Our experts highlight the most important research articles across the spectrum of topics relevant to the field of colorectal cancer

Expert panel: Cathy Eng, The University of Texas MD Anderson Cancer Center, TX, USA; Francesc Balaguer, Institute of Digestive & Metabolic Diseases, Hospital Clinic, Barcelona, Spain; Antoni Castells, Institute of Digestive & Metabolic Diseases, Hospital Clinic, Barcelona, Spain; Bruce Minsky, The University of Texas MD Anderson Cancer Center, TX, USA

Damania D, Roy HK, Subramanian H et al. Nanocytology of rectal colonocytes to assess risk of colon cancer based on field cancerization. *Cancer Res.* 72(11), 2720–2727 (2012).

Currently, only approximately 50–60% of individuals at risk for colorectal cancer (CRC) undergo screening, despite evidence that such screening, in particular colonoscopy, is quite effective in reducing disease incidence and mortality. Surveys indicate that while awareness and knowledge of CRC screening and its importance are quite high within the community, many who are at risk do not get screened. This is a consequence of a number of constraints, including fear, embarrassment, discomfort, lack of access to appropriate providers, inadequate insurance coverage and other factors. There is a great need, therefore, to develop and implement alternative screening strategies that are accurate, yet minimally invasive, inexpensive and accessible to the public. This need is driving research onto new approaches to colon cancer screening, such as high-resolution imaging and blood-based biomarker analysis. In the journal *Cancer Research*, Damania et al. report on the use of a novel imaging strategy, termed partial-wave spectroscopic (PWS) microscopy, to identify patients harboring precancerous colonic lesions. The strategy is based on the ‘field of inquiry’ concept, which refers to the existence of a broad pre-dysplastic field throughout the organ, within which stochastic mutational events leading to lesion development occur. Using a simple

cytology brush adapted to a colonoscope, the research team obtained rectal mucosal cells from 146 patients, and utilized PWS to measure a parameter termed disorder strength, or L_d , which is a measure of the density of macromolecules within the cells. They found that L_d increases with colonic lesion size and degree of advancement, with diminutive adenomas < small adenomas < advanced adenomas < frank cancers. The method was not confounded by age, gender, smoking history or alcohol consumption, and showed no disparity between left- and right-sided lesions. It was also capable of detecting hereditary nonpolyposis CRC. Thus, the PWS technique may enable detecting precancerous events using simply-obtained rectal mucosal cells. Although more research is needed, the technique has immense potential to increase colon cancer screening rates, and identify the subset of patients who should be recommended for colonoscopy.

– Written by Francesc Balaguer

Kastrinos F, Steyerberg EW, Balmaña J et al.; the Colon Cancer Family Registry. Comparison of the clinical prediction model PREMM_{1,2,6} and molecular testing for the systematic identification of Lynch syndrome in colorectal cancer. *Gut* doi:10.1136/gutjnl-2011-301265 (2012) (Epub ahead of print).

Lynch syndrome is the most common form of hereditary CRC and accounts for up to

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3–5% of all CRC cases. It is characterized by CRC at an early age, accelerated tumorigenesis and an increased risk for extracolonic tumors (especially endometrial). It is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes (i.e., *MSH2*, *MLH1*, *MSH6* and *PMS2*). The abnormal function of these genes leads to accumulation of errors during DNA replication, especially in repetitive sequences known as microsatellites. As a result, tumors of patients with Lynch syndrome characteristically demonstrate MMR deficiency, defined as the presence of microsatellite instability (MSI) and/or loss of expression of the corresponding MMR protein by immunohistochemistry (IHC), which is the hallmark of this disorder. The current cornerstone of this syndrome lies on its underdiagnosis, since unless a strong clinical suspicion, the vast majority of cases remain undetected. This fact precludes the opportunity to prevent future cancers through appropriate screening and risk-reducing options in the mutation carriers.

In this article, investigators from the Colon Cancer Family Registry (CCFR) compared the performance of PREMM_{1,2,6} (a prediction model recently developed that relies on personal and family history to identify patients and families who should undergo genetic evaluation) with MSI and IHC tumor testing in patients with CRC. Since the CCFR include both population-based and clinic-based cases, analyses were controlled by ascertainment.

Among the 1651 CRC patients, 239 (14%) were mutation carriers (90 *MLH1*, 125 *MSH2* and 24 *MSH6*). PREMM_{1,2,6} distinguished mutation carriers from non-carriers with area under the curve: 0.90 (95% CI: 0.88–0.92), compared with 0.77 (95% CI: 0.74–0.79) and 0.82 (95% CI: 0.80–0.84) for MSI and IHC, respectively. However, when stratified by ascertainment, all three modalities were equivalent in population-based cases (micros: 0.84, 0.82 and 0.88, respectively). The addition of IHC or MSI to the PREMM_{1,2,6} strategy increased the discriminatory value to 0.94 (95% CI: 0.92–0.96) and 0.93 (95% CI: 0.92–0.95), respectively. Finally, unlike IHC and MSI, PREMM_{1,2,6} performance was not affected by age at the time of CRC.

