Adjuvant Chemotherapy for Stage II Colon Cancer: The Debate Goes On

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At the time of initial diagnosis, stage II colorectal cancer (CRC) accounts for approximately 25% of all CRC cases. In general, stage II disease is associated with a good prognosis with 5-year overall survival (OS) above 80%. The United Kingdom QUASAR (Quick and Simple and Reliable) trial and several pooled analyses have documented a small but significant survival benefit of fluorouracil-based adjuvant systemic chemotherapy in patients with stage II disease.[1-3] Although oxaliplatin-containing regimens have a significant survival benefit in stage III CRC, they play only a limited role in stage II CRC. In particular, a subgroup of stage II patients with high-risk clinical features derive a significant survival benefit from oxaliplatin-containing adjuvant chemotherapy.

In this issue of *Journal of Oncology Practice*, Kannarkatt and colleagues[4] provide a succinct review of the current status of clinical and biological markers that have been used in treatment decision-making processes for adjuvant chemotherapy for stage II CRC. Stage II CRC is a heterogeneous group of cancers with different biology, and significant research efforts have focused on defining the key clinical and/or biological features that can identify the subgroup of stage II patients with an increased risk of cancer recurrence after curative surgical resection. Additional studies have focused on developing biomarkers to identify the group of patients who would benefit most from adjuvant chemotherapy. Several expert panels, including ASCO and European Society of Medical Oncology, have identified a set of high-risk clinical features that support the role of adjuvant chemotherapy with an oxaliplatin-containing regimen for stage II CRC, including T4 primary tumors, poorly differentiated tumors, perforation and/or obstruction, lymphovascular invasion, perineural invasion, and less than 12 lymph nodes in the surgical resection specimen.

Over the past 10 to 15 years, several prognostic biomarkers, including gene expression profiling, have been developed as a prognostic tool for stage II CRC. The two most widely used assays are the Oncotype DX and ColoPrint gene profiling assays. Although both gene assays can identify the subset of stage II patients with increased risk of disease recurrence, they seem to have only a limited role in predicting the specific type of adjuvant chemotherapy to be offered to patients as well as the true benefit of adjuvant chemotherapy.

The review by Kannarkatt et al[4] highlights the recent development of using circulating tumor DNA (ctDNA) as a biomarker for disease recurrence. Without question, ctDNA should be viewed as a promising biomarker for risk stratification of stage II CRC, which is independent of known clinical high-risk features. A recent report by Tie et al[5] showed that ctDNA was able to detect the presence of minimal residual disease after surgical resection in patients with stage II CRC. Moreover, patients with detectable ctDNA after surgery had disease recurrence in 79% of cases whereas those without detectable ctDNA had recurrence in only 9.8%. These results are quite promising and now need to be validated in larger clinical trials.

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The potential advantage of ctDNA in peripheral blood is that this represents a relatively noninvasive approach for determining disease recurrence in real time and risk of disease recurrence. However, the main limitation of ctDNA is that it cannot be used as a true predictive biomarker to identify the specific type of adjuvant chemotherapy that can be administered to an individual patient with stage II disease.

One important aspect that was missed in the Kannarkatt review related to the growing importance of the immune score (also known as Immunoscore) as a prognostic factor in CRC. Pagès et al[6] reported that stage I or II CRC with high densities of $CD45RO^+$ and $CD8^+$ cells in tumor regions (central tumor/invasive margin) had a 5-year OS of 86.2%, whereas those with low densities of these same immune cells had a 5-year OS of 27.5% (all $P < .0001$), showing that the immune score is prognostic in early-stage CRC independent of high-risk clinical features.[6] More recently, Galon et al[7] provided interesting data at the ASCO 2016 annual meeting, which validated the Immunoscore as an important prognostic marker in stage I, II, and III CRC from a worldwide consortium-based analysis of 1,336 patients with CRC. Impressively, the Immunoscore was able to predict disease-free survival and OS in patients with stage II CRC and was also able to identify a subgroup of high-risk stage II patients as the time to treatment recurrence was significantly reduced in patients with a low Immunoscore compared with those who had a high Immunoscore. Perhaps of even greater relevance is the potential for the Immunoscore to be used in the future to predict the subset of stage II patients who might be responsive to immunotherapies.

In conclusion, the debate continues on how to best approach patients with stage II CRC. Several well-characterized clinicopathologic features have identified the subset of high-risk stage II patients who benefit from more aggressive oxaliplatin-based adjuvant chemotherapy. However, in the larger majority of patients with average-risk disease, intense efforts have focused on developing a wide range of molecular biomarkers to help in the decision-making process regarding who should receive adjuvant chemotherapy. Unfortunately, although nearly all of the biomarkers identified to date can serve as prognostic factors for identifying stage II patients at increased risk of disease recurrence, none can be used to accurately predict whether they would truly benefit from adjuvant chemotherapy, let alone identify the specific type of adjuvant therapy. In this regard, the Immunoscore is an interesting and attractive biomarker because it provides important prognostic information that is independent of classic TNM staging. Moreover, the presence of a high Immunoscore may identify patients who would benefit most from adjuvant immunotherapy. In this regard, patients with microsatellite instability (MSI) –high stage II disease may also benefit from adjuvant immunotherapy if one were to extend the positive results of the anti–programmed cell death protein 1 antibody pembrolizumab in the treatment of MSI-high metastatic CRC.[8] Clearly, adjuvant clinical trials with specific immunotherapy agents alone or in combination with chemotherapy need to be conducted to confirm the potential predictive nature of the Immunoscore biomarker. It is conceivable that Immunoscore, MSI status, and/or the two markers combined may represent important predictive biomarkers for immunotherapy, and we eagerly await the results of future adjuvant clinical trials that incorporate immunotherapy-based agents. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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