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SESSION 1 – PANCREATIC CANCER

NEW DRUG DEVELOPMENT IN PANCREATIC CANCER
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Treatment of pancreatic adenocarcinoma remains a major challenge with median survival of patients with metastatic disease not exceeding one year. The advances in drug therapy over the past 3 decades were limited to cytotoxic drugs with no clinically meaningful benefit using targeted agents. Indeed, phase III trials of standard chemotherapy plus/minus targeted agents were uniformly negative. The tested agents included a range of drugs targeting a variety of molecular targets. Despite these setbacks there is optimism in developing therapies for this disease. Unlike other cancers, immunotherapy has not produced clinically useful benefit in patients with pancreatic cancer.

Several areas of research are currently at the clinical stage of investigation with some early promising data in pilot studies. These include the following:
1. **DNA repair**: molecular studies have identified a proportion of patients with pancreatic cancer who have tumors with DNA repair defects that include patients with the germline mutations in BRCA1/2 and PALB2 and extends further to include patients with tumors that have other DNA repair defects. Platinum compounds and/or PARP inhibitors represent treatment strategies with early evidence of benefit and are currently in clinical trials.

2. **Hyaluronan**: it is well recognized that the stroma plays an important role in the biology of pancreatic cancer. Hyaluronan is a stromal protein that is responsible for the difficulty in delivering drugs to the cancer cells. Preclinical work supports targeting hyaluronan (HA) to facilitate cell kill. Pegylated recombinant human hyalouronidase (PEGPH20) when combined with gemcitabine-nabpaclitaxel improved the progression free survival in patients whose tumors overexpressed hyaluronan in a phase II study. An ongoing phase III trials tests the combination in HA overexpressing patients.

3. **Tumor myeloid derived cells and macrophages**: the cellular component of the microenvironment in pancreatic adenocarcinoma is characterized by the infiltration by myeloid derived cells and tumor macrophages that influence the biological behavior of the disease including its immune-suppressed status. Pre-clinical evidence supports targeting those cells to improve the efficacy of cytotoxic therapy. An example is the use of CCR2 blockers to improve the efficacy of cytotoxic therapy. Targeting CCR2 demonstrated very interesting clinical activity in a pilot trial when combined with FOFLRIRNOX in locally advanced pancreatic cancer.

4. **Tumor metabolism**: Targeting tumor metabolism is another novel approach in improving the efficacy of cytotoxic therapy. An example is CPI-613 that results in a multi targeted approach by selectively blocking PDH and KGDH enzymes, triggering cell death. Early clinical data support this approach in patients with advanced pancreatic cancer.

5. **Stem cell signaling**: Preliminary data provide interesting results with the BBI-608, an orally administered drug targeting STAT3. An ongoing very large phase III study is testing the combination of this drug plus gemcitabine and nabpaclitaxel in patients with metastatic disease.

6. **Microsatellite instability**: There is evidence to support the use of immune checkpoint inhibitors targeting PD-1 in patients whose tumors are MSI-High. Approximately 1% of
patients of patients with pancreatic cancer may have microsatellite instability and be candidates for immune checkpoint therapy. Pembrolizumab is already approved for this indication by the FDA.

7. **Other targets:** Examples of other targets currently under investigation include NQO1 targeting by beta-lapachone, BTK, IDO, IL10, and variety of immune-modulating combinations.
MANAGEMENT OF HERIDITARY AND HIGH-RISK PATIENTS

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Since most patients with pancreatic cancer present with advanced disease, the best way to detect curable early-stage lesions is by pancreatic screening of asymptomatic individuals at increased risk of developing pancreatic cancer. The CAnce of the Pancreas Screening (CAPS) trials we have screened hundreds of individuals at increased risk of developing pancreatic cancer (based on family history or gene mutation status). Germline mutations in pancreatic cancer susceptibility genes (BRCA2, ATM, PALB2, CDKN2A) are the most commonly mutated genes that contribute to pancreatic cancer susceptibility, (PRSS1, MLH1, MSH2, TP53 and others are also rarely responsible). Among patients who meet criteria for screening there is an increased prevalence of pancreatic cysts compared to subjects undergo pancreatic imaging for other reasons. The prevalence of pancreatic cystic lesions increases with age, especially over age 60. Pancreatic imaging tests can identify cysts, but cannot identify very small invasive cancer or high-grade dysplasia (pancreatic intraepithelial neoplasia-3, PanIN-3) and most pancreatic ductal adenocarcinomas are thought to arise from PanIN. Initial studies describing the long-term outcome of individuals undergoing regular pancreatic surveillance finds that pancreatic cancers detected through screening are often down-staged to resectable-stage disease. Further improvements in imaging and biomarkers are needed to identify subcentimeter cancers and PanIN-3. Several marker strategies may help improve the early detection of pancreatic cancer including the analysis of cyst fluid and pancreatic fluid for mutations and the detection of circulating tumor DNA. The diagnostic yield of pancreatic screening will also improve with better risk assessment and selection of individuals most at risk of developing the disease. Prospective studies are needed to evaluate the utility of these approaches for patients undergoing pancreatic screening and surveillance. Understanding the inherited susceptibility to pancreatic cancer may also inform treatment decisions about chemotherapy among subjects who go on to develop pancreatic cancer.
MINIMALLY INVASIVE PANCREATIC RESECTION: READY FOR PRIMETIME?

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When comparing minimally invasive (MIS) pancreatectomy to the traditional open approach, one must assess the 1) perioperative outcomes, 2) oncologic outcomes, 3) effect on training and education, and 4) its value in terms of costs and resource utilization compared to patient benefit. For this talk, we will limit our discussion to the first 3 points. Also, one must evaluate pancreatoduodenectomy (whipple) separately from left-sided resections, also referred to as distal pancreatectomy.

When assessing the perioperative outcomes for MIS whipple, it is important to note that much of the experience is concentrated in a few centers, and even to just a few surgeons. In general, MIS whipple is associated with comparable perioperative outcomes with respect to complication rates, incidence of pancreatic fistula and delayed gastric emptying, and perioperative mortality. Specifically, comparative studies have failed to demonstrate a decrease in length of stay. In terms of oncologic outcomes, MIS whipple, when performed by experienced and select surgeons, has demonstrated similar results as open.

For distal pancreatectomy, the MIS approach has demonstrated improvements in complication rates and length of stay. Similar to MIS whipple, comparative studies have demonstrated non-inferiority in terms of oncologic results comparing MIS and open distal pancreatectomy. Given the perioperative improvements associated with MIS distal pancreatectomy, this seems to be the procedure of choice in well-selected patients in experienced hands. The use of laparoscopic, robotic, or hand-assist techniques is really up to the surgeon’s discretion and expertise.

In terms of training and education, the reality is that very few centers and surgeons actually perform MIS whipple. Thus, our trainees and fellows are not exposed, for the most part, to this
operation. MIS distal pancreatectomy, on the other hand, is a fairly straightforward procedure, is performed much more frequently and widely than MIS whipple, and can be taught with a fairly reasonable learning curve. Thus, MIS distal pancreatectomy is ready for prime time. However, MIS whipple still has some issues. It is not as reproducible, requiring a steep learning curve, and requires a dedicated investment from one’s career. In general, the major advances needed in the field of pancreas cancer need to be focused on disease management and systemic therapy. Technical advances from our current state will not push the field forward in a major way.

DEBATE: ROLE OF RADIATION THERAPY IN ASYMPTOMATIC PATIENT FOR LOCALLY ADVANCED PANCREATIC CANCER – PRO
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Abstract not available at time of printing.

DEBATE: ROLE OF RADIATION THERAPY IN ASYMPTOMATIC PATIENT FOR LOCALLY ADVANCED PANCREATIC CANCER – CON
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Locally advanced pancreatic cancer (LAPC), characterized by invasion or significant encasement of arterial and/or venous structures, constitutes one of the most common presentations of the disease, and approximately one-third of patients present at this stage. The survival of patients with LAPC is poor, with survival up to a year or less in most series. Historically, LAPC was
considered to be on a spectrum of metastatic disease, as demonstrated by the myriad of clinical
trials that included both metastatic and LAPC. The most optimal treatment options include
chemotherapy alone or chemotherapy and radiation therapy (RT) but this paradigm has been and
remains the subject of great debate, especially the role of RT. At the crux of the debate lies the
most important question: Is there a role for RT, in LAPC, given its proclivity for systemic
spread? On one hand, RT may slow the progression of local disease and possibly alleviate or
prevent symptoms including pain, biliary obstruction, bleeding, and bowel obstruction, but on
the other hand, the likelihood of micrometastatic distant disease is high, treatment is not expected
to be curative, and radiation can result in toxicity. Multiple clinical trials have attempted to
clarify the best treatment for these patients, including GITSG, FFCD/SFRO, ECOG, SCALOP,
GERCOR, and LAP 07 but failed to give decisive results. However, these data provide a
compelling but hypothetical rationale for induction chemotherapy followed by chemoradiation
with an aim to obtaining control of micrometastatic disease with systemic chemotherapy and
using subsequent chemo-RT for those demonstrating disease-control. This argument is further
nourished by the fact that now we have more effective systemic chemotherapy regimens such as
FOLFIRINOX and gemcitabine/nab-paclitaxel. Advances in radiotherapy technique such as
SBRT and expertise in LAPC have resulted in improved tolerance and benefits in palliation,
which warrants in future trials to identify the optimal integration of RT and further define the
most effective sequencing strategy to improve quality of life and survival. Precision medicine
would require identifying molecular signatures of tumors that are especially responsive to RT or
chemotherapy.

ERADICATION VIA PCD AND ADCP OF ENRICHED EpCAM+/CD44+
CIRCULATING CSCs AFTER LIQUID BIOPSY OF mPDAC PATIENTS IS
MEDIATED BY IMMUNOEPIGENOMIC-Tx (SEVINEX) COMPOSED OF
TARGETING BISPECIFIC scFv IMMUNONANOPARTICLES DELIVERING
ANTAGOMIRS FOR SILENCING OncomiRs 21 & 210

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Chairman of Nanomed and Multomics Int and Int

Society of Molecular and Genomic Medicine

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**Background:** The prognosis of pancreatic ductal adenocarcinoma (PDAC) remains to be extremely poor with very low life-expectancy, and survival-rates due to lack of clinical symptoms during its development, and potent resistance to conventional chemotherapeutic agents. Thus, novel diagnostic, prognostic, and therapeutic biomarkers are desperately needed, which will reflect the genetic and epigenetic alterations involving oncogenesis, and progression of PDAC.

**Methods:** Circulating tumour cells (CTCs) were obtained from metastatic PDAC patients with liquid biopsy from peripheral blood, and with the use of our CCSC technology, we performed enrichment of circulating cancer stem cells, and downstream molecular analysis of the cells with CLIA- waived next generation sequencing (NGS). A patient derived xenograft model was treated with stealth immunonanoparticles prepared for dual targeting with conjugated genetically engineered bispecific scFv antibody molecules for recognizing two different transmembrane metastatic-PDAC associated antigens EpCAM and CD44, and encapsulated modified anti-miRNA oligonucleotides (AMO) or antagonirs targeting short non-coding RNA oncomirs 21 and 210 expressing deleterious mutations. Post-treatment treated tumor cells were examined with transmission electron microscopy, and genomically with NGS.

