CLINICOPATHOLOGICAL FEATURES ASSOCIATED WITH THE HIGH RISK OF RECURRENCE OF STAGE II COLORECTAL CANCER: VARIABILITY AMONG GUIDELINES AND STUDIES, AND POTENTIAL IMPLICATIONS FOR MARKET ACCESS

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BACKGROUND

- Colorectal cancer (CRC) is the third most common cancer globally, with over 1.9 million cases diagnosed in 2022. The disease burden is expected to increase by 70.5% and reach 3.2 million cases by 2045 [1,2].
- Despite advancements in screening and treatment, patient prognosis remains highly variable, highlighting the need for better prognostic markers and personalized therapies [3].
- For stages 0-III CRC, curative surgery is the standard of care, with post-surgery risk assessments guiding adjuvant chemotherapy (ACT) decisions [4-6].
- While ACT is commonly recommended for stage III CRC due to the higher risk of recurrence, its role in stage II CRC remains less clear, making it a challenging area for clinicians [4-6].
- In stage II CRC, clinicopathological features, known as high-risk features (HRFs), are used to assess recurrence risk. High-risk patients face more than twice the risk of 3-year recurrence [7]. However, HRFs considerations are often subjective and have low concordance rates among individual pathologists [8]. Real-world data also suggest that the benefit of ACT is limited to patients with just two specific HRFs (T4 tumours and poorly differentiated tumours) [9].
- Clinical guidelines also highlight the importance of testing for microsatellite mismatch repair (MMR) [4-6]. Meta-analysis of 27 studies shows that patients with deficient MMR (dMMR) in stage II CRC were associated with higher overall survival and disease-free survival than those with proficient MMR (pMMR) [10].
- Despite the available methods, additional high-risk factors are being investigated to refine risk prediction, particularly when relying on clinicopathological HRFs. Emerging research suggests that circulating tumour DNA (ctDNA) could serve as a valuable biomarker for identifying high-risk stage II CRC patients who may benefit from more intensive treatment [4-6].

OBJECTIVE

- This study aimed to analyse how clinical practice guidelines use HRFs to define stage II high-risk CRC patients and to evaluate their application in ongoing research assessing the potential role of ctDNA in identifying high-risk patients.

METHODS

- A comprehensive literature search was conducted to identify key European and US guidelines regarding CRC, specifically focusing on HRFs in stage II disease. Relevant oncology society websites were searched to ensure a thorough review of current guidelines. Each guideline was systematically reviewed and compared based on criteria for defining HRFs.
- In addition to the guideline analysis, a parallel review of studies involving stage II CRC patients was performed, particularly those examining ctDNA as an additional biomarker of high-risk disease. Studies were selected based on their focus on the association between ctDNA levels and recurrence risk and their implications for treatment decisions.
- The results from both analyses were synthesised to highlight discrepancies among guidelines, and between guidelines and studies regarding consideration of HRFs. In addition, the results of the studies were analysed to assess the emerging role of ctDNA in supporting risk stratification in addition to HRFs in stage II CRC.

Table 1. High-risk factors of recurrence in stage II CRC patients according to ASCO, NCCN and ESMO guidelines.

High-risk feature	ASCO 2021 [4]	NCCN 2024 [5]	ESMO 2020 [6]
T4 tumours	YES	YES (stage IIB/IIC)	YES (including perforation)*
Lymph node sampling <12	YES	YES	YES*
Perineural invasion (PNI), lymphovascular invasion (LVI) or another invasion	YES (PNI or LVI)	YES (PNI or LVI)	YES (PNI or lymphatic invasion, or vascular invasion)**
Poorly or undifferentiated tumour grade (high grade)/histology	YES	YES	YES**
High-grade tumour budding	YES	YES	NO
Obstruction	YES (intestinal)	YES (intestinal)	YES**
Tumour perforation	YES	YES (lesions with localised perforation)	YES (associated with T4 tumour feature)*
Margins	NO	YES (lesions with localized perforation or close, indeterminate, or positive margins)	NO
High preoperative CEA levels (>5 ng/ml)	NO	NO	YES**

Abbreviations: CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.
** Major prognostic parameters for stage II risk assessment.*
*** Minor prognostic parameters for stage II risk assessment.*

RESULTS

- The European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines were analysed and demonstrated notable differences in their approach to HRFs in stage II CRC.
- The US guidelines included tumour budding and surgical margin, which were not mentioned in the European recommendations. Conversely, ESMO considered a high preoperative carcinoembryonic antigen (CEA) level an additional HRF, not included in the US documents. ESMO uniquely categorises HRFs into major and minor groups, which is not present in the US guidelines (Table 1) [4-6].
- Despite indicating specific risk factors, guidelines do not clearly define high-risk patients since each single risk factor present in a patient is sufficient to classify them as high-risk. Considering the low concordance of physicians in assessing clinicopathological risk factors and the lack of clarity about the association of risk factors with treatment benefits, defining an appropriate study population based on HRFs can become a challenge.
- Guidelines have recognised ctDNA as an emerging potential predictive factor; however, all ASCO, NCCN and ESMO have stated that there is insufficient evidence regarding its predictive value for chemotherapy to justify its routine use outside of clinical trials [4-6].

