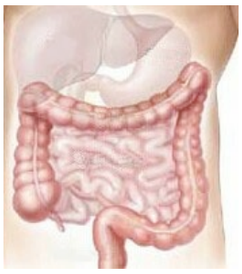
Colorectal Cancer Association of Canada

COLORECTAL CANCER RESEARCH UPDATES

Month Ending April 15th, 2016



The following colorectal cancer research update extends from January 16th, – April 15th, 2016 inclusive and is intended for informational purposes only.

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DRUGS / SYSTEMIC THERAPIES

1. Determining the Optimal Timing for Initiation of Adjuvant Chemotherapy After Resection for Stage II and III Colon Cancer (Feb 2016)

For patients with resected stage II and III colon cancer, optimal timing of adjuvant chemotherapy has been objectively determined to be within 6 weeks following surgery. Each additional week of delay was associated with a 7% decrease in survival. Findings stress the importance of decreasing delay to the initiation of therapy post-surgery to improve survival.

Sun, Zhifei, et al. "Determining the Optimal Timing for Initiation of Adjuvant Chemotherapy After Resection for Stage II and III Colon Cancer." Diseases of the Colon & Rectum 59.2 (2016): 87-93.

http://www.ncbi.nlm.nih.gov/pubmed/26734965

2. CDX2 -- New Prognostic Biomarker in Stage II Colorectal Cancer (Jan 20/16)

CDX2 protein is an important transcriptional factor involved in intestinal development. Findings demonstrate that stage II colorectal cancer (CRC) patients with CDX2-negative disease had lower 5-year disease-free survival (DFS) compared to those with CDX2-positive tumours. The use of CDX2 protein as a biomarker in stage II CRC patients can identify those who are likely to benefit from adjuvant chemotherapy – analysis has shown that 5-year DFS was higher for patients with CDX2-negative stage II CRC who received adjuvant chemotherapy compared to those who did not receive such therapy. While all stage III CRC patients are eligible for adjuvant chemotherapy according to clinical guidelines, the implementation of adjuvant chemotherapy into the standard of care for stage II CRC patients is still under debate given the lower rates of recurrence in this subgroup. Furthermore, despite improvements in the 5-year DFS for stage II patients with adjuvant chemotherapy within the trial, the increment of benefit still remained low – about 5% overall. It is important to consider that administering adjuvant chemotherapy comes with greater risk for complications (i.e. oxaliplatin induced neuropathy) that must be carefully considered against the true benefit of outcomes. In stage II CRC patients where only clinical staging is used to guide treatment decisions, however, the use of CDX2 biomarker may be an opportunity for oncologists to more adequately select patients likely to benefit from adjuvant therapy.

Dalerba, Piero, et al. "CDX2 as a prognostic biomarker in stage II and stage III colon cancer." New England Journal of Medicine 374.3 (2016): 211-222.

http://www.medscape.com/viewarticle/857470

3. Phase II Trial Evaluates NEXIRI Regimen for Heavily Pretreated KRAS Mutation-positive mCRC (Jan 22/16)

In a phase II trial (clinical trial phase in which testing of drug on patients assesses efficacy and safety), Sorafenib plus irinotecan (NEXIRI regimen) demonstrates promising activity in the treatment of patients with chemorefractory (cancer that proves resistant to treatment) KRAS mutation-positive metastatic colorectal cancer (mCRC). Findings demonstrate that the 2-year progression-free survival rate was 59% with NEXIRI, 23% with irinotecan monotherapy, and 22% with sorafenib monotherapy. The disease control rate was 59%,

25%, and 22% respectively. Furthermore, findings show a median progression-free survival of 3.7 months in the NEXIRI group, 1.9 months in the irinotecan alone group, and 2.1 months in the sorafenib alone group. Results have justified comparing the NEXIRI regimen to regorafenib or [trifluridine/tipiracil] monotherapies within this patient subgroup.

Samalin E, De La Fouchardiere C, Thezanas S, et al. Sorafenib and irinotecan combination for pre-treated RAS-mutated metastatic colorectal cancer patients: A multicentre randomized phase II trial (NEXIRI 2) [abstract]. J Clin Oncol. 2016;34.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-mcrc-nexiri-regimen-kras-mutation-treatment-risk/article/466927/

4. Adding Cetuximab to FOLFIRI Improved Response in Both Younger, Older Patients with mCRC (Jan 22/16)

Patients with metastatic colorectal cancer (mCRC) tend to be older, which has stimulated interest in subgroup analyses to evaluate efficacy and safety of treatments by age. In the first-line CRYSTAL trial, it was demonstrated that adding the anti-epidermal growth factor receptor (EGFR) antibody cetuximab, better know as erbitux, to first-line FOLFIRI (5-fluorouracil, leucovorin, irinotecan) improved progression-free survival (PFS – time before disease got worse), overall survival (OS), and objective response rate (ORR) in patients with KRAS wild-type mCRC (no mutation in the kras gene). In the phase III (clinical trial phase in which testing of the drug on patients examines efficacy, effectiveness and safety) CRYSTAL trial, it was observed that the addition of cetuximab to FOLFIRI improved PFS, OS, and ORR in both older and younger patients with wild-type KRAS mCRC, where patients were classified as being older than 65 years or younger than 65. It was noted that treatment-related adverse events were more common with the cetuximab + FOLFIRI than in FOLFIRI alone in both the younger and older populations.

van Cutsem E, Köhne C-H, Folprecht G, et al. Efficacy and safety of first-line cetuximab + FOLFIRI in older and younger patients (pts) with RAS wild-type (wt) metastatic colorectal cancer (mCRC) in the CRYSTAL study [abstract]. J Clin Oncol. 2016;34

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-mcrc-cetuximab-folfiri-better-treatment-response/article/466929/