**Results:** Post-treatment, the bispecific scFv induced the secretion of chemoattractants which recruited activated macrophages leading to antibody dependent cellular phagocytosis (ADCP) of the circulating PDAC stem cells. Furthermore, a synergistic eradicating action was exerted by the antagonirs, which silenced the two endogenous oncomirs 21 and 210 inducing a downstream genomic and epigenomic signaling pathway leading to immunoactivation, inhibition of hypoxic pathway, angiogenesis, tumor cell growth, proliferation and survival exhibited by inhibition of DNA synthesis and metabolic activity, according to MTT and BrdU assays, respectively. Furthermore, there was exhibited inhibition of migration, invasion, and metastatic factors. Finally, there was circumvention of chemoresistance pathways, and induction of D2 irreversible stage of type I programmed cell death (PCD) or apoptosis with a subsequent bystander killing effect of adjacent circulating metastatic PDAC stem cells according to electron histology with transmission electron microscopy (TEM).
Conclusion: A novel theranostic multifunctional approach mediated by biomarkers of circulating PDAC stem cells identified by NGS after liquid biopsy may lead to a precision medicine tailored approach mediated by nanotargeting of epigenomic deleterious mutations leading to the eradication of metastatic-circulating PDAC stem cells by induction of apoptosis and ADCP followed by a subsequent bystander killing effect (BKE).

SESSION 2 – HEPATOBILIARY CANCER

UPDATE OF THE SYSTEMIC TREATMENT OF HEPATOCELLULAR CARCINOMA
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Abstract not available at time of printing.

BRIDGE TO TRANSPLANTATION: TACE, Y90, SBRT, OR NOTHING?
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In patients with hepatocellular carcinoma (HCC) awaiting liver transplant (LT), local regional therapy (LRT) is commonly used to control tumor growth during the waiting period, serving as a bridge to LT. Traditionally, trans-arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are the most commonly used bridging treatments. Although there is no level I evidence that these treatments reduce the rate of dropout from the waiting list or improve post-transplant outcome, treatment has been shown to be cost-effective if the waiting time is expected
to be at least 6 months (1). Bridging therapy may also help refine candidate selection (2). Observing tumor response after LRT incorporates the “ablate and wait” principle (3), which aims to avoid transplanting tumors with poor biology that progresses rapidly despite LRT and also do poorly after LT (4). Conversely, there is a subgroup of patients with tumor characteristics that predict sustained response to LRT with a very low risk for waitlist dropout. These patients may not even need LT (at least not urgently) (5). For patients with initial HCC exceeding the conventional Milan criteria, “down-staging” of HCC to within Milan criteria using LRT under the UCSF protocol has shown excellent post-transplant outcomes (6), and will soon be implemented as a national policy.

**Y90 versus TACE**
Investigators from Northwestern recently reported the results of the PREMIERE trial (7), a single-center phase 2 prospective randomized study comparing conventional TACE with yttrium-90 (Y90) trans-arterial radioembolization. Enrolled patients were Child-Pugh class A or B and BCLC stage A or B with a total bilirubin <2 mg/dl and no evidence of macro-vascular invasion. There were 24 patients in the Y90 arm and 21 in the TACE arm. The median time to progression (TTP) was significantly longer with Y90 at >26 months compared to 7 months with TACE. There was no difference in EASL radiographic response (87% for Y90 versus 74% for TACE) and median survival (19 months for Y90 versus 18 months for TACE). One caveat to the PREMIERE trial is that assessment of TTP is hampered by the need for censoring at LT. Furthermore, comparison of TTP between treatments was based on a very small number of patients being followed for a sufficient duration. The authors also did not demonstrate a lower waitlist dropout rate in the Y90 group.

**SBRT vs TACE**
Published data on stereotactic body radiation therapy (SBRT) for HCC are still limited, but a few reports have suggested good safety and efficacy of SBRT as bridging treatment before LT (8, 9). In a retrospective study from Toronto (8), the results of SBRT in 36 patients were compared to that in 99 who received TACE and 244 who received RFA. The reasons for SBRT included impaired liver function precluding TACE, technical considerations, and HCC recurrence after TACE. The SBRT group was sicker at baseline and more patients in this group experienced
hepatic dysfunction after SBRT than TACE or RFA. The waitlist dropout rates between groups were similar (17% SBRT, 20% TACE, and 17% RFA). There were no significant differences between treatments in required perioperative procedures or complications including median blood loss, need for transfusion, median days in ICU/hospital, and vascular thrombosis. The intention-to-treat survival and post-transplant survival were not significantly different between the 3 groups.

Summary:
1. LRT plays an important role in bridging and down-staging of HCC to LT. Response to LRT may serve as an additional tool for selection of candidates for LT
2. TACE remains the first line bridging therapy
3. Results with Y90 are encouraging but there is still insufficient evidence for Y90 to overtake TACE
4. More data on SBRT are still needed but there is a potential role for SBRT when other LRT have failed or are no longer feasible
5. Caution is needed for using any LRT in patients with decompensated cirrhosis

References:


CHALLENGES IN THE SURGICAL MANAGEMENT OF HILAR CHOLANGIOCARCINOMA

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Complete resection remains the only potentially curative therapy for hilar cholangiocarcinoma. Unfortunately, patients most commonly present with unresectable or metastatic disease, and recurrence rates remain high after complete resection. Resectability of is dependent on multiple factors, including extent of biliary disease and associated vascular involvement. In addition to assessing the clinical performance of the patient, high quality preoperative imaging is important to assess the degree of bile duct and vascular involvement. Hepatic duct involvement with bilateral tumor extension to second order biliary radicals or encasement of the main portal vein
are relative contraindications to curative resection. The role of extended resections with vascular reconstruction for patients with extensive biliary and/or vascular involvement have been reported but is not universally accepted. Before and during surgery, careful assessment is also required to rule out distant metastases to lymph nodes outside of the regional lymph node basin. Routine lymphadenectomy is recommended by some. For patients undergoing an R0 resection, the 5-year overall survival rates range between 20–40%, with a median overall survival of 30 to 40 months. Unfortunately, despite a potentially curative resection, recurrence is common, including both distant and local sites. The role of liver transplantation for hilar cholangiocarcinoma is also controversial. Current reports suggest excellent long term outcomes of liver transplantation combined with multi-modal neoadjuvant and adjuvant therapy in highly selected patients. Management of hilar cholangiocarcinoma requires significant expertise in patient selection, interpretation of imaging, and technical surgery. In resectable patients, complete resection remains the only potentially curative treatment. However, despite potentially curative surgery, recurrence rates remain high. Given the rarity of this malignancy, further multi-institutional and international collaborative efforts are important to optimize management and improve outcomes.

References:

Intrahepatic cholangiocarcinoma (ICCA) is increasing in incidence, partly related to increase in the incidence of obesity, hepatitis and re-classification from the diagnosis-cancer unknown primary in the liver. Unresectable ICCA has several therapeutic options including chemotherapy, targeted therapy, radiation, liver-directed intra-arterial therapy, radio-embolization and clinical trials. Systemic chemotherapy is based on ABC-02 trial and consists of gemcitabine and cisplatin. This chemotherapy was associated with a median survival of 11 months, although the subpopulation of ICCA experiences a higher survival benefit. Intraarterial therapy is based largely on experience in hepatocellular cancer, which has a different vascular perfusion pattern. Clinical trials of intraarterial therapy for ICCA have been limited and most data are retrospective and also include co-administration of systemic chemotherapy. Administration of radio-embolization after systemic chemotherapy was associated with poor survival in a retrospective study. Furthermore, a phase III trial of radioembolization with concurrent chemotherapy was negative for metastatic colorectal cancer, a disease with similar vascular perfusion parameters at ICCA (SIRFLOX trial). Serious toxicities can occur with liver-directed therapies in upto 8% of the treated patients. The advent of molecular profiling has opened up many exciting therapeutic possibilities for ICCA and it is important in this situation that liver function not be compromised by liver directed approaches. In conclusion, liver directed therapies for unresectable ICCA are still experimental, may benefit a supopulation that remains to be defined. Systemic chemotherapy sequenced by targeted therapy, immunotherapy or radiation may be the optimal option at this time for unresectable ICCA.
DEBATE: OPTIMAL INITIAL TREATMENT OF LOCALLY UNELECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA – REGIONAL THERAPY

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Abstract not available at time of printing.

DNA REPAIR GENE SOMATIC ABERRATIONS AND TUMOR MUTATION BURDEN IN CHOLANGIOCARCINOMA

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Background: DNA repair genetic aberrations (GAs) are associated with higher tumor mutational burden (TMB) and response to check point inhibitors. The association between TMB, microsatellite instability (MSI) and sensitivity to immune checkpoint inhibitors was previously reported in many cancers. The incidence of DNA repair GAs in cholangiocarcinoma has not been widely reported in the literature.

Methods: A comprehensive genomic profiling of 330 cholangiocarcinoma formalin-fixed, paraffin-embedded tumor tissue was performed using next generation sequencing. We focused on 20 DNA repair genes that were previously described by TCGA. These included direct DNA repair genes (ATM, ATR, BRCA1, BRCA2, FANCA, FANCD2, MLH1, MSH2, MSH6, PALB2, POLD1, POLE, PRKDC, RAD50, SLX4) and caretaker genes that induce genomic instability (BAP1, CDK12, MLL3, TP53, BLM). TMB was classified into three groups; low (TMB-L; < 6 mutation/Mb), intermediate (TMB-I; 6 – 19 mutation/Mb), and high (TMB-H; ≥20 mutation/Mb). Furthermore, MSI status was assessed by a computational algorithm examining 114 intronic homopolymer loci.
**Results:** Direct DNA repair GAs were identified in 50 cholangiocarcinoma cases (15.2%) with \textit{ATM} GAs being the most common (6.4%). \textit{FANCD2, POLD1, POLE, PRKDC, RAD50, SLX4, BLM} mutations were not identified in our cohort. GAs in caretaker genes occurred more frequently (38.2%), predominately in \textit{TP53} (26.1%), and \textit{BAP1} (12.1%). TMB was evaluated in 161 patients with 114 patients having low TMB, 39 with intermediate TMB, and 9 with high TMB. Among patients with direct DNA repair GAs, 16 out of 30 (53.3%) had intermediate or high TMB as compared with 31 out of 131 (23.7%) patients without direct DNA repair GAs \((P < .0001)\). Furthermore, patients with caretaker GAs (N=66) also had significantly higher TMB [intermediate and high (42.4%)] than patients without these mutations (20%) \((P = .002)\). [Table 1] MSI was determined in 66 patients and classified as stable (N= 61), ambiguous (N= 2), and high (N = 3). All 3 patients with high MSI had direct DNA repair GAs \((P < .0001)\).

**Conclusion:** DNA repair GAs occur at a relatively high frequency of cholangiocarcinoma patients and are associated with high TMB. Future clinical trials targeting this subgroup with immune checkpoint inhibitors are warranted.

