on overall survival in appropriately selected BC patients presenting with metastatic disease. The burden of metastatic disease and the ability to perform a complete resection with negative margins must be taken into consideration, given the greater benefits when patients are able to achieve NED status. Such patients and potential early LRT should be discussed in multidisciplinary tumor board settings to improve locoregional control and prolong survival. Providers must consider patient age, comorbidities, and performance status.

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Exosomal DNA and miRNA: Biomarkers Predicting Response to Neoadjuvant Chemotherapy and Recurrence in Pancreatic Ductal Adenocarcinoma

Alessandro Paniccia, MD
Assistant Professor of Surgery

Neoadjuvant therapy (NAT) has been increasingly utilized in patients with localized pancreatic ductal adenocarcinoma (PDAC) in an attempt to increase the cohort of patients that can have access to surgical therapy. Administration of NAT has its own challenges. In a cohort of localized PDAC, data from our own institution and others have shown that disease progression during NAT occurs in 20% of the cases preventing any further therapy.[1,2] Moreover, even in the remaining cohort that is able to reach surgical resection following NAT, over 25% of patients will recur or die within six months from the initiation of neoadjuvant chemotherapy.

To date, there is a paucity of reliable biomarkers to guide patient selection, to monitor response to chemotherapy during treatment and to dependably predict early recurrence of disease. Currently, CA 19-9 is the most commonly utilized biomarker, although its effectiveness is limited. Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosome analysis—included under the general term of liquid biopsies—are emerging non-invasive tools for cancer diagnosis, prognosis, treatment selection, treatment monitoring, and recurrence detection.[3,4-8]

Recently, longitudinal analysis of KRAS mutant allele fraction from ctDNA and exoDNA demonstrated that longitudinal monitoring through exoDNA rather than ctDNA provided more reliable prognostic information.[9,10] Detection of ctDNA can be limited by their relative scarcity in circulation, especially in patients undergoing NAT, limiting their clinical utility.[11] Exosomes are tumor-derived nanometer-sized membrane-enclosed extracellular vesicles (EVs) that carry cancer-specific material, representing a source of high-quality nucleic acids, in addition to proteins and miRNA.[12,13] Exosomal surface biomarkers provide a means to enrich cancer from non-cancer-derived exosomes and increase detection rates for mutant KRAS exoDNA from 30% and 50% to rates of over 70% in localized PDAC.[9,10] Although ctDNA has been established and commercially available for sensitive mutation detection of cancers, exosomes can be a better source for mutation detection: 1) Exosome cargo content is enclosed and protected by a lipid membrane. We discovered that the exoDNA is less abundant than ctDNA in plasma. However, the detectable copy number is comparable and even slightly higher than ctDNA (lower RT-PCR Ct value), which indicates that exoDNA has better quality. 2) In fact, we and others demonstrated exoDNA are ~10 kbp fragments.[14,15] In contrast, ctDNA consists of mainly much smaller, 160-180 bp fragments due to nuclease cleavage.[16-18] In pancreatic cancer, structural variation is an important mutational mechanism.[19] The much longer DNA fragments make structural variations (e.g. insertion, deletion, translocation) readily detected in exoDNA, while quite challenging in ctDNA. 3) Exosomes also contain mRNA for mutation detection. A small volume of blood plasma, ~500 µl, can provide enough exosomal RNA for sequencing,[20] which is an alternative and source of conformation for exoDNA that is unavailable for ctDNA. 4) Exosomes are secreted from live cells, while ctDNA is likely derived mainly from dying cells. Hence, the analyses of cancer-derived exosomes can provide unique information of living cancer tissue within the patient's body.

Moreover, encouraging results have been reported with the use of miR as biomarkers for PDAC. Deregulated miR expression in pancreatic cancer cells has been extensively described.[21,22] However, circulating exomiR has not been well evaluated as biomarkers for localized PDAC largely due to the limited availability of clinical specimens. We identified two clinically relevant miR targets, namely miR196a and miR21. miR196a is highly enriched in pancreatic cancer cell-derived exosomes—especially in localized PDAC.[23,24] Recent reports suggest that miR196a promotes pancreatic cancer progression and may predict poor outcomes.[25,26] In addition, high miR21 expression was positively correlated with resistance to gemcitabine while lower miR21 expression can confer higher sensitivity to 5-fluorouracile.[22,27,28]

Therefore exosome-based liquid biopsies can be used as a screening tool to control therapeutic regimens during PDAC treatment from diagnosis to recurrence thus providing several advantages: early detection of recurrent cancer disease, monitoring chemotherapeutic regimen response, and identification of new therapeutic targets when comparing the genetic signature of circulating exoDNA and exomiR in plasma with the results of the solid biopsy.