5. Panitumumab Improves Overall Survival in Refractory KRAS Wild-type mCRC (Jan 22/16)

Panitumumab better known as Vectibix is a fully human anti-epidermal growth factor receptor (EGFR) antibody that, when bound to EGFR, reduces cell proliferation and induces apoptosis (cancer cell death). While no overall survival (OS) benefits have been previously observed with panitumumab monotherapy among wild-type KRAS (exon 2) patients with metastatic colorectal cancer (mCRC), it was indicated that other KRAS and NRAS mutations are predictive of anti-epidermal growth factor receptor treatments. In this phase III trial, it was sought to examine the OS benefit of panitumumab monotherapy with wild-type KRAS and NRAS (exons 2, 3, and 4) mCRC. Median overall survival was 10 months for panitumumab compared to 7.4 months without treatment. Median progression-free survival (PFS) was 3.6 months and 1.7 months, respectively. Wild-type RAS mCRC patients demonstrated a median PFS of 5.2 months with panitumumab compared to 1.7 months without. There was no OS benefit of panitumumab treatment among mutant RAS mCRC patients. Findings indicate that panitumumab significantly improved OS in patients with wild-type KRAS (exon 2) mCRC, with more pronounced improvements in OS and progression free survival among wild-type RAS mCRC patients. **Results support the importance of RAS testing at the time of diagnosis to better inform the use of panitumumab therapy for mCRC.**

Kim TW, Elme A, Kusic Z, et al. An open label, randomized phase III trial evaluating the treatment (tx) effects of panitumumab (pmab) + best supportive care (BSC) versus BSC in chemorefractory wild-type (WT) KRAS exon 2 metastatic colorectal cancer (mCRC) and in WT RAS mCRC [abstract]. J Clin Oncol. 2016;34

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-mcrc-panitumumab-kras-wild-type-survival-treatment/article/466928/

6. Vectibix® (panitumumab) And Best Supportive Care Improves Overall Survival Compared To Best Supportive Care In Chemorefractory KRAS And RAS Wild-Type Metastatic Colorectal Cancer (Jan 23/16)

RAS genes (KRAS and NRAS) code for proteins that play important roles in cellular proliferation, differentiation and apoptosis (cell death) pathways, making them important biomarkers in the specification of colorectal cancer treatment outcomes. Amgen's Phase III Vectibix trial is the first to analyse the efficacy of the drug by wild-type KRAS (exon 2) and in wild-type RAS (absence of mutations in exons 2, 3, and 4 of KRAS and NRAS) tumour mutation status, providing valuable information on overall survival (OS) in these patient groups. The study examines results of treatment with Vectibix and best supportive care (BSC) compared to BSC alone, demonstrating a statistically significant improvement in OS of patients with chemorefractory wild-type (no mutation) KRAS (exon 2) mCRC. Wild-type KRAS (exon 2) mCRC patients treated with Vectibix and BSC attained a median overall survival (OS) of 10 months compared to 7.4 months with BSC alone. Furthermore, patients with wild-type RAS mCRC treated with Vectibix and BSC achieved a median OS of 10 months compared to 6.9 months for patients treated with BSC alone. It was observed that patients with mutant RAS mCRC did not benefit from this treatment. The most commonly reported adverse effects were similar to the safety profile of Vectibix when given as a monotherapy, including skin, nail, gastrointestinal and electrolyte disorders.

http://www.prnewswire.com/news-releases/vectibix-panitumumab-and-best-supportive-care-improves-overall-survival-compared-to-best-supportive-care-in-chemorefractory-kras-and-ras-wild-type-metastatic-colorectal-cancer-300208694.html

7. FOLFOXIRI Plus Panitumumab Viable for Liver-only Metastatic Colorectal Cancer (Feb 25/16)

Given that previously ineligible patients with liver-only metastatic colorectal cancer may become eligible for curative resection following aggressive chemotherapy, this study sought to examine the effects of FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan) plus panitumumab (vectibix) as a possible frontline treatment. Findings demonstrate that FOLFOXIRI plus panitumumab is an efficacious treatment strategy for patients with metastatic KRAS wild-type colorectal cancer with liver-only metastases. In the phase II study, patients received FOLFOXIRI and panitumumab on the first day of each 14-day cycle. 60% of patients attained a partial response (cancer shrinks by at least one third) while 67% of patients who were eligible for resection at baseline all had complete resections with partial response. 33% of FOLFOXIRI + panitumumab patients experienced grade 3 diarrhea and rash, compared to 20% of patients who underwent surgery. *Despite the promising outcomes of FOLFOXIRI plus panitumumab treatment for the specified patient group, the study ended early due to emerging data indicating possible negative clinical outcomes for patients with exon 2 KRAS/NRAS mutations and oxaliplatin therapy.*

Bendell JC, Zakari A, Peyton JD, et al. A phase II study of FOLFOXIRI plus panitumumab followed by evaluation for resection in patients with metastatic. KRAS wild-type colorectal cancer with liver metastases only [published online ahead of print February 24, 2016].Oncologist.

http://www.oncologynurseadvisor.com/daily-oncology-news/colorectal-cancer-folfoxiri-panitumumab-liver-treatment-risk/article/479263/

8. The Next Frontier: The Promise of Immunotherapy in Gastrointestinal Cancers (Mar 24/16)

Keytruda (pembrolizumab) is part of a class of immunotherapeutic drugs which block receptors in the body that prevent the immune system from recognizing and eradicating cancer cells. Keytuda targets the programmed cell death 1 (PD-1) receptor, an important receptor in various gastrointestinal (GI) cancers. PD-1 receptor inhibitors such as Keytuda are effective at targeting tumours that have many mutations which causes the tumour cells to appear more foreign to the immune system and thus more likely to be identified. The challenge with colorectal cancer, however, is that many cancerous cells have a tendency to look a lot like normal colon cells, making it more difficult for the immune system to recognize and eradicate them despite the added help from an immunotherapy like **Keytuda**. A benefit of the drug is its lesser toxicity compared to chemotherapy, causing mild side effects such as fatigue, rash, stomach upset and joint pain, and in rare cases, causing other auto-immune disorders. Recently, immunotherapy approaches are being tried concomitantly with chemotherapy or radiation. If the chemotherapy or radiation is unable to destroy all the cancer, an immune response would still be triggered which would enable an immunotherapy such as Keytruda to gain better access to the target cells.