<table>
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<th>Table 1: Association between DNA repair GAs and TMB</th>
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<td><strong>TMB status</strong></td>
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<td>TMB-H and TMBI</td>
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Positron emission tomography (PET) is now widely used in the initial evaluation of esophageal and gastroesophageal junction tumors. It can detect otherwise occult metastases, affecting staging and treatment in a significant proportion of patients. An emerging application for PET is the assessment of response to induction chemotherapy. In particular, PET has the ability to discriminate treatment responders from nonresponders early in the course of induction chemotherapy. This can form the basis for further treatment decisions, such as a change in chemotherapy or the addition of concurrent radiotherapy. This approach of early response assessment to direct therapeutic decisions has been evaluated in the CALGB 80803 trial in the United States and the DOCTOR trial in Australia. In addition, the recently opened SCOPE 2 trial is evaluating the use of PET to direct radiation dose among patients who are responders or non-responders to induction chemotherapy. With emerging PET parameters, there is even the possibility of using PET evaluation after concurrent chemoradiotherapy to provide information regarding the utility of surgical resection. PET data can affect radiotherapy target definition, which may lead to improved tumor coverage in cases where the true extent of disease is not accurately reflected by computed tomography or endoscopic imaging.
DEBATE: SHOULD PET SCAN GUIDE PREOPERATIVE THERAPY IN ESOPHAGEAL CANCER?
CON
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Abstract not available at time of printing.

BEYOND FIRST LINE THERAPY OF ADVANCED GASTRIC CANCER
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Abstract not available at time of printing.

VEGF DIRECTED AGENTS IN ESOPHAGEOGLASTRIC CANCER
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Esophagogastric adenocarcinomas are common worldwide and are a leading cause of cancer-related death. Most patients are diagnosed at a late stage with nearly 50% of patients having locally advanced, unresectable or metastatic disease at the time of presentation. In 2017, an estimated 44,940 new cases of esophagogastric cancer (16,940 esophagus and 28,000 gastric) are projected in the United States with an estimated 26,650 deaths (15,690 esophagus and 10,960 gastric).[1] Prognosis for patients diagnosed with esophagogastric cancer is generally poor with
five-year survival less than 5%. Cytotoxic chemotherapy palliates symptoms and improves survival but there is more work to be done.

There have been many studies investigating the use of targeted agents in the treatment of metastatic esophagogastric cancers with targets of interest including her2, VEGF, MET and EGFR. With the results of the TOGA trial, trastuzumab in combination with fluoropyrimidine and cisplatin was approved for first line therapy in patients with her2 amplified gastric cancers.\[2\] Unfortunately, the data with agents targeting the MET \[3\] and EGFR \[4\] pathways have not been as promising. The story with VEGF directed agents continues to unfold. There were initially many small Phase II studies demonstrating a benefit to adding bevacizumab to cytotoxic chemotherapy. This led to a multi-national randomized Phase III study evaluating the addition of bevacizumab to a fluoropyrimidine / cisplatin backbone.\[5\] Surprisingly, there was no statistically significant difference in overall survival with the addition of bevacizumab. Given that this was a multi-national study, regional differences in outcomes were evaluated and there was a suggestion toward improvement in survival for patients treated in the Americas (though there were very small numbers). Since this initial study, interest in VEGF directed therapy for esophagogastric cancers has continued as new agents have become available.

In the first line setting, there is another Phase III study that evaluates the addition of bevacizumab to capecitabine and cisplatin in a Chinese population (AVATAR).\[6\] Two hundred and two patients were randomized and the study was negative, with no difference in either overall survival or progression free survival. There are also two additional Phase II studies that evaluate the addition of ramucirumab [7] or ziv-aflibercept **. Both of these studies also failed to show an improvement in overall or progression free survival. There is currently no role for the addition of VEGF directed therapy for the first line treatment of metastatic esophagogastric cancers.

VEGF directed therapy has also been evaluated in the second line and it is here that we see the benefit. The REGARD study evaluated the use of single agent ramucirumab, a recombinant human anti-vascular endothelial growth factor receptor-2 antibody, versus best supportive care \[8\]. While the response rate was low, there was improved OS and PFS with the use of
ramicurimab. The RAINBOW study evaluated the use of ramicurimab in combination with paclitaxel versus paclitaxel alone [9]. This was also a positive study with improvement in OS with the addition of ramicurimab. There are also two additional studies evaluating tyrosine kinase inhibitors that target the VEGF pathway [10, 11]. The INTEGRATE study evaluated the use of regorafenib, an oral multikinase inhibitor, versus best supportive care in a multinational population [11]. This trial was designed to evaluate the activity of regorafenib against a defined standard and so was not designed to note differences between the populations. However, there were trends toward improvement in PFS and OS. Finally, apatininb, a small molecule tyrosine kinase inhibitor that binds selectively to VEGFR2, was evaluated in a Chinese population [10]. There were significant improvements on both OS and PFS, which led to the approval of this agent by the China Food and Drug Administration.

Despite the initial disappointment with the results of the AVAGAST study, we have continued to investigate the use of VEGF-directed therapy in metastatic esophagogastric cancer. AVAGAST helped highlight the fact that there may be regional differences in disease biology that could explain the differential responses – and these need to be explored. There is ongoing investigation into biomarkers that might identify those who will benefit. We also need to explore the potential biological differences between the first and second line and between patients with esophageal, gastroesophageal junction, or gastric adenocarcinomas.

References:


When immune therapy emerged as a major breakthrough in cancer treatment, the initial belief was that immune therapy would not be effective for GI tract cancers. In the last year consistent clinical evidence has emerged which clearly demonstrates that checkpoint inhibition can result in significant clinical benefit for patients with gastric esophageal and other GI cancers. Recent approvals for any tumor with microsatellite instability and, more recently, PDL 1 positive upper GI cancers is a testament to the ongoing research and focus in this incredible arena.

As with many other cancer types, immune therapy using checkpoint inhibitors in gastric and esophageal cancers demonstrates benefit in a subset of patients. Given the cost and potential toxicity of these agents, it is imperative that we uncover biomarkers which can accurately predict responsiveness. The discovery that microsatellite unstable cancers responded well to these medicines has led through to a landmark FDA decision to approve a therapy for any type of cancer that carries this molecular characteristic. Also unprecedented, no formal diagnostic molecular test (companion diagnostic) was approved along with the therapeutic agent. There is a great deal of confusion about the best methodologies to measure microsatellite instability. Techniques from immunohistochemistry to fragment analysis to novel NexGen sequencing all have demonstrated utility as a very high clinical benefit rate is observed when MSI is found by any of these techniques, but they are not consistent across studies or samples. Further characterization is clearly warranted as not all patients with microsatellite and stable tumors will respond to immune therapy.

As was seen in lung cancer, checkpoint inhibitors did perform better in PDL 1 positive tumors. However, there are clear responses in patients when the marker is negative. Tumor mutational load has emerged as an important biomarker which may complement and augment our ability to
determine which patients respond in which do not. Clearly further investigation is needed to refine the science.

Most importantly, how will be leverage these breakthroughs and extend the benefit to other patients. Checkpoint inhibitors as single agents will only work in those tumors where the immune system has already recognized the tumor and has mounted an attack against it. Combination studies with vaccines and other immune stimulating agents are ongoing in the hopes that this will generate a broader benefit rate across more patients. There continues to be the great need for further clinical research in this field.

All patients with metastatic gastric and esophageal cancer should have molecular testing for PDL1 and for microsatellite instability. If either of these characteristics is present then checkpoint inhibition should be considered as one of the standard approaches for therapeutic intervention in those patients with metastatic disease. Further work will hopefully uncover more patients that will benefit through combinations of treatment.

RESOURCE UTILIZATION AND TREATMENT VARIABILITY IN THE CARE OF PATIENTS WITH ADVANCED/METASTATIC GASTRIC OR COLORECTAL CANCER

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Background: Previous work has shown variability in treatment patterns of patients with gastric cancer in the US, demonstrated by the high number of unique treatment regimens used across lines of therapy, whereas more homogenous patterns are observed among patients with colorectal cancer (CRC). This study was designed to describe health care resource utilization (HCRU) of patients with advanced/metastatic gastric cancer or CRC, respectively, to explore the relationship between treatment variability and HCRU.
Methods: A retrospective observational study using Truven Marketscan claims data was conducted. Eligible patients were diagnosed with advanced/metastatic gastric cancer or CRC between July 1, 2004 and December 31, 2015, ≥18 years old at diagnosis, and were treated with chemotherapy, biologic or targeted anti-cancer therapy. HCRU variables included hospitalizations, emergency room (ER) visits, supportive medication use, and hospice care. Treatment variability was measured using the Herfindahl-Hirschman index (HHI) at the state level. HHI scores range 0 to 1, with lower scores representing greater variability. HHI scores by state were divided into quartiles; patients within those quartiles were grouped for HCRU analysis. Chi-square test was used for categorical variables and ANOVA for continuous variables.

Results: A total of 9,073 gastric cancer patients and 55,403 CRC patients met eligibility criteria with advanced/metastatic disease. Mean age was 62.2 (standard deviation, SD=12.4) and 61.6 (SD=12.6) years and 64.2% and 51.1% were male in the gastric and CRC cohorts, respectively. Ranges of HHI scores were 0.0383-0.1778 for gastric and 0.1304-0.2778 for CRC in the first-line treatment setting. For advanced/metastatic CRC and gastric, 17.4% and 18.8% of patients were hospitalized, 23.6% and 25.6% had ≥1 ER visit, 17.6% and 20.2% received granulocyte colony stimulating factor (GCSF) agents, and 9.2% and 11.7% received erythropoiesis-stimulating agents (ESA) during first-line therapy, respectively. There was a statistically significant difference by HHI score quartiles for HCRU use including hospitalization (p=0.003), deaths in hospital (p=0.04), ≥1 ER visits (p<0.001), patients with ER visits leading to hospitalization (p<0.001), and supportive care use (GCSF, ESA, bisphosphonates, opioids, anti-emetics, and nutritional support; all p<0.01) for the CRC cohort. However, statistically significant differences for the gastric cancer cohort were observed for fewer HCRU categories such as number of patients hospitalized (p=0.02), ≥1 ER visits (p=0.02), number of ER visits (p=0.003), GCSF use (p=0.004), ESA use (p<0.001), nutritional support (p=0.007), opioid use (p=0.02), and anti-emetic use (p=0.004). No consistent increasing or decreasing trends were observed across the quartiles regardless the indication of a statistical difference.

Conclusions: There is a statistically significant relationship between higher treatment variability and increased HCRU for the CRC cohort. Consistent differences by quartile of treatment
variability as measured by the HHI were not observed for gastric cancer, which could be due to the very high variability of treatment patterns in gastric cancer (e.g. no homogeneous quartile for comparison). These data suggest that high treatment variability could be associated with greater resource use in advanced/metastatic gastrointestinal cancers. Due to the retrospective nature of this analysis, causality of the relationship cannot be inferred.

SESSION 4 – HOT TOPICS IN GASTROINTESTINAL ONCOLOGY

CELLULAR THERAPY FOR CANCER AND POTENTIAL APPLICATIONS TO GI ONCOLOGY
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Abstract not available at time of printing.

DNA METHYLATION: VERSATILITY IN TUMOR DETECTION AND SITE-PREDICTION
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Abstract not available at time of printing.
Radiotherapy (RT) plays an essential role in the treatment of GI malignancies. Technological advances in RT delivery has allowed for better normal tissue sparing while maintaining accurate target dose delivery. This talk will focus on specific examples were the following new technologies will be discussed: intensity modulated RT (IMRT), stereotactic body RT (SBRT) and proton therapy.