Table 2. High-risk stage II CRC definition identified in the research studies.

High-risk feature	Tie 2016 [11]	Tie 2022 [12]	Anandappa 2021 [13]	Elbaiomy 2023 [14]
pMMR	YES (plus at least one other HRF)	YES (plus at least one other HRF)	NO*	NO*
T4 tumours	YES	YES	YES	YES
Lymph node sampling <12	YES	YES	YES	NO
LVI	YES	YES	YES	YES
Poor tumour differentiation	YES	YES	YES	YES
Obstruction/ perforation	NO	YES (tumour perforation, bowel obstruction)	YES (primary tumour during the pre-operative period)	YES (obstruction, perforation)
PNI, peritoneal involvement	NO	NO	YES (PNI, peritoneal involvement)	NO

Abbreviations: HRF, high-risk feature; LVI, lymphovascular invasion; pMMR, proficient mismatch repair; PNI, perineural invasion.
** It was not included in the definition of high-risk stage II CRC but was analysed in the study concerning patient recurrence.*

- Four studies were identified (1 RCT and 3 observation cohort studies) including stage II CRC patients with postoperative ctDNA analysis. They were stratified into low and high-risk groups according to defined risk factors [11-14].
- Two studies classified high-risk group as patients with pMMR tumours and at least one of clinicopathological HRFs. While 2 other studies included only clinicopathological features in their definition [11-14].
- Differences were also observed in terms of clinicopathological factors used for high-risk group classification. One study did not include lymph node sampling, while another did not include obstruction/perforation. Only 1 of the 4 included PNI. Importantly, all studies included T4 and poor tumour differentiation, which are considered to have the greatest impact on the treatment outcome (Table 2) [11-14].
- Studies results also indicated that the prognostic impact of postoperative ctDNA status was independent of clinicopathological risk classification showing a high risk of recurrence in ctDNA-positive patients [11-14].

CONCLUSIONS

- **Until valid and unambiguous markers are available for stage II CRC, the heterogeneity in classifying patients as high-risk and the uncertainty about the impact of HRFs on treatment outcomes may pose significant challenges for the development, assessment, and global market access strategies of new products.**
- **HTA bodies and payers may question the feasibility of identifying the target population, the generalizability of study results, and the reliability of conducted indirect treatment comparisons.**
- **When targeting high-risk CRC patients and defining HRF-based inclusion criteria, variations across local guidelines and actual clinical practices should be addressed. Additional mitigation strategies could include adaptive study designs, large sample sizes with comprehensive patient data collection, and advanced statistical methods. These approaches would support more robust subgroup analyses and enable more precise adjustments for patient characteristics across diverse populations.**

REFERENCES

1. IARC. 2024. CRC Incidence.
2. IARC. 2024. CRC Projected incidence to 2045.
3. Gan T et al. Biomed Eng Comput Biol, 2024. 15, 11795972241293516.
4. Baxter N et al. J Clin Oncol, 2021. 40(8): p. 892-910.x.
5. NCCN. 2024. Version 5.2024 - August 22.
6. Argiles G et al. Ann Oncol, 2020. 31(10): p. 1291-1305.
7. Frago R et al. ANZ J Surg, 2020. 91(1-2): p. E25-E31.
8. Fotheringham S et al. Gastroenterol Rep (Oxf). 2019 Jun;7(3):151-161.
9. Li D et al. Transl Cancer Res. 2022 Apr;11(4):689-698. 4
10. Petrelli F et al. Anticancer Research, 2019, 39 (12) 6431-6441.
11. Tie J et al. Sci Transl Med, 2016. 8(346): p. 346ra92.
12. Tie J et al. N Engl J Med, 2022. 386(24): p. 2261-2272.
13. Anandappa G. J Clin Oncol, 2021. 39: p. abstr 102.
14. Elbaiomy M et al. Annals of Oncology, 2023. 34: p. S16.