Another anti-PD-1 drug, **Opdivo (nivolumab**) demonstrated a 14% response rate in patients with metastatic gastric, esophageal or gastroesophageal cancer. Despite this low success rate, it was observed that 27% of patients whose tumours expressed PD-L-1 (the protein that normally binds to PD-1 receptor) did respond, alerting oncologists to the potential of this protein as a prognostic biomarker for treatment response. Other antibodies have also shown modest success in gastric cancers, including **Cyramza (ramucirumab**) and the experimental apatanib, both of which target the angiogenic factor VEGFR2. Genomic sequencing to identify patients with gastric tumours that have abundant mutations, thereby increasing their probability of responding to immunotherapy treatment, has been a pre-treatment approach adopted by more oncologists in recent years.

A major development in cancer immunotherapy in recent years has been the ability to take immune-boosting T cells from the blood of patients, re-engineer them to recognize unique proteins present on cancer cells, and then infuse them back into the body so they can search and destroy the tumour cells. Known as **chimeric antigen receptor T cell (CAR T cell) therapy**, it has achieved success in blood-based cancers but has encountered difficulties in GI cancers and other solid cancers as there are countless protein markers associated with them. To get around this problem, another technique called "**adoptive cell transfer**" involves take tumour samples from a patient and isolating tumour-reactive white blood cells which can recognize the unique mutations in the tumour and launch an immune attack against them. These white blood cells can be grown outside the body and then infused back into the patients to launch an attack on the tumour cells in the body. These new treatment approaches are highly personalized and essentially require the creation of a new drug for each cancer patient. However, given that 90% of all patients who die of cancer die of solid tumours, new treatment approaches are in great need.

http://www.curetoday.com/publications/cure/2016/gastrointestinal-2016/the-next-frontier-the-promise-of-immunotherapy-in-gastrointestinal-cancers

SURGICAL THERAPIES

9. Lap Approach To Colorectal Cancer Surges Since COST Trial (Mar 29/16)

The 2004 COST (Clinical Outcomes of Surgical Therapy) trial demonstrated equivalency of cancer outcomes between laparoscopic and open operations in the treatment of colorectal cancer. Recent investigation of the trends of use and adoption of laparoscopy since the COST trial reviewed data from 2000-2009, observing that in 2000, about 1% of colon and rectal resections were performed laparoscopically in the U.S. By 2004 and the COST trial, utilization was at about 3%, and by 2009 had reached 30%. It was noted that utilization varied by geography, with greatest use (33%) in metropolitan hospitals, 27% rurally, and 23% in urban locations. Furthermore, use of laparoscopy varied by tumour location, with the proportion of right-sided resections increasing from 3% (2004) to 37% (2009) and rectal cancer resections increasing from 2% (2004) to 15% (2009). The uptake of laparoscopic resection for tumours of varying stages and sizes also increased over time – in 2004 fewer than 5% of T1 to T4 tumours were laparoscopically removed. By 2009, the number had risen to 40% of early-stage tumours and a far greater proportion of large T4 tumours were being resected laparoscopically. Overall, trends demonstrate the increasing role for minimally invasive surgery and the importance of availability of technology in rural and urban settings to reduce barriers to adoption.

http://www.generalsurgerynews.com/In-the-News/Article/04-16/Lap-Approach-To-Colorectal-Cancer-Surges-Since-COST-Trial/35749

10. Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress (Apr 1/16)

For colorectal cancer that has metastasized to the liver, surgery is often used to remove the tumours. In the majority of cases, the cancer comes back; it is suspected that the body's healing response to surgical stress may be contributing to the cancer's recurrence. Neutrophils are the body's first immune cells to respond to injury post-surgery. These cells release web-like DNA called neutrophil extracellular traps (NETs) into the bloodstream to aid in capturing pathogens that may have entered the body. In recent years, NETs relevance to cancer has been established, with findings demonstrating that cancer patients' serum post-surgery contained NETs, and a higher risk of recurrence was found where there was a greater amount of NETs. Mice treated with DNAse minimized NET levels as well as metastasis rates. Researchers suspect that NETs can capture circulating cancer cells and actually activate their ability to proliferate and metastasize. Future research aims to find therapies which can control NETs without interfering with neutrophils' beneficial immunological functioning.

S. Tohme et al., "Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress," Cancer Res, doi:10.1158/0008-5472.CAN-15-1591,2016.

http://www.the-scientist.com/?articles.view/articleNo/45578/title/Tumor-Traps/

SCREENING

11. Annual fecal immunochemical test screening associated with high sensitivity for colorectal cancer (Jan 25/16)

The development of non-invasive and effective screening tests for colorectal cancer (CRC) is an essential step in regulating a disease that is the second leading cause of cancer death in the US. Fecal immunochemical test (FIT) is a mail-deliverable fecal blood test that can be performed at home without dietary or medication restrictions. Through 4 rounds of annual FIT screening, a retrospective study examined the performance of FIT as a population screening tool. FIT sensitivity in detecting CRC, FIT positivity (indicating the percentage of patients with positive results), and positive predictive values for adenoma (polyps) and advanced adenoma were highest in round 1, remaining lower but stable in subsequent rounds. While fewer than half of patients completed round 1 of screening, over 75% of patients that did complete the test continued the program for the remaining 3 rounds. Positive FIT results were associated with a high degree of follow-up, with 78.4% of patients with positive FIT results undergoing a colonoscopy within 1 year, and over 96% of participants undergoing some form of follow-up within 12 months of cancer identification. The study is limited in that it did not compare FIT to usual care or other screening methods. Furthermore, the study did not examine whether patient outcomes were actually improved after indication of cancer through FIT screening. Overall, the study indicates that FIT may be a valuable and effective population-level CRC screening method.