Unlike 3-dimensional conformal RT, intensity modulated RT (IMRT) incorporates a planning technique, called inverse planning, whereby both target volumes and organs at risk are delineated by the radiation oncologist. A treatment plan is then generated through an optimization process that uses volumetric and dosimetric constraints (i.e., radiation prescription) for both target volumes and organs at risk, as inputs. The cumulative effect is that the prescription dose conforms around delineated target volumes, significantly reducing doses to adjacent normal tissues. The advantages of this technology have most clearly been seen in the treatment of anal cancer. The use of IMRT is associated with a reduction in Grade 3+ skin, GI/GU, and hematologic toxicity.

Stereotactic body RT (SBRT) is typically delivered in 1-5 treatments and can employ many of the same strategies and couples a high degree of anatomic targeting accuracy and reproducibility with high doses of ionizing radiation. This maximizes the cell-killing effect on the target while minimizing injury to adjacent normal tissues. Both SBRT and IMRT incorporate rigorous image guidance, accounting for day-to-day variations in location of the target volumes and adjacent normal tissues. The proposed benefits of a shortened course of RT are two-fold. First, radiobiological principles suggest that large fractional doses of radiation increase the biologically effective dose. Second, by shortening the overall treatment time, patients can more quickly
proceed to systemic therapies. This technology is being increasingly utilized in both pancreatic and primary and metastatic liver cancers and the subject of ongoing investigation.

The physical properties of protons are distinctly different from photons in that there is minimal exit dose. Proton therapy may be beneficial for certain malignancies, such as esophageal cancer, given the potential to reduce exit dose through the heart and lungs. Although there are no prospective trials of proton therapy, there is an ongoing randomized trial of proton versus photon therapy in the treatment of esophageal cancers with concurrent chemotherapy.

IMRT and proton therapy achieve a common end- reducing dose to normal tissues while maintaining target coverage. These advances in treatment delivery, coupled with respiratory motion assessment and management has paved the way for delivering larger RT doses over a 1-5 treatments with SBRT. Ongoing studies will assess the relative benefit of these technologies and integrating these techniques with systemic therapies to treat GI malignancies.

RATIONAL SURVEILLANCE STRATEGIES IN GI MALIGNANCIES
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Mayo Clinic
Scottsdale, Arizona

A wide variety of follow-up strategies are used for patients with gastrointestinal cancers following curative surgery. Current evidence suggests improved rates of curative secondary treatment following identification of recurrence among patients who participate in a surveillance program after initial curative resection of colon or rectal cancer. CEA, chest and liver imaging as well as colonoscopy improve survival through early diagnosis of recurrence. However, the optimal strategy of surveillance for office visits and testing is not yet fully defined. It is important to note that specific considerations should be in place for the detection of local recurrence in the case of rectal cancer.
In contrast, for patients with non-colorectal cancer, the level of intensive follow up is less certain, reflecting the absence of curative options following recurrence for those patients. The efficacy of treating clinically occult disease versus symptomatic disease remains unclear in this group of patients at this time and more prospective data is needed to confirm the value of more intense follow up. Patterns of recurrence are very different in various non-colorectal cancers and may complicate the type of follow up. For example, following resection, HCC tends to recur more locally, whereas the pattern following transplantation is more at extrahepatic sites. Pancreas cancer is almost universally a systemic disease with very few effective treatment options and as such intensive follow up is likely futile. Finally, in gastric cancer the detection of asymptomatic recurrence may prolong overall survival, a more intensive surveillance interval (less than 6 months) did not seem to affect outcome.

SESSION 5 – LOCALIZED/ADJUVANT COLORECTAL CANCER

RECTAL CANCER TNT
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Abstract not available at time of printing.

BEYOND FIRST LINE AND SECOND LINE THERAPIES OF COLORECTAL CANCER (INCLUDING IMMUNOTHERAPY)
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Abstract not available at time of printing.

DEBATE: THE IDEA TRIAL AND RECTAL CANCER:
PRO

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Abstract not available at time of printing.

DEBATE: THE IDEA TRIAL AND RECTAL CANCER: CON

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The IDEA collaboration included more than 12000 patients with stage 3 colon cancer from 7 studies and 12 countries. Randomization was 3 versus 6 months of adjuvant FOLFOX or CapeOX (depending on the individual trial). The trial did not meet the pre-specified boundaries for non-inferiority and we cannot be 95% confident that the outcome will be equivalent with the shorter course. Or, in other words despite a massive analysis we have more than 5% uncertainty that equivalent results will be achieved with only 3 months of therapy. Some patients are likely to lose a chance for cure and the 3-month course should be rejected.
Surgery represents the only curative treatment for stage I-III midgut and pancreatic neuroendocrine tumors (NETs). Defining the probability of postoperative recurrence is critical to develop evidence-based recommendations on timing and duration of follow-up evaluations as well to design adjuvant studies that take into account estimates of baseline risk of recurrence. Several retrospective series have reported a recurrence rate of 30-40% in patients with midgut NET who underwent R0/R1 resection. In the most recent series, the rate of recurrence has been described as steady over an eight-year period with a subsequent drop-off, and no relapses were reported in patients with stage I tumors at diagnosis. Moreover, resection of 17 or fewer lymph nodes predicted relapse and shorter disease-free survival, thus suggesting that an appropriate lymphadenectomy rather than simple segmental bowel resection may be preferable in patients with midgut NETs. In patients with localized or locally advanced pancreatic neuroendocrine tumors, 5-year relapse-free survival rates for stages I through III have been reported to be 78%, 53% and 33% respectively when using the AJCC classification. According to the ENETS classification, 5-year relapse-free survival rates were 100%, 70% and 53% in stage I to III respectively. At present, no studies have evaluated whether the mENETS classification has a better capability to predict post-operative relapse in patients with pancreatic NETs. A retrospective analysis of 211 patients with G1/G2 non-functioning pancreatic NETs has recently reported a recurrence rate of 17%. In about 70% of cases, recurrences were located in the pancreatic remnant, and the median time to relapse was 43 months. Tumor grade, perineural invasion and lymph node metastasis were found to predict relapse. Prospective studies with fixed surveillance schedules and very long duration of follow-up are required to obtain accurate
estimates of recurrence risk in patients with surgically resected midgut or pancreatic NETs. Identification of biomarkers capable of predicting relapse in such patients is critical.

**SURVEILLANCE GUIDELINES FOR STAGE I-III NETs TREATED OPERATIVELY**

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*Sunnybrook Health Sciences Centre*

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Abstract not available at time of printing.

**Ga68-DOTATATE SCAN: WHAT IS ITS IMPACT ON NET MANAGEMENT?**

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Abstract not available at time of printing.

**DEBATE: SOMASTOSTATIN RECEPTOR IMAGING SHOULD BE PART OF SURVEILLANCE STRATEGY VS. CROSS-SECTIONAL IMAGING ONLY: PRO**

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*Duke University School of Medicine*

*Durham, North Carolina*

Abstract not available at time of printing.
Introduction: Patients with low stage neuroendocrine tumors can be treated with surgery, and in some cases all sites of known tumor can be resected. These patients require surveillance imaging after surgery to monitor for recurrent tumor or the development of new metastatic disease. Computed tomography (CT) has been the standard of care for surveillance imaging in these patients, supplemented with magnetic resonance imaging (MRI) as needed. Fused positron emission tomography/CT (PET/CT) utilizing gallium-68 (Ga-68) \( \text{DOTATATE} \) is now approved for imaging in the United States of America (USA). Ga-68 DOTATATE PET/CT detects neuroendocrine tumors with very high sensitivity and has been shown to alter clinical management at initial staging, compared to imaging modalities currently in use. The use of Ga-68 DOTATATE PET/CT is recommended in initial staging, but the use in surveillance imaging in the USA is unclear at this time.

Methods/Results: The literature regarding the sensitivity and accuracy of CT, MRI and Ga-68 DOTATATE PET/CT was reviewed in order to assess the utility of these modalities with regards to surveillance imaging. Most of the available literature discusses the use of Ga-68 DOTATATE PET/CT for initial staging and the impact this can have on clinical management. Several series have shown use of Ga-68 DOTATATE PET/CT changes management in a significant percentage of patients, compared to the use of currently employed imaging techniques alone. There is less discussion regarding the use of Ga-68 DOTATATE PET/CT for surveillance imaging, although in this setting Ga-68 DOTATATE PET/CT also has been found to detect recurrent tumor and new metastatic disease with high accuracy. The sensitivity of Ga-68 DOTATATE PET/CT and CT/MRI vary by anatomic location. For example, MRI has slightly higher sensitivity for liver
metastases but Ga-68 DOTATATE PET/CT has much higher sensitivity for metastatic lymph nodes vs. CT or MRI (~90% vs. ~60%). There are potential issues with the use of Ga-68 DOTATATE PET/CT for routine surveillance imaging: increased cost, less widespread availability, false positive results and quantification of the benefit vs. traditional surveillance imaging.

**Conclusions:** There are questions regarding the use of Ga-68 DOTATATE PET/CT for routine surveillance imaging after resection of low stage neuroendocrine tumors. At the current time, there is insufficient data to recommend Ga-68 DOTATATE PET/CT for routine use in surveillance imaging, although it offers advantages in some cases (e.g. problem solving in certain cases or when cross-sectional imaging is negative but there is suspicion of recurrent tumor).

**OVERVIEW OF NEW TREATMENTS: **\(^{177}\)LuDOTATATE AND TELOTRISTAT

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*Associate Professor*

*Moffitt Cancer Center & Research Institute*

*Tampa, Florida*

Peptide receptor radiotherapy (PRRT) with \(^{177}\)Lutetium-dotatate represents an important emerging therapy for patients with somatostatin receptor expressive neuroendocrine tumors (NETs). By attaching a radionuclide to a somatostatin receptor analog, PRRT enables targeted delivery of radiation to somatostatin receptor expressing neuroendocrine tumor cells. Single arm studies using Yttrium-90 and Lutetium-177 labelled somatostatin analogs have established the safety and efficacy of PRRT in patients with progressive NETs. The NETTER-1 study was the first randomized, phase 3 study to evaluate a radiolabeled somatostatin analog. 229 patients with progressive, somatostatin-receptor positive midgut NETs were randomized to receive \(^{177}\)Lu-dotatate vs. high dose octreotide LAR with a primary objective of improvement progression-free survival (PFS). The trial demonstrated a 79% improvement in risk of progression or death with a median PFS of 8.4 months on the octreotide arm of the study vs. not reached on the \(^{177}\)Lu-dotatate arm. There was also a highly encouraging trend towards overall survival improvement on preliminary analysis (hazard ratio 0.4, p=0.0043).
A recent analysis of a large prospective database of Dutch patients treated with $^{177}$Lu-dotatate at Erasmus Hospital in Rotterdam provides additional information on the long term efficacy and safety of this treatment. Results show objective response rates of 31% in midgut NETs and 55% in pancreatic NETs. With a median follow-up on 78 months, 2.2% of patients developed irreversible bone marrow toxicity (myelodysplasia ion 1.5% and acute leukemia in 0.7%). There was no evidence of significant treatment-related renal toxicity.