Through our UPMC Pancreatic Cancer Multidisciplinary Clinic, we are currently enrolling all treatment-naïve patients with a new diagnosis of pancreatic adenocarcinoma in a prospective longitudinal study to evaluate the utility of incorporating tumor-derived exosomal analysis as a clinical tool to monitor and guide NAT. The National Pancreatic Foundation research grant is supporting this work.

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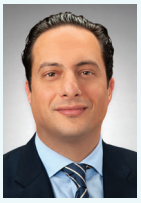
Faculty News



After an extensive national search, **Amer H. Zureikat, MD, FACS**, was appointed vice chair of surgery for surgical oncology in the Department of Surgery at UPMC. Dr. Zureikat has also been appointed chief of Surgical Oncology at UPMC Hillman Cancer Center, and was awarded the UPMC Chair of Clinical Surgery. He is the division chief for gastrointestinal surgical oncology in the Department of Surgery at UPMC and associate professor of surgery at the University of Pittsburgh School of Medicine. Dr. Zureikat received his medical degree from the Royal College of Surgeons in Ireland (RCSI) in Dublin. He completed his residency at the University of Chicago and his fellowship in surgical oncology at UPMC.

Dr. Zureikat specializes in cancers and diseases of the pancreas, stomach, liver, and duodenum, and practices state-of-the-art robotic surgery. In addition to his extensive surgical experience, he has authored or co-authored more than 200 peer-reviewed publications and reviews focusing on outcomes of GI and pancreatic cancer, and robotic and minimally invasive pancreatic surgery. Dr. Zureikat also is the principal investigator on several clinical trials at the University of Pittsburgh and has trained and mentored surgeons nationally and internationally in robotic surgery.

M. Haroon Choudry, MD, FACS, has been appointed director of Hillman's David C. Koch Regional Perfusion Therapy Center. Dr. Choudry is an associate professor at the University of Pittsburgh School of Medicine and a surgical oncologist with extensive experience in treating complex abdominal cancers using surgical and regional perfusion techniques, in which chemotherapy is delivered directly to the site of the cancer rather than systemically. Dr. Choudry received his medical degree from Agha Khan University Medical School in Karachi, Pakistan, and completed both a residency in general surgery and a research fellowship in surgery at the Milton S. Hershey Medical Center in Hershey, Pa. He completed his fellowship in surgical oncology at UPMC.

Welcome New Faculty

Melanie C. Ongchin, MD, FACS, joined UPMC in 2019 and is a surgical oncologist specializing in the treatment of recurrent malignancies and peritoneal carcinomatosis. Dr. Ongchin is board-certified in general surgery and complex surgical oncology. She received her medical degree from the University of Medicine and Dentistry of New Jersey, New Jersey Medical School in Newark, N.J. Dr. Ongchin completed a research fellowship at Roswell Park Cancer Institute in Buffalo, N.Y., and completed her residency at the State University of New York at Buffalo, followed by her fellowship in surgical oncology at UPMC.

Alessandro Paniccia, MD, joined UPMC in 2019 and is a surgical oncologist specializing in pancreatic and hepatobiliary surgery, with research interests in pancreatic cancer and hepato-pancreato-biliary minimally invasive surgery. Dr. Paniccia is board-certified in surgery and received his medical degree from Sapienza University of Rome in Italy. He completed residencies in general surgery at Johns Hopkins University in Baltimore and the University of Colorado. He also completed a research fellowship at the University of Colorado, followed by a fellowship in complex surgical oncology at UPMC.

Samer T. Tohme, MD, joined the UPMC Liver Cancer Center in 2020 and is an assistant professor of surgery at the University of Pittsburgh School of Medicine. Dr. Tohme specializes in comprehensive care for a full range of liver diseases, including primary and metastatic liver cancer, benign liver masses, chronic hepatitis, cirrhosis, and bile duct and gallbladder diseases. Dr. Tohme is board-certified in general surgery. He received is medical degree from the American University of Beirut in Lebanon and completed his residency in general surgery and fellowships in complex general surgical oncology and hepatobiliary and pancreatic surgery at UPMC.

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