Jensen CD, Corley DA, Quinn VP, Doubeni CA, Zauber AG, Lee JK, et al. Fecal Immunochemical Test Program Performance Over 4 Rounds of Annual Screening: A Retrospective Cohort Study. Ann Intern Med. 2016;164:456-463.

http://www.2minutemedicine.com/annual-fecal-immunochemical-test-screening-associated-with-high-sensitivity-for-colorectal-cancer/

12. New guidelines urge colonoscopy surveillance after CRC resection (Feb 18/16)

The U.S. Multi-Society Task Force on Colorectal Cancer has updated recommendations which address the timely and appropriate use of colonoscopic surveillance in post-resection CRC patients to prevent metachronous (multiple separate primary cancer occurrences) cancer or diagnose recurrent and metachronous cancer at an earlier stage. The updated data demonstrate that postoperative colonoscopy is linked to lower overall mortality, but not cancer-specific mortality. This suggests that its value lies mainly in

perioperative clearing and prevention of metachronous CRC. The task force recommends that CRC patients undergo colonoscopy for perioperative clearing before surgery or within 3 to 6 months post-surgery if an obstructing cancer is found. Surveillance colonoscopy should occur 1, 4, and 9 years post-surgery or perioperative colonoscopy, and then at 5-year intervals until the end of the surveillance period determined by the patient and their physicians. Recommendations do not apply to patients with Lynch Syndrome and normal guidelines for polyp surveillance intervals should be followed in the case of neoplastic polyp detection. For patients with rectal cancer, it is recommended that additional local surveillance with flexible sigmoidoscopy or endoscopic ultrasound every 3 to 6 months for 2 to 3 years post-surgery is completed as such patients have an increased risk for local recurrence compared to colon cancer patients. The new guidelines do not recommend the fecal immunochemical test or fecal DNA screening as acceptable surveillance methods post-surgery due to insufficient evidence, relying primarily on colonoscopic surveillance or CT colonscopy/barium enema for patients with obstructing CRC.

Kahi, Charles J., et al. "Colonoscopy Surveillance After Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer." Gastrointestinal Endoscopy (2016).

http://www.healio.com/gastroenterology/oncology/news/online/%7B71105f45-3590-4031-8cc2-4111115d219a%7D/new-guidelines-urge-colonoscopy-surveillance-after-crc-resection

13. Annual Fecal occult blood test screening for Colorectal Cancer was not successful, study says (Feb 21/16)

A 150,000 participant study indicated that a mere 0.3% adhered to an annual colorectal cancer (CRC) screening using the fecal immunochemical test (FIT) or fecal occult blood test (FOBT) over a consecutive 10-year observation period. Despite United States Preventive Services Task Force recommendation for FOBT and FIT for CRC screening, it appears that the sensitivity of the combined testing for neoplasia detection remains poor. Furthermore, study data demonstrate that annual adherence to fecal blood test screening is extremely low and among patients who do use the tests, average use was one test every four years. The study suggests drawing attention towards alternative screening methods such as Cologuard (a fecal screening test that identifies colon cancer-linked mutations in free-floating DNA), which demonstrates higher sensitivity in detecting colorectal cancer and is also backed by a nation-wide colon cancer compliance service to ensure improved adherence to screening.

http://www.pulseheadlines.com/annual-fecal-occult-blood-test-screening-for-colorectal-cancer-was-not-successful-study-says/18225/

14. Drug combination reduces polyps for patients with high risk for colorectal cancer (Mar 22/16)

Familial adenomatous polyposis (FAP) is an inherited disorder which places patients at an increased risk for polyps and cancer. Thus far, surgical and endoscopic management of polyps is difficult and chemoprevention has proved unsuccessful. Sulindac is a non-steroidal anti-inflammatory drug (NSAID) that inhibits tumour growth. Erlotinib is an epidermal growth factor receptor inhibitor (EGFR inhibitor), specifically targeting EGFR tyrosine kinase, which is highly expressed and sometimes mutated in various forms of cancer. The combination of these two drugs was found to effectively reduce the number of polyps in participants with FAP compared to placebo, demonstrating significance after 6 months of therapy. An acne-like rash was observed in 87% of participants receiving treatment compared to 20% of participants receiving placebo. Such adverse events may limit the use of such treatments at the doses applied in the study.