Telotristat ethyl is a novel treatment for refractory diarrhea in patients with carcinoid syndrome. This hormonal syndrome occurs primarily in patients with metastatic midgut NETs, and is characterized by flushing, diarrhea and by fibrosis of the right heart valves. Diarrhea and carcinoid heart disease are thought to be caused primarily by secretion of serotonin, whereas flushing is typically caused by other vasoactive substances. Telotristat acts by blocking tryptophan hydroxylase, a rate-limiting enzymatic step in the conversion of the amino acid tryptophan into serotonin.

The TELESTAR study was a 3-arm phase 3 trial designed to evaluate telotristat (in combination with somatostatin analog) in patients with history of carcinoid syndrome and refractory diarrhea (defined as at least 4 bowel movements per day). During a 12-week double-blind period, patients were randomized to receive two doses of telotristat (either 250mg or 500mg po tid) vs. placebo, while continuing their somatostatin analog. The trial demonstrated a statistically significant mean reduction in bowel movements during this 12-week period with an absolute reduction of 0.8 BMs on the 250mg dose. Urine 5-HIAA levels improved by roughly 50% on average compared to placebo. The drug was FDA approved at the 250mg tid dose.
USING FACT-G AND PROMIS-29 TO EVALUATE THE ASSOCIATION BETWEEN DURATION OF SOMASTOSTATIN ANALOG USE AND QUALITY OF LIFE IN PATIENTS WITH CARCINOID SYNDROME IN THE UNITED STATES

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Background: This study assessed the association between duration of somatostatin analog (SSA) use in patients with carcinoid syndrome symptoms (CSS) and quality of life (QoL) using the validated FACT-G and PROMIS-29 instruments.

Methods: Patients with CSS in the US were recruited via Neuroendocrine Cancer Awareness Network for an online, anonymous survey between July-October 2016. Eligible patients were ≥18 years old with CSS and received either SSA or non-SSA treatment for CSS control. The survey consisted of demographic and clinical questions, as well as FACT-G and PROMIS-29 questionnaires. Descriptive and multivariable regression analyses, adjusting for patient characteristics, were performed. Duration of SSA use was categorized into quartiles (<2.7, 2.7-4.42, 4.43-8.0, and >8.0 years).

Results: Among 117 patients, 76.9% were female and 87.2% Caucasian with mean age of 58.0 years. Most patients (N=115, 98.3%) received SSAs in the past month. The mean ± SD duration of SSA use was 6.1 ± 4.7 years. Selected FACT-G subscale and PROMIS-29 subdomain scores are presented in Table 1. Descriptive analysis suggested that patients receiving SSA treatment for >8 years had higher (better) FACT-G scores than reference group <2.7 years. Multivariable
models showed significant increases in FACT-G by 11.3 points (total score; P=0.033), 4.1 points (physical wellbeing [PWB]; P=0.013) and 3.7 points (functional wellbeing [FWB]; P=0.034) for patients treated with SSA >8 years compared to those treated for <2.7 years (reference group). SSA duration >8 years was not significant for any PROMIS-29 domain: 3.4 points (physical function; P=0.098), 3.6 points (social roles/activities; P=0.111), and 4.2 points (fatigue; P=0.093).

Conclusions: Selected response items in FACT-G were more sensitive to SSA treatment duration in CS patients compared with PROMIS-29. This may be due to FACT-G’s PWB and FWB subscales containing disease- and treatment-specific items whereas PROMIS-29’s general QoL attributes were designed for a wide range of chronic diseases. Additionally, the positive association of SSA treatment duration with FACT-G QoL may be explained by long-term effectiveness and tolerability of SSAs. However, there is also the possibility that selection bias favoring patients with more indolent disease (in longer duration group) may have had some effect on the results. Future studies may distinguish between these possibilities.

Table 1. Select Quality of Life Scores: PROMIS-29 and FACT-G (N=117)

<table>
<thead>
<tr>
<th>PROMIS-29 scores</th>
<th>Possible Range</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS-29 domain T-score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>22.9 - 56.9</td>
<td>42.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Ability to participate in social roles and activities</td>
<td>27.5 - 64.2</td>
<td>44.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.7 - 75.8</td>
<td>59.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FACT-G scores</th>
<th>Possible Range</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G total</td>
<td>0 - 108</td>
<td>67.6</td>
<td>20.0</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>0 - 28</td>
<td>17.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Social well-being</td>
<td>0 - 28</td>
<td>18.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Functional well-being</td>
<td>0 - 28</td>
<td>15.3</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; PROMIS, Patient-Reported Outcomes Measurement Information System.

Notes:
[1] Higher score indicates better quality of life.

SESSION 7 – ADVANCED COLON CANCER
BRAF mutations are found in about 7-10% of metastatic colorectal cancer (mCRC). (Seligmann et al., 2017) Approximately 80% of all BRAF mutations are BRAFV600E (hereby referred to as “BRAF mutant mCRC”).(Jones et al., 2017). BRAF mutation is a biomarker of poor prognosis in mCRC.(Seligmann et al., 2017) These patients are more likely to have right sided, MSI-high tumors, with peritoneal metastases and poorer overall survival (OS) (median OS (mOS): 10 months) compared to BRAF wild-type (WT) patients (mOS: 17 months), P<0.001.(Seligmann et al., 2017) These patients also have poor outcomes even after liver metastasectomy with shorter recurrence free survival (RFS) (median RFS of 6 vs. 14 months) and OS compared to BRAF-WT tumors.(Schirripa et al., 2015)

Although, the prognostic value of BRAF mutation is well established, its predictive role is contentious. The predictive value for anti-EGFR antibody based therapy (hereby referred to as “anti-EGFR therapy”) is unclear. The PRIME trial and a meta-analysis (7 RCTs) demonstrated insufficient evidence to definitively conclude that RAS-WT, BRAF mutant patients attain a different treatment benefit from anti-EGFR therapy compared with RAS WT/BRAF WT patients. (Douillard et al., 2013; Rowland et al., 2015) To date, with regards to conventional cytotoxic chemotherapy in mCRC, BRAF mutation has been found to not be predictive of benefit from irinotecan or oxaliplatin based chemotherapy. (Richman et al., 2009). A pooled analyses of randomized first-line cytotoxic chemotherapy trials showed that BRAF mutant patients had fairly similar PFS (5.7 versus 6.3 months; adjusted HR: 1.14, P=0.26) to BRAF WT cases.(Seligmann et al., 2017) In fact, TRIBE study investigating triplet cytotoxic regimen (FOLFOXIRI) showed mOS of 37 months in RAS/BRAF WT subgroup compared with 13 months in BRAF mutant subgroup., However the effect was not significantly different across molecular subgroups (pinteraction=0.52).(Cremolini et al., 2015) The response rate (RR) with bevacizumab + FOLFOXIRI in BRAF mutant patients was 56%.
Due to these poor outcomes on current treatments, investigations involving novel therapies to combat this subset have been an area of active interests. BRAF mutant melanoma was successfully targeted using single agent BRAF inhibitors (Vemurafenib and Dabrafenib) and their combinations with MEK inhibitors. (Chapman et al., 2011; Hauschild et al., 2012; Larkin et al., 2014; Long et al., 2014) Disappointingly, these agents and combinations have failed to recapitulate the impressive activity in melanoma where the RR is between 50-70%. Single-agent BRAF inhibitors have shown no meaningful clinical activity in patients with BRAF mutant CRC with RR of 5%. (Kopetz et al., 2015) This low activity is a result of rapid feedback activation of EGFR after BRAF inhibition.(Prahallad et al., 2012) The combination strategies developed have been equally substandard. BRAF inhibitors with either anti-EGFR antibodies or MEK inhibitors have shown response rates of below 20%. (Corcoran et al., 2015; Yaeger et al., 2015) A recent randomized study in second/third-line setting with vemurafenib, cetuximab and irinotecan showed some increase in PFS (4.4 months) but RR of 16%. (Kopetz et al., 2017). Further combinatorial strategies such as BRAF, EGFR and MEK inhibition (BEACON CRC (NCT02928224) study: Encorafenib + Cetuximab + Binimtinitib) is ongoing in beyond first line setting and although initial data has been encouraging, this is far from conclusion. (Huijberts, 2017).

In summary, targeted therapies in BRAF mutant mCRC have been unsatisfactory at best thus far. No data exists showing the superior efficacy of these targeted therapies to conventional cytotoxic chemotherapy in first-line setting. The limited activity in further lines of therapies has been uninspiring so far to challenge outcomes of first line cytotoxic therapies. Therefore, as of today, chemotherapy remains the standard of care for BRAF mutant mCRC and in fact one could consider a more aggressive therapy using triplet cytotoxiccs to manage this aggressive subset of patients.

**Bibliography**


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DEBATE: BRAF V600E CRC-FIRST LINE THERAPY
The purpose of my talk is to summarize and highlight two regimens incorporating targeted therapies for patients with $BRAF^{V600E}$-mutant colorectal cancer. These studies speak for themselves about the emerging role of targeted therapies in patients with colorectal cancers and summarize the advances in management and understanding of $BRAF^{V600E}$-mutant colorectal cancer.

The first study that was presented at the American Society of Clinical Oncology (ASCO) conference at Chicago this year by Dr. Scott Kopetz from M.D. Anderson is on the ‘VIC’ regimen. The VIC regimen incorporates vemurafenib as the BRAF inhibitor, irinotecan as the chemotherapy backbone alongside cetuximab as the anti-EGFR agent. Upstream upregulation of EGFR justifies the rationale for it to be combined with BRAF inhibitors. A progression free survival of 4.4 months, response rate of 16% and a disease control rate of 67% was noted in these patients treated on this study. Crossover was allowed so overall survival was not significantly different. The study group and the reviewers cited this as a potential new treatment option for patients with $BRAF^{V600E}$-mutant colorectal cancer given the promising results.

The second regimen is an ongoing clinical trial, the data for which was presented at the 2017 European Society for Medical Oncology Congress in Madrid, Spain. It is called the ‘BEACON’ CRC study. It incorporates the MEK inhibitor Binimetinib, the BRAF inhibitor Encorafenib And Cetuximab Combined. In the 30 patients, the data for which was presented at ESMO, overall response rate was 41% including 1 complete response. If this was restricted to patients who had only 1 prior line of therapy, the overall response rate was 59%. What was fascinating was the fact that ‘out of 28 patients with both a BRAFV600E mutation and a post-baseline assessment,
27 showed tumor regression. Furthermore, 76% of patients overall were continuing on therapy after a median duration of exposure of 5.6 months’, which is unprecedented.

In summary, targeted therapies in various combinations represent emerging new treatment options for patients with $BRAF^{V600E}$-mutant metastatic colorectal cancer. Bringing trials to frontline setting would be of great value to fulfil the unmet need for patients with $BRAF^{V600E}$-mutant colorectal metastatic cancer.

Future directions include the assessment of heterogeneity and identification of mechanisms of resistance through incorporation of ‘liquid biopsies’ (circulating tumor DNA testing). Correlative studies on some of these trials are underway and some have already identified potential mechanisms of resistance. These could serve as evolving targets and lead to development of other novel combinations of therapy.

Finally, while the discussion has been focused on $BRAF^{V600E}$-mutant metastatic colorectal cancer, work from our group and collaborators have identified the non-V600E BRAF-mutations as a distinct entity. This surprisingly actually has far superior prognosis as compared the $BRAF^{V600E}$-mutant as well as the $BRAF$-wild type metastatic colorectal cancers. The results of these were published in the Journal of Clinical Oncology in August of 2017.

