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New Insights into the Adjuvant Treatment of Stage II Colon Cancer

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Introduction

New cases of Colorectal Cancer (CC) in the United States are estimated to exceed 106,000 in 2022, which represents approximately 10% of all tumors [1], with more than one-third diagnosed at a localized stage [2]. Stage II disease generally has a favorable prognosis, with a 5-year Disease-Free Survival (DFS) between 68% and 83% with surgery alone [3]. However, a subgroup of stage II patients has a high risk of recurrence and a relapse rate of 40% to 50%; this overlaps with stage III prognosis, and Adjuvant Treatment (ACT) is recommended [4,5]. Usually, these subgroups are represented by T4 tumors, tumors with <12 nodes sampled, occluded or perforated tumors, Lymphovascular Invasion (LVI), tumor budding and poorly/undifferentiated (G3) tumors [6]. The simultaneous presence of one or more of these risk factors results in an increased probability of recurrence. This was shown by an exploratory analysis of IDEA data, in which the 5-year DFS was 74.8% for stage II patients (pts) with two or more risk factors compared with 87.3% with one risk factor [7]. However, efforts are continuing to find other relevant factors that can more accurately identify stage II tumors at high risk of recurrence and therefore in need of ACT. Finally, an outstanding question is how long ACT should last (3 *vs.* 6 months) among these stage II tumors requiring ACT, which truly need oxaliplatin-containing regimens and exclusive fluoropyrimidines. Overall Survival (OS) improves significantly with ACT if any of the risk factors are present. In contrast, it is rarely administered in low-risk stage II tumors [8]. Recently, the American Society of Clinical Oncology (ASCO) updated its guidelines on "Adjuvant Therapy in Stage II Colon Cancer", addressing important new issues, such as emerging evidence regarding dMMR/MSI-H and circulating tumor DNA (ctDNA) [9]. Based on this update, we aim to review the most recent findings in the literature on this topic.

Pathological risk factors

Using traditional clinical and pathological risk factors, Cadham et al. [10] recently designed a new Prognostic Index (PI), which identified three risk groups in stage II CC who did not receive ACT and with 5-year rates without relapse of 88%, 80%, and 51% for low-, intermediate-, and high-risk patients, respectively. However, multivariate analyses identified LVI (yes *vs.* no), Tumor (T) stage (T4 *vs.* T3), tumor location (ascending or transverse *vs.* descending), margin status (positive *vs.* negative), and histology (signet ring cell or mucinous *vs.* classic adenocarcinoma) as high-risk factors in determining time to relapse and evaluated the benefit of ACT on the 5-year outcomes. For pts who received ACT, the 5-year rate without relapse was 85%, 85%, and 68% for low-, intermediate-, and high-risk patients, respectively [10].

Molecular biology

The ASCO Update also addressed whether there is any benefit of ACT for tumors with dMMR (MSI) *vs.* pMMR (MSS). The evidence remains too controversial to recommend ACT only on the basis of microsatellite status; therefore, the ASCO recommendations are against ACT in dMMR or MSI pts and urge physicians to consider ACT in pMMR or MSS only if high-risk factors are present [9,11]. These conclusions were confirmed by univariate and multivariate retrospective analyses performed by Mohamed et al. on 2293 stage II CC pts who had dMMR or MSI. In particular, high-risk features were prognostic in this subgroup of pts, and ACT improved OS specifically in patients >65 years of age and with concomitant high-risk features [12]. Recently, Oneda et al. [13] suggested ACT with oxaliplatin plus Capecitabine (CAPOX) for 3 months in stage II MSI with additional high-risk factor CC pts. Insight toward better management of stage II CC pts comes from an interesting study that proposed the identification of a 3-gene signature (MKQ signature) for predicting prognosis based on microsatellite status. Although MSI-H is usually regarded as a protective factor in early CC, Huang et al. [14] found three genes, MSMB, KRT23 and QPRT that were related to DFS. This signature could place stage II MSI-H pts into subgroups of high and low

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risk of relapse. Of note, different MKQ signatures were found to be associated with different immune cell infiltration of tumors.

Considering the number of sampled nodes and using data from SEER (Surveillance, Epidemiology and End Results) on 80,296 stage II/III CC pts, Wu et al. [15] reemphasized the negative impact of an inadequate number of examined lymph nodes on OS in stage II CC pts. Specifically, pts considered N0 stage with <8 lymph nodes examined would have a worse prognosis than N1 stage pts.

ctDNA is considered a prognostic biomarker of recurrence in resected CC. Tie et al. [16] first published an observational study on 230 pts and demonstrated that ctDNA had prognostic value with regard to recurrence and metastases in early CC. Moreover, the recurrence-free survival in positive ctDNA pts not treated with ACT was zero. Further studies are warranted, and we are waiting for the results of the CIRCULATE trial that aimed to prospectively evaluate ctDNA-guided ACT in stage II CC pts [17].

Immunoscore and microenvironment

The importance of the microenvironment in influencing the aggressiveness of a T is well known. The Immunoscore (IS) measures the host immune response at the T site, quantifying CD3+ and CD8+ TILs at the invasive margin and T core [18]. Several retrospective analyses have demonstrated that the immune microenvironment assessed by IS is a strong predictor of the risk of relapse [19]. However, this score is rarely used in clinical practice [20]. Recently, the European Society of Medical Oncology (ESMO) guidelines have recommended that IS be considered, along with TNM staging and risk factors, in decision-making for some pts with early-stage CC [3].

Discussion

The best management of stage II CC remains controversial. In addition to the traditional risk factors that are associated with an increased risk of recurrence, new outcome indicators have recently emerged that may help oncologists choose the best postoperative approach. These indicators relate to tumor characteristics as well as those of the microenvironment. The most promising seem to be microsatellite status and ctDNA. Unfortunately, to date, definitive results are lacking, but the most recent guidelines suggest the importance of considering these new factors when deciding whether to administer ACT. Some limitations of these findings are that almost all data came from retrospective studies and that results are still difficult to reproduce on a large scale.

Conclusion

The selection of appropriate stage II CC pts for ACT remains a challenge. New indicators are emerging, and further prospective studies are warranted to define the best post surgery approach.

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