Samadder N, Neklason DW, Boucher KM, et al. Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis: A Randomized Clinical Trial. JAMA. 2016;315(12):1266-1275.

http://www.sciencecodex.com/drug_combination_reduces_polyps_for_patients_with_high_risk_for_colorectal_cancer-178465

15. Banking on Blood Tests (Apr 1/16)

When cancer is present in the body, its existence becomes apparent in the blood. Whether it is through tumour cells which begin their metastatic migrations, or by means of vesicles or free-floating DNA released by cancer cells, such material inevitably becomes present in the bloodstream. This material is rich in biomarkers which can be used to indicate the presence of cancer and predict its progression and response to treatment. Such blood-based diagnostics or liquid biopsies are gathering significant interest as their goal is to detect cancer before symptoms appear, at a time when most tumours are far easier to treat. **Cologuard** is the only cancer screening test approved by the FDA based on free-floating tumour DNA, screening for colon-cancer linked mutations in free-floating DNA present in patients' stool. Cancer screening through the blood, however, is likely to carry tumour DNA from cancers outside of the gastrointestinal tract, allowing the patient to be scanned for a wider number of cancer types. Due to lack of evidence of effectiveness of such screening methods in asymptomatic, at-risk patients, most commercial interest in liquid biopsy is currently focused on more prognostic applications of the tests such as identifying drug-targetable mutations, predicting metastasis and observing tumour response to therapy in already diagnosed patients. For example, Janssen's Diagnostics' CellSearch assay counts the number of circulating tumour cells (CTCs) in a given volume of blood. This assay is used to monitor how metastatic cancers respond to treatment, where a decrease in CTCs post-treatment indicates a positive response and an increase in CTCs indicates shorter progression-

free and overall survival. Another area of interest for blood-based cancer screening tests is derived from the same technology used by non-invasive prenatal testing (NIPT), which assays fetal DNA in a sample of maternal blood for mutations and genetic conditions. A third area of interest of liquid biopsies bases its cancer detection on the exosome, or what was once thought to be “cellular junk”. The exosome is a storage unit secreted by the cell containing many kinds of molecules that diagnostic tests can detect. Furthermore, exosomes are far more abundant in the blood compared to CTCs or free-floating DNA. As the field of liquid biopsies continues to improve, they are a promising tool in detecting cancer at earlier stages of the disease. For now, they remain a tool used mainly in cases of more advanced stage patients.

http://www.the-scientist.com/?articles.view/articleNo/45584/title/Banking-on-Blood-Tests/

16. CT Colonography and FIT Yield Different Participation and Detection Rates (Jan 13/16)

A study aimed at determining the ideal screening method for colorectal cancer examined patient participation in CT colonography and fecal immunochemical test (FIT). It was found that computed tomography (CT) colonography with reduced patient preparation had greater participation compared to full preparation CT colonography, with participation highest for first-round FIT. Detection rates were 3 times higher for CT colonography compared to FIT. It was noted, however, that the true impact of FIT screening is observed only after repeated rounds. Due to the vast differences in colorectal cancer screening methods, it was concluded that no one test or program design makes one screening method better than the other, but rather it is follow-up to the screening tests that is essential in impacting disease outcomes.

http://www.oncologynurseadvisor.com/colorectal-cancer/ct-colonography-fit-yield-different-participation-rates/article/464801/

RADIATION THERAPIES/INTERVENTIONAL

17. In Some Rectal Cancers, 5 Days of Radiation as Good as 5 Weeks (Jan 20/16)

Locally advanced rectal cancer is either unresectable or borders the threshold of inoperability. Patients with locally advanced rectal cancer may undergo preoperative radiation therapy with the aim of reducing tumour size in hope of increasing resection rates and overall disease outcomes. To date, the standard of care has been long-course radiation (28 days) combined with chemotherapy. A phase III trial has emerged with findings that demonstrate that a short-course radiation (5 days) combined with chemotherapy has similar effectiveness and less toxicity than the current standard of care. The short-course option provides a more convenient, less toxic and less expensive treatment that appears to be equally as effective to the standard chemoradiation. The trial demonstrated that despite having similar 3-year disease-free survival between the experimental short-course chemoradiation and the control standard chemoradiation groups, there was a trend toward greater overall survival at 3 years in the experimental group. Furthermore, there was significantly less acute toxicity of neoadjuvant treatment in the short-course chemoradiation group compared to the standard chemoradiation group, though the rate of patients with grade 3+ toxicity was similar in both groups. To date, the use of short-course radiation in locally advanced rectal cancer is variable by region, with greater popularity in Europe than in the U.S.

http://www.medscape.com/viewarticle/857496

18. SIRFLOX Regimen Delays Liver Progression in Metastatic Colorectal Cancer (Feb 25/16)

Findings demonstrate the combination of selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres to the standard FOLFOX chemotherapy did not improve progression-free survival (PFS) in patients with metastatic colorectal cancer (mCRC), but did result in a significant delay (31% risk reduction) of disease progression in the liver. Adverse effects of grade 3 or higher occurred in 73.3% of patients assigned to FOLFOX alone compared to 85.4% of patients assigned to FOLFOX + SIRT, with the latter group experiencing a significant increase in hematologic toxicities. It was noted that these findings were the first to evaluate PFS in the liver, and more extensive evidence and context is required to determine whether this significant improvement in control of existing liver metastases translates into a significant improvement in survival.

van Hazel GA, Heinemann V, Sharma NK, Findlay MPN, Ricke J, Peeters M, et al. SIRFLOX: randomized Phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6(plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin OncolFeb 2016.

http://www.cancernetwork.com/colorectal-cancer/sirflox-regimen-delays-liver-progression-metastatic-colorectal-cancer

19. Radiofrequency ablation seen to promote immune response in advanced colorectal cancer patients (Mar 8/16)

Findings demonstrate that preoperative radiofrequency ablation (RFA) stimulated anti-tumour immune responses in patients with primary colon tumours with liver metastases. RFA is considered the best alternative therapeutic option to surgery for patients with colorectal cancer with liver metastases. RFA

involves an alternating current electrical energy which generates heat to destroy tumour cells. Results from this study suggest that RFA stimulates a systemic inflammatory response and signalling for help from immune white cells or T-cells. The immune response, however, stimulates the expression of programmed cell death ligand 1 (PD-L1), an immune-inhibitory protein within the tumour microenvironment, which, in binding its receptor, programmed cell death -1 (PD-1), prevents the immune system from recognizing and eradicating cancer cells. Experiments in mice demonstrated that an anti-PD-1 antibody inhibited the effect of RFA induced PD-L1, resulting in a more potent immunological response when RFA was combined with an anti-PD-1 antibody compared to RFA or anti-PD-1 antibody alone. For patients who are non-responsive to PD-1-based immunotherapy, RFA acts to synergize the immunotherapy by stimulating an inflammatory response in the colon tumour environment making it more accessible to T cells. This suggests potential use of RFA as an adjuvant immunotherapy for patients with multiple metastases.