**GENE EXPRESSION PROFILES (CMS) IN CRC: CAN THEY GUIDE THERAPY?**

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TNM staging is the primary prognostic tool in clinical practice, but it does not provide insight into colorectal cancer (CRC) tumor biology. Gene expression profiling allows simultaneous analysis of thousands of genes, and allows tumors to be categorized according to biology, rather than stage. Despite the widespread use of gene-expression based subtyping, differences in
bioinformatics and analytical techniques have historically limited the broad application of gene expression platforms. In 2015, Guinney et al. (Nature Medicine 21, 1350–1356 [2015]), published consensus molecular subtypes (CMS) for CRC based on the combined analyses of six independent research groups. CMS include the following categories:

- CMS 1 (MSI-Immune): This subtype is characterized by hypermutated tumors, deficient mismatch repair (dMMR), CIMP-H, BRAF mutations, and immune infiltration. This group of patients has inferior survival after relapse.
- CMS 2 (Canonical): This subtype is characterized by high levels of gene amplification (SCNA-high), as well as WNT and MYC activation.
- CMS 3 (Metabolic): This subtype is characterized by low levels of gene amplification (SNCA-low), RAS mutations, and metabolic deregulation.
- CMS 4 (Mesenchymal): This subtype is characterized by high levels of gene amplification (SCNA-high), stromal infiltration, TGF-β activation, angiogenesis, matrix remodeling, and epithelial to mesenchymal transition (EMT).

At the ASCO 2017 Annual Meeting, the prognostic and predictive capabilities of CMS were retrospectively evaluated from three randomized clinical trials: PETACC-8, FIRE-3, and CALGB 80405. The key features and patient populations included in these clinical trials are noted in Table 1.

Table 1.
Overall, the frequencies of CMS categories were similar between the three clinical trials. As shown by the FIRE-3 investigators, CMS 1 was more likely to occur on the right-side of the colon, and CMS 2 was more likely to occur on the left side of the colon. As predicted by the initial Guinney et al. publication, PETACC-8 demonstrated that CMS 1 was more likely to be BRAF mutated and CIMP-H, and have deficient mismatch repair (dMMR). PETACC-8 confirmed that RAS mutations are more likely to occur in CMS 3 tumors. “Quadruple negative tumors” (KRAS WT/ BRAF WT/ CIMP-/ pMMR) were more likely to be CMS 2.

Consistent with the analysis from Guinney et al., PETACC-8 demonstrated that CMS 4 was associated with inferior disease-free survival (DFS) compared to the other subtypes. In the Guinney et al. analysis, CMS 1 had the shortest survival after relapse (SAR), and CMS 2 had the longest SAR. Similarly, in both CALGB 80405 and FIRE-3, overall survival (OS) was longest in CMS 2, and survival was shortest in CMS 1. These findings independently confirmed the prognostic capabilities of CMS.

The predictive capabilities of CMS were also evaluated by investigators from PETACC-8, CALGB 80405, and FIRE-3. In PETACC-8, the CMS 1 subtype showed a deleterious effect of cetuximab on disease free survival. CALGB 80405 also showed inferior survival for cetuximab compared to bevacizumab in CMS 1. Cetuximab did not have a deleterious effect in all clinical trials analyzed. In FIRE-3, there was no difference in survival between bevacizumab and cetuximab in the CMS 1 category.

In summary, these clinical studies showed that CMS accurately reflect tumor biology and prognosis. Additional validation is needed in a prospective clinical trial to determine whether CMS can be used as a tool to predict response to therapy.

OPTIMAL TREATMENT SEQUENCE IN mCRC – MAKING USE OF ALL OPTIONS
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Abstract not available at time of printing.
HEPATOBILIARY CANCER

TUMORAL RESPONSE AND TUMORAL PHENOTYPIC CHANGES IN DIETHYLNITROSAMINE-INDUCED HEPATOCELLULAR CARCINOMA AFTER SALIRASIB AND SORAFENIB ADMINISTRATION IN RAT

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\textbf{Background:} Several intracellular signalling pathways are deregulated during hepatocarcinogenesis. MAPK and mTOR pathways seem to play a key role in liver tumor progression in experimental models as well as in humans. Vascular endothelial growth factor also contributes to angiogenesis in hepatocellular carcinoma (HCC). The aim of our study was to test the putative synergic antitumor effect of Salirasib and Sorafenib (molecules acting on these signalling pathways), in a diethylnitrosamine (DEN)-induced HCC in rat. Changes in tumor phenotype during treatment were also studied.

\textbf{Methods:} Seventy-six male Wistar rats were used, in accordance to the accepted practices of the National Academy of Sciences. DEN was continuously administered in drinking water for 9 weeks, in order to induce cirrhosis and liver cancer. A laparotomy was performed after tumoral
induction phase, to confirm cirrhosis and tumor development. Surviving rats were randomized and treated with Salirasib (10mg/Kg) and/or Sorafenib (7.5 or 15mg/Kg) during 4 weeks. Rats were finally sacrificed and each lesion more than 2 millimeters was removed and processed for histological and immunohistological analyses, including Ki67 as a marker of tumor proliferation.

**Results:** All rats developed cirrhosis and cancer, as confirmed on conventional histology. Mortality rate was significantly higher in the treated rats than in the control group (p=0.002). There were no significant differences in the number of tumor lesions when comparing treated and control groups. However, the tumor burden (WHO criteria) was significantly smaller in the treated group (p=0.029). Interestingly, 62.5% of the rats treated with Salirasib and/or Sorafenib developed cytokeratin-7 and -19 positive hepatocellular carcinoma (HCC/CHC), while this phenomenon was observed in 5 of 25 animals (20%) in the control group (p=0.018). Ki67 immunostaining showed significantly reduced tumor cell proliferation in treated rats (p=0.001).

**Conclusions:** (1) A synergistic effect of Sorafenib/Salirasib combined administration could not be observed in this study; (2) both chemotherapeutic agents administered alone or in combination were associated with tumoral phenotypic changes in the majority of rats (62.5%), irrespectively of types of therapy; (3) the mechanism of such de-differentiation did not seem to be explained by increased tumor cell proliferation. This work points to the significant risk of phenotypic change of HCC into putatively more aggressive HCC/CHC in patients receiving chemotherapeutic agents administered to downstage the tumor. The understanding of de-differentiation mechanisms will require more molecular studies.

**Abdominal Imaging Surveillance in Post-Fontan Adult Patients: Risk of Chronic Liver Disease and Hepatocellular Carcinoma**

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**Purpose:** The purpose of this study was to quantify the incidence of hepatocellular carcinoma in adults with post-Fontan cardiac physiology.

**Methods:** IRB approved and HIPAA compliant, this study involved a retrospective review of electronic medical records, and abstraction of radiologic data for patients undergoing follow up after the Fontan procedure. Reports for three imaging modalities i.e. US, CT and MRI performed for all Fontan patients between January 1st 1993 and January 1st 2016 were identified to assess for hepatic complications. Information on age, sex, date of Fontan procedure and viral hepatitis infection were also assessed.

**Results:** 145 patients (M: 78, F: 67) had follow up imaging data after the Fontan procedure. At first scan, (median 19 years), about a third [55/145] had a normal scan, 37% [54/145] demonstrated increased liver heterogeneity, and others had portal hypertension, cirrhosis or both. Going further, 78% [113/145] of these patients had further follow up scans. Fifty six percent [62/113] patients showed no further changes during entire follow up period while 54% [51/113] showed more changes during follow up (median 4.8 years) including five [4.5%] that developed hepatocellular carcinoma (median 6 years follow up, 23 years post Fontan). One of these patients had hepatitis C infection. Only 19% [21/113] of patients had normal scan findings at the end of the entire follow up period.

**Conclusion:** Hepatic complications are very common in patients with post Fontan cardiac physiology. Furthermore, there is a moderate to high risk of developing hepatocellular carcinoma in these patients.

**Detection Glypican-3 CTL as an Early Diagnostic Marker in Hepatocellular Carcinoma Egyptian Patients**

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**Background:** HCC is the fifth most common form of cancer worldwide. Patients in early stages have a much higher chance of curative response with different treatment options. Glypican-3
(GPC3) is a member of the Glypican family of glycosylphosphatidylinositol-anchored cell-surface heparin sulfate proteoglycans. GPC3 is highly expressed in the HCC cells and tissues. The prediction of the overexpression of GPC3 in HCC is related to the development of HCC in a background of chronic hepatitis (CH) and/or liver cirrhosis (LC). The aim of this work is to assess circulating glypican-3 cytotoxic T lymphocytes (CTLs) as an early marker for diagnosis of hepatocellular carcinoma (HCC) in Egyptian patients.

**Methods**: The study included 100 participates, of which 26 were patients with post hepatitis C liver cirrhosis (group I), 26 were patients with early stages of HCC (group IIa), 28 were patients with late stages of HCC (group IIb), and 20 were healthy volunteers with matched age and sex as a control group (group III). The patients were selected from the outpatient clinic and inpatient department of the National Liver Institute, Menoufiya University. Glypican3 CTLs were detected by flow cytometry. Two monoclonal antibodies are used, one directed against human leukocyte surface marker CD8-fluoresce in isothiocyanate. The other is monoclonal anti-human GPC3-phycoerythrin (PE) and then we compared these results with α-feto protein results, as it is considered the only clinically proven HCC biomarker.

**Results**: Glypican3 CTLs can be used for early detection of HCC patients with 96% specificity and 98% sensitivity.

**Conclusion**: Glypican3 CTLs can be used as markers for early detection of HCC patients.

**ESOPHAGEAL/GASTRIC CANCER**

**Multimodal adjuvant therapy with concurrent chemoradiation with capecitabine in gastric cancer**

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**Background:** Gastric cancer remains one of the most common malignancies worldwide. Despite the significant advances in surgical treatment and multimodality strategies, prognosis has modestly improved over the last two decades. The prognosis of advanced GC remains poor, even after radical surgical treatment, with a 5-year overall survival of 20-30% for T3-T4/N+ patients. There is a high risk of locoregional and distant recurrence, and this requires multidisciplinary management in order to improve outcomes. Locoregional relapse remains one of the main issues and the combined chemoradiation treatment seems to be one of the preferred approaches. This study aims to evaluate the efficacy and toxicity of adjuvant concurrent chemoradiation with capecitabine.

**Patients and method:** The study included 70 patients having histologically proven adenocarcinoma of the stomach or GE junction; stage Ib–IV post gastrectomy with D2 lymph node dissection.

All the patients received radiotherapy by IGRT or IMRT technique with dose of 45-50.4 Gy in 25-28 fractions concurrently with capecitabine 825-1000 mg/m² BID. Emphasis was laid on documenting the toxicity of the treatment & nutritional status of the patients during treatment.

**Results:** The median follow-up period was 30 months, the 2-year disease free and overall survivals were 60.2% and 70%, respectively. 15 patients relapsed during the follow up period. 10 patients presented with loco-regional recurrences. 5 patients had distant metastases in lung or liver or brain.

