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Getting Knit-PI3Ky: PIK3CA Mutation Status to Direct Multimodality Therapy?

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Abstract

There is high morbidity associated with local recurrence of rectal cancer. However, the adjuvant therapies given to prevent such recurrences also have significant side effects and associated risks. The ability to select patients with the highest risk of recurrence and greatest therapeutic response will improve rectal cancer care.

In this issue of *Clinical Cancer Research*, He and colleagues present a retrospective mutational analysis on tumors from a well-characterized cohort of stage I-III rectal cancer patients (1). Their investigation presents the prevalence of the common KRAS, PIK3CA, and BRAF oncogenic mutations in rectal cancer, a cancer often grouped with colon cancers in molecular analyses. Furthermore they identify an association of PIK3CA mutations with local disease recurrence, a clinically significant outcome in patients after surgery.

These results are a timely contribution to the goal of using molecular profiles to personalize cancer care. The hope is to characterize molecular details of individual tumors for both prognostic and predictive means, allowing providers to further optimize treatment regimens. The ability to predict benefit from therapy is important both to patients whose tumor would be responsive to treatment (and should be offered that therapy) and, equally importantly, to those whose tumor would not be affected by the treatment (and thus should either be treated with an alternative option or forego therapy). Inherent to cancer therapy are unwanted side effects and long-term health risks; protecting the subset of patients with a low chance of response from treatment effects is clinically meaningful.

Early stage rectal cancer is a prime example in which individualized cancer medicine would be beneficial. The prognosis for rectal cancer, including likelihood of local recurrence, distance recurrence, and mortality, is dependent on the stage of disease at diagnosis. Eighty percent of patients will present with nonmetastatic disease (stage I-III) and are candidates for curative-intent therapy. Surgery alone can be curative in more than 90% of patients with stage I disease but less than 50% in most subgroups of stage III disease. Given the high recurrence rate with surgery alone, adjuvant therapy for resected stage II and III cancers has

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Disclosure of Potential Conflicts of Interest

L. Cantley has been a consultant for GSK, Amgen, Merck, Exelixis, Genentech, Novartis, Biogen, BMS, and Millennium.

been formally recommended since the 1990 National Institutes of Health (NIH) Consensus panel (2). The optimal combination and timing of these treatments continues to be actively investigated, but is typically a combination of chemotherapy and radiation.

With additional treatments, prognosis has been improved, but disease recurrence (both local and distant) and treatment toxicities remain a clinical challenge. In distinction from colon cancer, local recurrences are a critical issue in rectal cancer. The bony constraints of the pelvis limit surgical access to the rectum, leading to a lower likelihood of achieving negative margins. Total mesorectal excision (TME), in which the rectum with its surrounding perirectal fat and lymph nodes is removed as a single specimen, has become accepted as the standard surgical technique in rectal cancer resection. In a study conducted by the Dutch Colorectal Cancer Group (the source of the samples for He and colleague's article), the local recurrence rate 2 years after TME was 8%, less than historically reported rates (3). However, an 8% local recurrence rate is substantial given the morbidity of such an event, including significant pain and bowel dysfunction. Trials of radiation have shown improvements in local recurrence rates over surgery alone (2–6). The downside of radiation therapy includes acute toxicities of fatigue, diarrhea, and local irritation, and long-term side effects, which may include incontinence, sexual dysfunction, secondary malignancies, and radiation enteritis. Distant recurrences affect the survival of rectal cancer patients. As in local recurrences, the likelihood of a recurrence in the liver, lung, distant lymph nodes, and other sites is most closely associated with the stage of disease at diagnosis. For patients whose tumor penetrates through the muscle layer of the rectum or with involvement of local lymph nodes, the addition of chemotherapy perioperatively (concurrent with radiation and for additional cycles alone) improves disease-free and overall survival (7).

It is worthwhile to examine how these treatments, devised from studying large populations, affect individual care. Patients with advanced stage III disease have a risk of recurrence of around 50%. By treating this group as a whole, the risk is reduced to around 25% (7). This 25% absolute rate reduction can be converted into the number needed to treat. In this scenario, for every four patients treated, one patient will benefit from the treatment. Further, these statistics also imply that two of the four patients will receive therapy and will not need it (they were cured with surgery alone), and one of the four patients will undergo the toxicities of therapy and still develop recurrent disease. These numeric exercises illustrate that the ability to identify patients with (1) the highest rate of recurrence and (2) the highest rate of response to therapy will allow us to optimally target therapy.

In their study, He and colleagues identified PIK3CA mutation as a prognostic marker for local recurrence in rectal cancer. Though this prognostic factor did not translate to distant or overall recurrence, as described above, local recurrences and the resulting morbidity are clinically significant. Their results will need corroboration within other cohorts of rectal cancer patients. If consistently confirmed, mutational analysis of PIK3CA could help ascertain risk of local recurrence.

Importantly, this study was isolated to patients who did not receive adjuvant therapy. As such, they were not poised to address whether PIK3CA mutation is predictive for therapy response. Analysis of the treatment arm of the Dutch TME study, reportedly in progress, should reveal the effect of PIK3CA mutation on radiation response. If an interaction between PIK3CA mutations and short course preoperative radiation is shown, testing for these mutations may aid in treatment decisions for some patients. Because PIK3CA mutations do not predict distant recurrences, the decision to offer chemotherapy would still be dependent on disease stage. However, the use of radiation (which only impacts local recurrences) potentially could be individualized.

Ideally, larger cohorts that allow subset analyses by stage should be tested. Such analyses may show that stage I patients, who are not currently considered for any neoadjuvant or adjuvant therapy, with PIK3CA mutations should be offered radiation. Alternatively, potentially subgroups of stage II or III rectal cancer patients who currently receive perioperative radiation could be spared radiation toxicity if their tumor lacked PIK3CA mutation. More helpful would be a panel of molecular markers that could truly fine tune the use or withholding of perioperative treatment. Additional genetic material has been stored from these tumors suggesting that we can look forward to additional molecular studies from this cohort.

Though not addressed in this study, KRAS, PIK3CA, and BRAF mutations and their predictive effect on response to molecular targeted therapy continue to be actively investigated. Epidermal growth factor receptor (EGFR) inhibitors are now excluded from the treatment regimens of patients with KRAS mutations (8). The effect of BRAF and PIK3CA on EGFR inhibitor's response remains inconclusive. Drugs targeted to PI3K are now entering phase II trials (9), and a drug targeted to BRAF is in phase I trials (10). The clinical effect of these drugs, both on the patient population as a whole and in molecularly characterized subsets, will be of both clinical and biologic interest (Fig. 1).

This investigation highlights an important area of clinical cancer care: how to optimize patient selection for aggressive therapy. Advances in other fields suggest that there is reason to expect progress. Patients with early stage breast cancer are now routinely categorized molecularly for prognosis and chemotherapy response (11). With continued studies such as this, we can treat rectal cancer more effectively, more safely, and with fewer untoward side effects.

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Fig. 1.

A schematic of receptor tyrosine kinase (RTK) activation of the PI3K and RAS-ERK pathways. The molecules in red demarcate the targets of drugs in early stage clinical trials. Studies in the preclinical arena suggest that single agent treatment with targeted drugs may be of utility in small genetic subsets. However, because of redundancy, negative feedback loops, and the genetic complexity of most tumors, these drugs may need to be used in combinations for their ultimate clinical success (9).