Shi, Liangrong, et al. "PD-1 Blockade Boosts Radiofrequency Ablation–Elicited Adaptive Immune Responses against Tumor." Clinical Cancer Research 22.5 (2016): 1173-1184.

http://immuno-oncologynews.com/2016/03/08/adding-immunotherapy-to-rfa-may-benefit-colorectal-cancer-patients-with-liver-metastasis/

20. Magnetic resonance-guided high intensity focused ultrasound for recurrent rectal cancer: a pilot study

Magnetic resonance-guided focused ultrasound (MRg-FU) is an non-invasive, outpatient therapy that is currently being studied at Sunnybrook hospital for the thermal treatment of **recurrent cancer cancer**. A specially designed ultrasound applicator focuses a beam of low intensity ultrasound energy at the tumour. Magnetic Resonance Imaging (MRI) is used to identify the tumour and focus the ultrasound beam, while providing real-time thermal mapping to observe proper heating of the tumour to induce cell death without incurring extensive damage to surrounding healthy tissues. A study to examine the effects of therapeutic hyperthermia (warming) delivered through MRg-FU in combination with standard radiation therapy and chemotherapy aims to determine whether such approaches can be safely combined in the treatment of recurrent rectal cancer. This study is being conducted among twenty recurrent rectal cancer patients who are currently ineligible for surgery.
*see attachment

21. PET/MRI Plus CT Helps Determine Colorectal Cancer Treatment (Jan 13/16)

Study findings suggest that whole body position emission tomography (PET)/magnetic resonance imaging (MRI) can help to more accurately select treatment strategies in colorectal cancer (CRC) patients. It was sought to determine whether it was clinically valuable to add PET/MRI to the standard contrast-enhanced multidetector computed tomography (CECT) when evaluating patients with CRC. Results demonstrated that PET/MRI added value to CECT in 27.5% of patients, amongst whom 23.5% had improved characterization and 3.9% had additional detection of extracolonic lesions. These evaluations resulted in 21.6% of patients undergoing a change in treatment strategy. These findings suggest that concomitant PET/MRI do add value in the detection of metastatic lesions and indeterminate lesion characterization, thereby aiding in the selection of more streamlined treatment strategies.

http://www.diagnosticimaging.com/petmr/petmri-plus-ct-helps-determine-colorectal-cancer-treatment

PSYCHOSOCIAL

22. Financial Status Affects Quality of Life of Newly Diagnosed Patients (Mar 30/16)

Many studies examining the relationship between cancer and financial stress tend to focus on post-diagnosis correlations. A recent study sought to assess any relationship between a patient's financial burden and their symptoms and quality of life (QOL) reported *upon diagnosis* with lung or colorectal cancer. Findings demonstrate that patients who reported limited financial reserves equivalent to two months or less at the time of diagnosis also reported significantly more pain, greater symptom burden and poorer mental and physical quality of life when compared to patients who had more than twelve-months of financial reserves. This effect held true after adjusting for stage of disease, co-morbidity, income, age and insurance. It was observed that as a patient's financial reserves decreased, so did their self-reported well-being, a direct correlation that persisted in survivor-reported outcomes after a one year period. These results suggest that attention by healthcare professionals to assess patients for signs of financial distress at the initial diagnosis would be beneficial. Furthermore, these results emphasize the importance of clinicians to seek out appropriate resources and treatment options for financially burdened patients prior to diagnosis.

Lathan C, Cronin A, Tucker-Seeley R, et al. Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer [published online ahead of print February 29, 2016]. J Clin Oncol.

http://www.curetoday.com/articles/financial-status-affects-quality-of-life-of-newly-diagnosed-patients

OTHER

23. Why Is Colorectal Cancer Targeting the Young? (Jan 20/16)

It has been observed that among individuals 50 years or older, colorectal cancer (CRC) incidence and mortality rates have been on the decline. The screening and surveillance programs that make colonoscopy and stool testing more available and accessible to this population has been credited for this decline. Despite this fact, CRC incidence in the U.S. and other developed countries among individuals under the age of 50 years has been increasing. Furthermore, mortality rates among young adults with CRC tend to be high, given the fact that patients in this age group tend to be diagnosed with late-stage disease. A study revealed that 86% of individuals under the age of 50 years were symptomatic at the time of diagnosis. Compounding this fact, younger patients may often misinterpret signs and symptoms of CRC delaying their access to further medical attention, while physicians often miss symptoms of early-onset CRC resulting in initial misdiagnoses in young patients up to 50% of the time. In the past, it was believed that cases of CRC in individuals under the age of 50 could be attributed to hereditary syndromes, such as Lynch Syndrome, which would predispose them to developing cancer. Findings demonstrated that today, over 75% of CRC diagnoses in young adults occur in people who have no family history of predisposing syndromes. An analysis of epidemiological data of adults under the age of 50 demonstrated that large increases in the incidence rates of obesity and diabetes parallel the increasing incidence of CRC. The Never Too Young Coalition aims to address early-onset CRC through action, education, and research, and is taking such measures as better educating physicians about the signs and symptoms related to early-onset CRC so that fewer cases in young patients are missed or misdiagnosed. Furthermore, the coalition aims to better inform the medical community about the importance of family history and the role of genetic testing in young individuals at risk for CRC.

