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Enhancing Prognostication in Colorectal Cancer: Insights from PROSPeCT Trial

Patients with colorectal cancer often succumb to metastatic disease, which may not be evident at diagnosis. Adjuvant chemotherapy post-surgery aims to eliminate micrometastases, but it can lead to overtreatment. Identifying patients who genuinely need adjuvant therapy depends heavily on prognosis, primarily determined by tumour and nodal stage. However, patients with the same-stage tumours can have vastly different survival rates. The emergence of neoadjuvant therapy for both colon and rectal cancer underscores the necessity for better preoperative identification of high-risk patients. Though various prognostic models for colorectal cancer exist, they are underutilised and often lack promising predictors such as imaging, genetic, and immunohistochemical biomarkers. To address this gap, a prospective multicenter trial was designed to enhance the accuracy of predicting colorectal cancer recurrence by incorporating novel imaging, genetic, and pathological markers.

Metastatic Disease Prediction in Colorectal Cancer through Multicenter Cohort Trial

PROSPeCT (Improving PRediction Of metaStatic disease in Primary coloreCTal cancer) was a prospective, multicenter cohort trial designed to enhance prediction of metastatic disease in colorectal cancer. Following good clinical practice principles, it involved 13 hospitals from November 2011 to 2016. Adult patients with confirmed or suspected primary colorectal cancer were eligible. Exclusions included certain medical conditions and non-cancer diagnoses. Participants underwent CT perfusion imaging of the primary tumour along with staging CT scans. Radiologists analysed perfusion scans using various kinetic models, while pathologists assessed tumour characteristics, including DNA mismatch repair status and expression of various proteins. Clinical management decisions were made based on standard practices, and participants were followed for 36 months or until death, with regular monitoring for disease recurrence.

Insights into Recurrence Prediction in Colorectal Cancer

The PROSPeCT trial enrolled 448 participants with colorectal cancer, of which 326 were included in the final cohort. Most participants underwent surgery, with a subset receiving adjuvant or neoadjuvant therapy. The majority had locally advanced tumours and were node-positive. Over the three-year follow-up, 81 participants experienced disease recurrence, primarily metastasis, and some developed new primaries or died. Venous invasion was associated with recurrence. CT perfusion analysis did not reveal significant differences between participants with and without recurrence. Immunohistochemical and somatic mutation analyses also did not show clear associations with recurrence. Prognostic modelling using standard TNM staging showed moderate sensitivity and specificity for predicting recurrence. Adding CT perfusion or genetic and immunohistochemical markers to the baseline clinicopathological model did not substantially improve prediction accuracy. Kaplan-Meier curves and prediction measures confirmed the limited improvement from incorporating additional markers. Overall, the promising markers studied did not enhance the prediction of colorectal cancer recurrence beyond standard clinicopathological factors.

Advancing Prognostication in Colorectal Cancer

The PROSPeCT trial aimed to advance prognostication in colorectal cancer by integrating novel biomarkers with standard clinicopathological variables. Despite the established utility of TNM staging, it's acknowledged that this approach may overlook valuable prognostic information. Multivariable prognostic models offer a promising avenue for personalised patient management but encounter challenges such as overfitting and limited generalizability. In this context, the trial validated that a clinicopathologic model outperformed TNM staging alone, demonstrating improved specificity while maintaining comparable sensitivity. This enhancement enables clinicians to navigate the delicate balance between minimising overtreatment and effectively detecting disease recurrence, with the choice of threshold influenced by patient preferences.

However, the inclusion of promising biomarkers such as CT perfusion imaging, genetic mutations, and immunohistochemical markers did not substantially augment prediction beyond the baseline clinicopathological model. This outcome underscores the complexities and pitfalls inherent in biomarker research, where initial promise may not always translate into clinically meaningful improvements.

The study underscores the imperative for rigorous methodology in biomarker investigations and underscores the necessity for comprehensive

models that encompass both clinical and biological data. While the baseline model exhibited promise, further validation within clinical settings is imperative. Moreover, the study suggests exploring additional factors like extramural vascular invasion in future research endeavours to refine prognostic models.

Despite inherent limitations, the findings provide valuable insights into the intricate landscape of prognostication in colorectal cancer and underscore the critical importance of judicious evaluation of promising biomarkers before their integration into clinical practice.

Source: **European Radiology**

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