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Predictive Blood Biomarkers for Neoadjuvant Chemoradiotherapy-Treated Locally Advanced Rectal Cancer

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Introduction

Treatment of locally advanced rectal cancer requires a multimodal approach that combines neoadjuvant radiotherapy or chemoradiotherapy with surgery. Predicting tumour response to CRT can help guide clinical decision making and improve patient care while avoiding unnecessary toxicity and morbidity. Circulating biomarkers have the advantage of being easily accessible and tracked over time. In recent years, biomarkers such as proteins, blood cells, and nucleic acids have been studied for their predictive value in oncology. We conducted a comprehensive literature review to summarise the status of circulating biomarkers predicting response to CRT in LARC. There were 49 publications retrieved, with 47 full-text articles, one review, and one systematic review. These studies looked at circulating markers, inflammatory biomarkers, hematologic markers, lipids, and circulating nucleic acids.

Description

Curative surgery with total mesorectal excision and en bloc removal of the mesorectal nodes is recommended by European and American medical oncology guidelines. Neo-adjuvant radiotherapy or chemo-RT is used to reduce the risk of local recurrence. For 6 weeks, CRT combines 45-50.4 Gy radiation in 25 fractions of 1.8-2 Gy with radio-sensitizing chemotherapy with capecitabin or fluorouracil. RT alone consists of 25 Gy of radiotherapy delivered in 5 fractions of 5 Gy. Surgery is performed between 1 and 12 weeks after the completion of neoadjuvant therapy. Longer waiting times have been shown to increase the likelihood of pathological complete response rather than improve local control. The best time to perform surgery is currently unknown. CRT and SCRT with delayed surgery are currently considered standard of care and interchangeable [1].

Pre-treatment is the most important time point for predicting neoadjuvant treatment effect because it can guide the clinician in selecting the best approach prior to administering any treatment. CEA is the most studied circulating marker in this context. In eight of twenty-one studies, it shows a significant association with tumour response in univariate and multivariate analyses. The most commonly used cut-off value is 5 ng/mL. Sensitivity ranges from 61.7% to 92.6% with this cut-off, and specificity ranges from 41.8% to 63%. Because of these characteristics, CEA is not a clinically relevant biomarker and is not currently used to guide clinical decisions. The detection of MGMT promoter hypermethylation in cfDNA is a second circulating biomarker associated with poor tumour response to CRT.

However, these findings are based on two small studies and should be replicated in a larger patient cohort. Other markers investigated during the pre-CRT window yielded inconclusive results, no association, or a positive association. The most recent were shown in only one study and were not replicated. Single liquid biomarkers tested after CRT before surgery are more consistently associated with tumour response. Some markers, such as ctDNA, are only related to tumour response when measured during this time period. This observation emphasises the significance of selecting the appropriate time point of analysis for each biomarker. CEA was found to have a frequent and significant association with tumour response in eight studies out of eleven. Increase in test sensitivity.

However, because neo-adjuvant CRT has already been administered, this time point is of less clinical significance. However, it could supplement clinical, radiological, and endoscopic assessments for patients on the watch and wait track. Nonetheless, because none of the studies reviewed address this topic, the true added value of these biomarkers in the watch and wait setting must be specifically studied. The authors used two different strategies to improve the predicting value of circulating biomarkers: testing at multiple time points to assess biomarker change over time and ratio or testing of multiple biomarkers. Typically, one time point before CRT and one time point before surgery are chosen for measuring change over time and ratios [2-5].

Conclusion

Although circulating biomarkers hold great promise, their inconsistency, low statistical power, and low specificity and sensibility prevent them from reliably predicting tumour response to CRT. To confirm early results, additional validation and standardisation of methods and technologies are required. Finally, a multimarker model that includes both circulating and tissue (tumour and microenvironment) biomarkers appears to hold the most promise for future clinical involvement of circulating biomarkers in LARC patients.

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Conflict of Interest

There are no conflicts of interest by author.

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