Ten patients could not complete the entire chemoradiation treatment due to gr III toxicity or due to the progressive disease. 10 patients presented with gr III toxicities; low hemoglobin in 5, vomiting in 2 patients and neutropenia in 3. GI toxicity was the most common toxicity encountered. There was no gr III/IV diarrhea or skin lesions.
Conclusion: Oral capecitabine concurrently with radiation therapy is effective and safe with acceptable toxicity. Encouragement for the development of multicenter randomized trials will address the optimal sequence and timing of CT, RT in respect to surgery.

GASTROINTESTINAL STROMAL TUMORS SECRETE GHRELIN AND EXPRESS GHRELIN RECEPTORS

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Background: Gastrointestinal stromal tumor (GIST) mainly occurs in the fundus ventriculi. Ghrelin is a multifunctional protein polypeptide, which can promote the occurrence and development of tumor. It is mainly produced in the fundus ventriculi. But the misdiagnosis rate and postoperative recurrence rate is high. This study was to determine the serum ghrelin level in the normal population, patients with GIST before and after operation. And The expression of ghrelin and its receptor was determined in GIST tissue and The expression of ghrelin in adjacent normal tissue in the same patient. We hope that ghrelin can provide a new idea for the diagnosis and prognosis of GIST.

Methods: Preoperative and postoperative serum of 78 patients with GIST and 69 normal persons was collected and determined the level of serum ghrelin by ELISA. Expression of ghrelin and ghrelin receptors in GIST tissue (47 cases) was determined and Expression of ghrelin in adjacent normal tissue was determined at same time by immunohistochemical. We observed whether there were statistically significant differences in statistical analysis.

Results:
1) the average ghrelin in the serum of normal people was 20.14 pg/ml, and 31.25 pg/ml for GIST patients. P=0.034.
2) The mean value of serum ghrelin in 78 patients with GIST was 31.25 pg/ml before operation and 22.5 pg/ml after operation. P=0.023.
3) Ghrelin and its receptor expression positive rate was 100% in GIST (47 cases). Among them, Ghrelin: (+) 12%, (++) 29%, (+++) 38%, (++++) 20%.
Ghrelin receptors: (+) 4%, (++) 23%, (+++) 27%, (++++) 46%.

4) The expression of ghrelin in tumor tissue was about 2.23 times than that of adjacent normal tissues.

**Conclusions:** Gastrointestinal stromal tumors secrete Ghrelin and express ghrelin receptors. Ghrelin may serve as an effective indicator for the diagnosis and prognosis of GIST.

**LOCALIZED/ADJUVANTV COLORECTAL CANCER**

**ORAL HEALTH STATUS OF ULCERATIVE COLITIS PATIENTS: A COMPARATIVE STUDY**

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**Introduction:** Inflammatory bowel disease (IBD) is a complex civilization disease and has a prevalence of up to 0.2% in the Asian countries. The disease preferentially manifests in the second and third decade of life. Oral soft tissue lesions can precede or occur concomitantly with the intestinal symptoms. It was reported that IBD patients have higher prevalence of dental caries than healthy controls as a result of nutritional deficiencies and changes in salivary and microbiological conditions in the oral cavity. Prior studies showed a higher prevalence of aphthous ulcer and dental caries. There is only little information about the oral health status of UC patient, as often they are dealt only by the general physician. The aim of this study was to assess the dental caries and periodontal disease status in patients with ulcerative colitis – an inflammatory bowel disease.

**Materials and Methods:** After obtaining ethical clearance from the institutional review board of Lifeline hospital, a record based case-control study was conducted on 20 UC patients and 20 healthy controls. Oral hygiene habits, oral soft tissue changes, the decayed, missing and filled tooth surface (DMF – S) index, periodontal status (CPI) index and clinical attachment loss (CAL) were evaluated in each patient and in the controls.
**Results:** In patients with UC, 28 oral lesions were found compared with 3 lesions in the control group. There was a significantly higher prevalence of dental caries in patients with UC \((p=0.000)\) compared with controls with an OR for DMF-T of 2.71. (95% CI: 1.21- 7.62)

**Conclusion:** Patients with UC had a higher prevalence of dental caries and oral lesions compared with a healthy control group. Altered dietary habits and malabsorption may probably be the main cause for this condition. Strict oral hygiene should be recommended, and the regular use of fluoride treatment for prevention of dental caries appears justified.

**ASPIRIN UTILIZATION, COMPLIANCE AND PREVENTION OF COLORECTAL CANCER – A SINGLE CENTRE PERSPECTIVE**

*Keir Forgie, Cindy McKinley-Brown, Krystal Schimp-Manuel, Gurpreet Singh Ranger*

**Background:** Recent randomised controlled trials indicate daily low dose aspirin may reduce the risk of colorectal cancer by up to 20%. Aspirin is currently prescribed or self-administered regularly to prevent heart disease.

In considering wider population-based chemoprevention against colorectal cancer, a greater understanding of community use, compliance, adverse effects, and patient awareness is required. We performed a prospective observational study on aspirin use in our local population to examine these issues.

**Method:** Prospective data was collected using questionnaires and chart review over a six month period from every patient attending our general surgical clinic at Upper River Valley Hospital, regarding aspirin use, comorbidities, adverse effects and awareness of effect against colorectal cancer.

**Results:** 520 patients were studied (exclusion criteria – age < 18 years, or > 100 years).

**Aspirin group:** 137 patients; male: 72, female: 65. Mean age 65.8 years (range: 23-100). 76.6% were taking aspirin 81mg. 32.9% did not know what dose they were taking, 5.8% were taking a dose over 300mg. 62% of patients were taking aspirin on physician advice.
Only 25.6% of patients stated they never missed a dose of aspirin, 39% admitted to missing doses weekly to monthly, and 3% never took it despite prescribed. 5.8% reported side effects - minor bruising, bleeding or GI upset, no serious complications were reported. Only 9.5% were aware of the anticancer effects of aspirin.

*Non-aspirin group*: 383 patients; male: 135, female: 248. Mean age 53.3 (18-90). 1% had used aspirin in the past and ceased treatment. 4.7% knew of anticancer effects. Mean age aspirin group vs. non-aspirin group differed significantly (unpaired t-test, p<0.001). Patients not on aspirin were more likely to be female, aged over 40, and with heart disease (IHD), diabetes or on more than 5 concurrent medications (Fisher’s exact test; p=0.0005, p<0.0001, p=0.002). There was no significant difference between the groups in anticoagulation use, additional NSAID use or smoking (p = 0.51, p = 0.20, p = 0.19). Knowledge of anticancer effect showed a trend to significance (p = 0.06) favoring the aspirin intake group, with main sources of information being the media or internet.

**Conclusions:** Patients on aspirin in our community tend to be older, with less co-morbidities and concurrent medication use compared to non-aspirin users. This group showed a trend to significance of being aware of the anticancer effects of aspirin, but overall awareness was suboptimal, and physician involvement in this area appears to be low. Our results also demonstrate over 40% of our patients are non-compliant with treatment. Our results have implications in planning programs for the use of regular low dose aspirin in the chemoprevention of cancer, especially in higher risk groups.

**THE LONG NONCODING RNA TPTE2P1 PROMOTES PROLIFERATION OF COLORECTAL CANCER**

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**Purpose:** Long non-coding RNAs (lncRNAs) play important roles in tumor formation and
progression. However, the detailed mechanism of TPTE2P1 in colorectal cancer (CRC) has not been well studied, which was the main topic in this study.

**Methods:** Expression levels of TPTE2P1 in CRC tissues and cell lines was measured by using real-time PCR analysis. Then MTT and colony formation assay was used to evaluate the effect of TPTE2P1 on cell proliferation. Flow cytometry was carried out to test the influence of TPTE2P1 on cell cycle and apoptosis. And the associated signaling pathway proteins were quantitated by western blot. Finally, the role of TPTE2P1 was analyzed in vivo.

**Results:** The expression levels of TPTE2P1 was significantly elevated in colorectal cancer tissues and cell lines. TPTE2P1 knockdown inhibited cell proliferation and leads to cell arrested at S phase. TPTE2P1 knockdown also caused cancer cells apoptosis by activation of the Bcl-2/caspase 3 signaling cascade. Additionally, knockdown of TPTE2P1 exerted tumor-suppressive effects in vivo.

**Conclusions:** TPTE2P1 is up-regulated in CRC and plays essential role in regulation cell proliferation in vitro and tumor formation in vivo.

**NEUROENDOCRINE TUMORS (NET)**

**Outcomes of Locoregional Treatment for Unifocal Progression in Widespread Metastatic Gastroenteropancreatic Neuroendocrine Tumors**

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**Background:** New systemic treatments have improved the therapeutic landscape for patients with progressive, metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). While drugs such as everolimus are appropriate for patients with widespread disease progression, local treatment approaches may be more appropriate for patients with unifocal areas of metastatic
progression. These treatments, such as resection, radiofrequency ablation (RFA), hepatic arterial embolization (HAE), or radiation, can control discrete sites of progression, allowing patients to continue their existing systemic therapy, and sparing them toxicities of a new systemic treatment.

**Methods:** We reviewed the records of patients treated at a large NET referral center to identify patients seen between 1/2014 and 5/2017 with metastatic GEP-NETs who underwent a local treatment for focal or oligometastatic progression. Patients undergoing lobar HAE for the control of widespread hepatic metastases or cytoreductive hepatic surgery were not included. The primary endpoint was time to new systemic therapy. Secondary endpoints included time to any additional intervention (systemic or local), progression free survival, and side effects related to locoregional therapy.

**Results:** 59 patients were identified who underwent a form of local treatment for a progressive metastatic tumor in the setting of widely metastatic disease. 27.1% underwent surgical resection, 28.8% had RFA, 25.4% had external beam radiation, and 18.6% underwent selective HAE. With a median follow-up of 17 months, 19 patients (32.2%) eventually progressed to the extent that they received salvage systemic treatment. 6 patients (10.2%) progressed and received further local treatment of progressive disease. Median time to new systemic treatment was 42 months (95% CI, 9.7-74.3 months). Median time to any additional intervention was 21 months (95% CI, 11.4-30.6 months). There were 4 deaths, all of which had progressed and received further systemic treatment.

**Conclusions:** We identified a large cohort of patients with metastatic GEP-NETs who underwent a local treatment for unifocal progression in the setting of widespread metastases. Control of local sites of progression enabled the majority of patients to remain on their existing systemic treatment and avoid potential toxicities associated with salvage systemic therapy.
Colon neuroendocrine tumors (NETs) are uncommon. Currently, the impact of the number of metastatic lymph nodes (LNs) and lymph node ratio (LNR) on survival has been well investigated in others colon malignancies, but both remains unclear for patients with colon NETs.

**Background:** Colon neuroendocrine tumors (NETs) are uncommon. Currently, the impact of the number of metastatic lymph nodes (LNs) and lymph node ratio (LNR) on survival has been well investigated in others colon malignancies, but both remains unclear for patients with colon NETs.

**Methods:** Surgically resected patients with histologically proven nonmetastatic colon NETs were queried from the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 2011. Patients with lymph nodes involved were investigated and categorized into four LNs-based classification (≤4, >4-10, >10-13, and >13) or three LNR-based subgroups (≤0.51, >0.51-0.71, and >0.71) according to threshold, determined by Harrell’s C statistic. Univariate
and multivariate survival analysis were performed by log-rank test and cox stepwise regression analysis, respectively.