http://www.medscape.com/viewarticle/857294

24. Link Between Obesity and Increased Risk for Colorectal Cancer May Be Therapy Target (Jan 16/16)

Obese individuals are 50% more likely to develop colorectal cancer compared to individuals of normal weight. Findings from a recent study demonstrate that high caloric intake decreases expression of an intestinal hormone important in activating a tumour suppression pathway in the GI tract. Through the use of genetically engineered mice, it was discovered that obesity caused either by excess fat or carbohydrate consumption, or both, causes a decrease in the expression of the hormone guanylin. This hormone is produced by the cells that make up the intestinal epithelium (lining of the intestinal wall). This hormone activates its receptor, guanylyl cyclase C (GUCY2C), whose activity stimulates and tightly regulates the constantly regenerating intestinal epithelial cells. It is common in colorectal cancers for the guanylin gene to be deactivated, and morbidly obese individuals have an 80% reduction in the expression of the guanylin gene compared to individuals of healthy weight. Once this tumour suppressing pathway is diminished, intestinal epithelial cells begin to regenerate abnormally without the GUCY2C regulatory mechanisms to deactivate them. It is known that this pathway deactivation occurs early in the development of cancer. In the study, transgenic mice carried a transgene that maintained guanylin expression high despite high caloric intake, which resulted in sustained tumour suppression activity. The drug linaclotide (Linzess), used to treat irritable bowel syndrome with constipation and chronic idiopathic constipation, is structurally similar to guanylin. Researchers believe that Linzess or other structurally similar drugs could be used as a potential hormone therapy to maintain expression of GUCY2C tumour suppression pathways to prevent colorectal cancer in obese individuals.

Lin, Jieru E., et al. "Obesity-Induced Colorectal Cancer Is Driven by Caloric Silencing of the Guanylin–GUCY2C Paracrine Signaling Axis." Cancer research 76.2 (2016): 339-346.

http://www.oncologynurseadvisor.com/colorectal-cancer/link-obesity-colorectal-cancer-therapy-target/article/467248/

http://www.dailymail.co.uk/health/article-3405199/How-overeating-gives-CANCER-Excess-calories-turn-hormone-intestine-blocks-colon-cancer.html

https://www.sciencedaily.com/releases/2016/01/160115084806.htm

25. Predictive Proteins: Elevated Levels Trigger Metastatic Progression of Cancer Cells (Feb 26/16)

Findings have demonstrated that increased levels of certain members of the guanine nucleotide exchange (GEF) protein family in cancer cells trigger increased G protein signalling, thereby stimulating the proliferation and metastasis of various cancers. Furthermore, increased expression of each GEF is correlated to shorter, progression-free survival in metastatic colorectal cancer patients. These findings suggest GEFs may serve as more precise indicators of disease state and prognosis. It is also known that GEF-activated G protein signalling is involved in circulating tumour cell (CTC) functioning, which is used by primary tumours to seed secondary tumours in other parts of the body. Counting CTCs is used as a prognostic and predictive biomarker in observing effectiveness of therapies and detecting early signs of metastasis. Counting CTCs, however, is limited in its screening potential as it does not profile more specific characteristics of CTCs that determine how likely the cells are to cause further malignancies. The study findings on GEF and G proteins may prove valuable in fine-tuning CTC screening for more accurate analysis of disease course and patient survival.

https://health.ucsd.edu/news/releases/Pages/2016-02-28-elevated-protein-levels-trigger-metastasis.aspx

26. Small, regular dose of aspirin keeps colorectal cancer at bay (Mar 3/16)

Long-term aspirin use has been associated with a modest but significant reduction of overall cancer risk, particularly gastrointestinal cancers. The U.S. Preventative Services Task Force recommends taking aspirin regularly for colorectal cancer (CRC) prevention. Findings from a longitudinal study examining two large cohort studies over a 32 year period demonstrated that a weekly aspirin dosage of 0.5-1.5 standard aspirin tablets reduced the risk of developing colorectal cancer by 19%. Such dosage was not correlated with a reduction in other kinds of major cancer. This suggests that aspirin may have an impact on mechanisms specifically involved in the development of GI tract cancers. It was also found that significantly more cases of GI cancers were prevented among individuals who did not partake in any kind of screening. These results suggest that aspirin use may be a potential low-cost alternative to endoscopic CRC screening in resource-limited settings or as a complement to existing CRC screening approaches to offset poor adherence rates.

http://www.medicalnewstoday.com/articles/307323.php

27. Metformin May Prevent Colorectal Cancer (Mar 3/16)

Metformin is an oral anti-diabetic drug which, in low doses, was found to reduce the prevalence and overall number of metachronous adenomas after polypectomy in patients with a high risk for adenoma recurrence. (Adenomas are polyps which can turn cancerous if not removed from the colorectum). The phase III study enrolled non-diabetic patients with previous polypectomy to receive a low dose of metformin (250mg) orally or placebo for 1 year. After 1 year, prevalence of total polyps was 38.0% in the treatment group and 56.5% in the placebo group. Prevalence of adenomas was 30.6% and 51.6%, respectively. 11% of patients experienced grade 1 adverse events, suggesting that low-dose metformin for 1 year for non-diabetic patients is safe, and is a potential treatment in the chemoprevention of colorectal cancer.