The results of this study illustrate that PREMM_{1,2,6} and IHC show an excellent performance in distinguishing mutation carriers from noncarriers, and perform best when combined. Since computing risk prediction for all newly diagnosed CRCs may not be achievable, the authors propose an algorithm based on IHC testing in all CRC patients <70 years, and the use of PREMM_{1,2,6} in those older than 70 years, since IHC specificity decreases significantly after the age of 70 years due to *MLH1* promoter hypermethylation.

– Written by Francesc Balaguer and Antoni Castells

Dewdney A, Cunningham D, Tabernero J *et al.* Multicenter randomized Phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and pre-operative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J. Clin. Oncol.* 30(14), 1620–1627 (2012).

Treatment of locally advanced rectal cancer has remained largely unchanged following the pivotal German rectal trial [1], which established neoadjuvant chemoradiation therapy as the standard of care prior to surgical resection. Investigators have since attempted to evaluate the radiosensitizing properties of oxaliplatin as well as the biological agents. Chau *et al.* have previously published their results of intense neoadjuvant chemotherapy (oxaliplatin plus capecitabine [XELOX; Xeloda®]) prior to total mesorectal excision (TME) in a high-risk rectal population (EXPERT trial) noting a promising 3-year relapse-free survival of 74% [2]. The EXPERT-C trial is an extension of this original concept. High-risk rectal cancer was defined by high-resolution thin slice MRI (3 mm): tumor <1 mm of mesorectal fascia, T3 tumor at or below the levators, extramural extension ≥4 mm, T4 tumor, or presence of extramural venous invasion. Patients (n = 165) were randomized to: XELOX (four cycles) followed by concurrent chemoradiation therapy (with capecitabine), followed by TME and adjuvant XELOX (four cycles);

or to XELOX (four cycles) plus weekly cetuximab followed by concurrent chemoradiation therapy (with capecitabine plus cetuximab), followed by TME and adjuvant XELOX (four cycles) plus cetuximab. The primary end point was complete response. The study was amended specifically for *KRAS* wild-type/*BRAF* wild-type tumors. However, the use of cetuximab failed to establish a difference in complete response ($p = 1.0$), but did result in an improved response rate ($p = 0.028$) and overall survival (hazard ratio: 0.27; $p = 0.034$). Nonetheless, the benefit of oxaliplatin and cetuximab in the treatment of locally advanced rectal cancer is of questionable value.

– Written by Cathy Eng

References

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- 2 Chua YJ, Barbachano Y, Cunningham D *et al.* Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a Phase 2 trial. *Lancet Oncol.* 11(3), 241–248 (2010).

Bannas P, Weber C, Adam G *et al.* Contrast-enhanced [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography for staging and radiotherapy planning in patients with anal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 81, 445–451 (2011).

Since the development of chemoradiation in the 1970s, the staging of anal cancer has moved to nonsurgical methods. Imaging techniques such as rectal ultrasound, computed tomography, MRI, PET, and most recently, PET/CT are available to help with nonsurgical staging. Accurate imaging and staging is central to successful radiation field design and treatment. Compared with these imaging modalities, does the use of combined PET/CT increase the accuracy of staging and radiation field treatment planning?

Bannas and colleagues from University Hospital Hamburg-Eppendorf, Germany,

report a retrospective analysis of 22 consecutive patients with a variety of stages of squamous cell cancer of the anus treated with conventional chemoradiation. The goal of the study was to determine the benefit of ^{18}F -FDG-PET/CT in both staging and radiation treatment planning for anal cancer. Patients underwent a complete workup including history and physical, endorectal ultrasound and anal biopsy.

Patients then underwent radiation treatment planning based on clinical presentation and individual PET and CT images were independently evaluated for their identification of the local tumor (primary and lymph nodes) and distant metastasis. The CT- and PET-based stage and proposed radiation treatment plans were compared with the PET/CT-based stage and radiation treatment plan. This allowed a direct comparison of the clinical impact of the three imaging modalities: CT, PET and combined CT/PET.

Overall, compared with either CT or PET alone, the PET/CT upstaged two patients and downstaged four patients. The key finding was that PET/CT resulted in changes in the radiation field treatment design in 23% of the patients when compared with either CT or PET alone.

The data suggest that in patients being treated with chemoradiation for squamous cell cancer of the anus, PET/CT is superior to either CT or PET alone for staging and results in a change in field design in approximately a quarter of patients. This has implications for the design of accurate radiation fields. The preliminary results are interesting and should be examined in a larger cohort of patients.

– Written by Bruce Minsky

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