**RESULTS:** 851 patients with positive nodes met the inclusion criteria. Among them, higher LNR and LNs classification were associated with worse survival rate. The 10-year NETs-specific survival rate was 78.3% (74.2-82.6%), 61.3% (52.4-71.7%), 40.8% (20.7-80.7%) for patients in the ≤4, >4-10, and 10-13 LNs groups, respectively. For patients in >13 LNs group, 10-year NETs-specific survival rate was not available, for the maximal follow-up in this group was 108 months. When patients were classified based on LNR, the observed 10-year NETs-specific survival rate was 79.9% (74.8-85.5%) for ≤0.51, 57.4% (43.8-75.2%) for >0.51-0.71, and 40.0% (31.0-51.5%) for >0.71. In stratified analysis, higher LNs and LNR groups having worse prognosis only were accompanied by patients with advanced T stage (T3-T4). With regard to stage migration, LNR-based system failed to show superiority to LNs-based classification.

**CONCLUSION:** Current TNM staging classification could be improved by taking into account the count of metastatic node and LNR instead of simple record of lymph node status (N1 or N0) for colon NETs.

**ADVANCED COLON CANCER**

**FOUR CASES OF IRINOTECAN-INDUCED DYSAERTHRIA IN PATIENTS WITH GASTROINTESTINAL CANCERS**

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**Background:** Irinotecan is one of the most commonly used chemotherapeutic agents. It is predominantly used to treat colorectal cancer, esophageal cancer and pancreatic cancer. Irinotecan is inhibitor of topoisomerase I and works to prevent DNA replication and cell division. Common side effects of irinotecan include diarrhea, nausea, vomiting, bone marrow suppression and cholinergic-like syndromes. Dysarthria is not a known common side effect of
irinotecan and here we describe 4 cases of patients treated with irinotecan developing slurred speech and difficulty speaking.

**Methods:** We report four patients who received irinotecan either in combination with 5-FU or with 5-FU and oxaliplatin who developed dysarthria while receiving their infusion of chemotherapy. One patient was being treated for metastatic colon cancer, one for metastatic pancreatic cancer, one of pancreaticobiliary origin and the last for pancreatic neuroendocrine tumor. All four patients were young women between 36 and 45 years of age.

**Results:** All four patients who developed dysarthria had resolution of symptoms with discontinuation of irinotecan. All four with given intravenous diphenhydramine and one was also given atropine and intravenous steroids and the dysarthria reversed within one hour. One patient was admitted to the hospital and had a CT head, MRI brain, MRV brain and echo that were all negative for any suggestion of stroke or hemorrhage as a cause of neurologic symptoms. No other neurotoxicity was noted in the acute setting. One patient had previously received irinotecan with no reaction. The other three were receiving irinotecan for the first time. One patient was then switched to topotecan and had a similar reaction. Another patient was given irinotecan again with no neurologic symptoms. The last was not treated with irinotecan again.

**Conclusions:** There is little data describing the neurologic symptoms of dysarthria related to irinotecan infusion. Here, we have four patients that were treated with diphenhydramine and caused reversal of symptoms. The mechanism of action of this side effect is unknown. However, it is clear that it is reversible and not life-threatening. It is unclear if reinitiating the drug after developing dysarthria is safe as some patients tolerated reinitiation of the drug it while others had the same symptoms again. Nonetheless, all the providers should be aware of this rare, but possible, side effect and be trained to treat it quickly and appropriately as it is a very frightening time for the patients being affected.
INVESTIGATING THE ROLE OF ACID CERAMIDASE IN THE RADIOTHERAPY RESPONSE OF AN IN VITRO MODEL OF COLORECTAL CANCER

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The University of Liverpool, United Kingdom

Background: Chemoradiotherapy (CRT) is often employed to treat locally advanced rectal cancer, however, response to treatment is highly variable and may delay access to treatment of systemic disease. The Association of Coloproctology has highlighted the necessity for predictive biomarkers in their review of national research. Our group has employed proteomic profiling of patient tissue samples before and following surgical resection and CRT to demonstrate that acid ceramidase (AC) expression is associated with poorer CRT response. Immunohistochemical (IHC) analysis of a tissue microarray (TMA) of 111 patients has independently verified this finding.

Aims: To investigate the role of acid ceramidase (AC) in the radiosensitivity of an in vitro model of colorectal cancer.

Methods: Differential AC protein expression of four colorectal cell lines was confirmed by Western blotting. Radiosensitivity of these cell lines was examined using standard clonogenic assays, and counting individual colony survival post-exposure to increasing doses of x-ray radiation. Knockdown of AC using siRNA was performed, and clonogenic assays were repeated to establish the impact of AC inhibition on radiosensitivity.

Results: Colorectal cancer cell lines with greater cellular AC protein expression (LIM 1215 and MDST8) demonstrated higher colony survival compared to those with lower AC expression (HT29, HCT 116) at specific radiation doses. Titrated siRNA concentrations from 40nM - 80nM achieved >70% knockdown of AC expression across all cell lines. Three colorectal cell lines with differential AC expression (HCT-116, HT-29 and LIM - 1215) were treated with siRNA for AC. Clonogenic assays confirmed that siRNA knockdown reduced colony formation efficiency
and improved radiosensitivity across all cell lines. HT29 (0.52 control vs 0.13 knockdown at 1Gy); HCT (0.24 control vs 0.09 knockdown at 1Gy); LIM 1215 (0.88 control vs 0.43 knockdown at 0.25Gy).

Conclusions: High AC expression in rectal cancer correlates with radioresistance. In vitro analysis confirms that biological (siRNA) manipulation of AC levels in a colorectal cell line improves radiosensitivity. Further work is required to determine the therapeutic and prognostic potential of AC in rectal cancer in the colorectal cancer cell lines studied. If translatable, AC could possibly serve as a novel response biomarker in patients selected to undergo CRT in colorectal cancer.

Overexpression of Sirt7 Promotes Human Colorectal Cancer Cell Colony Formation Through Inhibiting SESN2-mediated Autophagy
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Background: Sirt7, a member of the sirtuin family, deacetylates Histone H3K18ac thus maintaining oncogenic transformation. But less is known about the relationship between colorectal cancer development and progression. Here we explore the role of Sirt7 in colorectal cancer cell autophagy and colony formation.

Methods: Expression of Sirt7 protein and mRNA in human colorectal cancer specimens and cell lines were assessed using immunohistochemistry and immunoblotting. The effects of Sirt7 expression on colony formation and autophagy was evaluated after shRNA knockdown. The levels of autophagy related proteins (Beclin1, ATG5, ATG7, SESN2 and p62) were also determined. The upstream regulators of SESN2 were determined using ChIP assay and its effect on autophagy and colony formation was further verified after shRNA knockdown in colorectal cancer cells.

Results: Sirt7 was markedly and reproducibly upregulated in human colorectal cancers and their cell-line derivatives. Knockdown of Sirt7 in human colorectal cancer cell lines HCT116 and
SW620 dramatically reduced their colony formation. Mechanistic analyses showed that Sirt7 overexpression inhibited SESN2-mediated-autophagy and further promoted human colorectal cancer cell colony formation. Moreover, Sirt7 overexpression decreased Sp1 protein expression and further reduced Sp1 interaction with SESN2 promoter, leading to the decrease of SESN2 transcription level.

**Conclusions:** Our results provide the mechanistic link between autophagy and human colorectal cancer cell colony formation. The signaling axis along Sirt7-Sp1-SESN2-autophagy that is highly operative in colorectal cancer cells might be explored further for developing novel diagnostic and therapeutic approaches to manage advanced colorectal cancers.

**Medullary Colon Cancer: A Case Report**

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**Background:** To help support the recognition and establishment of a relationship between Medullary Colorectal Carcinoma (MCC) and Lynch Syndrome.

**Methods:** An 87-year-old male presented with anemia, syncope and bright red blood per rectum. A colonoscopy was performed and the patient was found to have a cecal mass, which was resected laparoscopically and sent to pathology. Initial staining showed a highly aggressive poorly differentiated carcinoma. However, after further testing, all lymph nodes were found to be negative and showed high-grade tumor with no extension prompted further staining.

IHC stained positively with calretinin, pancytokeratin, epithelial membrane antigen and low molecular weight cytokeratin, cytokeratin 20 and CDX-2. Failed to stain with cytokeratin 7,
CD45, S-100, synaptophysin and chromogranin. This confirmed the diagnosis of primary colonic medullary carcinoma.

**Results:** Although a high-grade carcinoma, medullary carcinoma is not aggressive and is amenable to curative resection. This patient required no further treatment after resection as final staging showed tumor to be pT2N0.

**Conclusion:** A case of medullary colon carcinoma is a rare discovery in an older male requiring high clinical suspicion when abnormal tumor characteristics are present. Due to the abnormal pathology that appeared to have highly aggressive tendencies without lymph node invasion, further staining was performed and the patient was diagnosed with Lynch Syndrome. Confirmation of this diagnosis is important, as a relationship between MCC and Lynch Syndrome may exist. If proven, this would prompt genetic testing and counseling for family members with the potential to earlier identify neoplasms related to Lynch Syndrome.

**OUR LOCAL EXPERIENCE WITH CARCINOSARCOMA OF THE COLON AND REVIEW OF ALL REPORTED CASES**

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**Introduction:** Carcinomatoid sarcoma of the colon is a very rare diagnosis, with only 35 cases reported worldwide so far.

A 59-year old male presented to our facility with a rapidly enlarging abdominal mass arising from the right colon, and liver metastases. He was treated with a palliative extended right hemicolectomy, and is currently on chemotherapy.

We performed a review of all reported cases of colonic carcinosarcoma in the literature, and with our own case, have developed some parameters of the disease and treatment guidelines for clinicians who may encounter this rare entity.
Method: A review of all language literature using various search terms including “carcinomatoid sarcoma of the colon, colon carcinosarcoma”. Data was obtained from all papers, and from our case, and by direct communication with authors.

Results: 35 cases have been reported in the literature between 1980-present date.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number of Cases</th>
<th>Mean Age(yrs)</th>
<th>Male:Female</th>
<th>Tumor Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1990</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990-2000</td>
<td>10</td>
<td>63.5 (13-86)</td>
<td>1:1.3</td>
<td>11.5 (2-36.5)</td>
</tr>
<tr>
<td>2001-2010</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011-2017</td>
<td>5</td>
<td></td>
<td></td>
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</tbody>
</table>

43% of patients had metastases at the time of presentation, and median survival is 5 months (0-48). 15 patients underwent chemotherapy, with 2 receiving intraperitoneal chemotherapy with hyperthermia.

Conclusion: Carcinomatoid sarcoma of the colon is more common in females, with age of onset in the sixth decade. An increasing number of cases have been reported over the last 30 years. These cancers also have a different immunohistochemical profile to adenocarcinoma of the colon with features of both sarcoma and carcinoma. Lymph node spread usually is carcinomatous. Typically, these cancers have extremely rapid onset, and are aggressive. They usually present with a short history of a rapidly enlarging abdominal mass and metastases. Immediate palliative surgery, and early adjuvant chemoradiotherapy might extend survival in these cancers, but response to treatment and overall survival is poor – generally because these tumors are so advanced at time of presentation.