Higurashi T, Hosono K, Takahashi H, et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial [published online ahead of print March 2, 2016].Lancet Oncol.

http://www.cancertherapyadvisor.com/gastrointestinal-cancers/colorectal-cancer-metformin-treatment-risk/article/480813/

28. How dogs can smell cancer and what it means for the future of diagnosis (Mar 24/16)

Cancer involves many changes to the metabolic state and/or level of metabolites produced by cancer cells compared to healthy cells. Volatile organic compounds (VOCs) make up some of the metabolites and become present in the exhaled breath, feces, blood, urine and sweat. Dogs happen to have a very sensitive sense of smell - it was observed in one study that a trained Labrador was able to distinguish colorectal cancer samples from those of healthy individuals with very high sensitivity (0.91) and specificity (0.99). Different cancers will produce different VOCs, which can then be detected by gas chromatography-mass spectrometry (GC-MS), a means by which the composition of a gaseous mixture (i.e. a patient's exhaled breath) can be analyzed. This method could theoretically be used to detect these compounds and thus identify different types of cancer through an electronic sensor, though further research on the unique metabolite makeup associated with each type of cancer is yet to be conducted.

http://www.forbes.com/sites/quora/2016/03/24/how-dogs-can-smell-cancer-and-what-it-means-for-the-future-of-diagnosis/#14b5ca297ce5

29. Active surveillance improves colostomy-free survival in rectal cancer (Jan 15/16)

For rectal cancer patients, surgical resection is a common management option. Surgery risks fatal complications as well as incontinence, sexual dysfunction and permanent colostomy. Findings from a recent study demonstrate the improved clinical outcomes were associated with chemoradiotherapy followed by watch-and-wait surveillance for rectal cancer patients. In the study, patients who underwent chemoradiotherapy and achieved a complete clinical response were offered active surveillance while those who did not were offered surgical resection, if eligible. While no significant differences were observed in 3-year non-regrowth disease-free survival and 3-year overall survival between the active surveillance and surgery groups, patients managed with active surveillance had a significantly higher rate of 3-year colostomy-free survival (74% compared to 47% in the surgery group). Such watch-and-wait approaches are gaining in popularity as patients wish to avoid many of the serious complications associated with rectal surgery.

Perez RO. Complete clinical response in rectal cancer: a turning tide. **Lancet Oncol.** ***2016;17(2):125–6.***

Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. **Lancet Oncol.**

http://www.healio.com/hematology-oncology/gastrointestinal-cancer/news/online/%7B8754a362-5f1e-4f6b-a3eb-7ce4ee0100c9%7D/active-surveillance-improves-colostomy-free-survival-in-rectal-cancer

NUTRITION/HEALTHY LIFESTYLE

30. Vitamin D may have a role in CRC immunoprevention (Jan 29/16)

Findings demonstrate that high levels of plasma 25-hydroxyvitamin D were correlated with a decrease in the risk for tumours with high-level immune response, but no effect for tumours with low-level immune response. It is known that immune cells in the tumour microenvironment can convert 25-hydroxyvitamin D [25(OH)D] to bioactive 1α,25-dihydroxyvitamin D3, which is able to stimulate immune cells as an autocrine (substance produced by the cell that acts on the same cell) and paracrine (substance produced by the cell that acts on a neighbouring cell) factor. These results suggest there may be a **role for vitamin D in cancer immunoprevention** via a tumour-host interaction.

Song, Mingyang, et al. "Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status." Gut 65.2 (2016): 296-304.

http://www.healio.com/gastroenterology/oncology/news/online/%7B214bff83-263d-4936-ba38-b49961507a2d%7D/vitamin-d-may-have-a-role-in-crc-immunoprevention

31. Drinking Coffee Decreases Risk of Colorectal Cancer (Apr 1/16)

Findings demonstrate the **link between a daily cup of coffee and a lowered risk for colorectal cancer** (CRC). One to two servings of coffee a day was associated with a 26% reduction in risk of developing CRC after adjusting for known risk factors. CRC risk was reduced by 50% if the number of coffee servings was more than 2.5 per day. The effect was found to hold true for caffeinated and decaffeinated coffee. It is believed that the protective effects of coffee can be attributed to its complex brew of antioxidants including chlorogenic acids, polyphenols, and caffeine; melanoidins which promote colon motility; and dipterenes such as cafestol and kahweol, which have anti-carcinogenic activity. While evidence to support an inverse, dose-response correlation between coffee and CRC risk is increasing, further research is required before coffee drinking can be advocated as a preventative measure.

S. L. Schmit, H. S. Rennert, G. Rennert, S. B. Gruber. "Coffee Consumption and the Risk of Colorectal Cancer". **Cancer Epidemiology Biomarkers & Prevention*, 2016; 25 (4): 634 DOI: 10.1158/1055-9965.EPI-15-0924***

http://www.genengnews.com/gen-news-highlights/drinking-coffee-decreases-risk-of-colorectal-cancer/81252554/

32. It's not just meat: carbs can raise cancer risk, too (Apr 6/16)

The World Health Organization has indicated that eating processed meats (i.e. smoked and cured meats, lunch meats) can increase risk of developing colorectal cancer. A study revealed how certain types of carbohydrates may also increase a person's cancer risk – it was demonstrated that individuals who consumed a greater proportion of **refined "bad" carbohydrates were 88% more likely** to develop prostate cancer. Consuming large quantities of processed meats and sugary beverages boosted the risk significantly. Women who consumed a greater proportion of "good" carbohydrates such as fruits, vegetables, whole grains and legumes in their diet experienced a 67% decreased risk of developing breast cancer. Diets rich in legumes such as lentils and beans were observed to have a powerful effect on lowering overall risk of cancer by about 32%. These findings were consistent with previous studies which have indicated that diets rich in refined carbohydrates have a powerful impact on body fatness and on the dysregulation of insulin and glucose, factors which may increase cancer risk. It was noted, however, that more rigorous studies must be conducted to determine more exact causal pathways linking refined carbohydrates to cancer development.

http://www.popsci.com/its-not-just-meat-carbs-can-raise-cancer-risk-too