Prognostic factors of cancer recurrence in patients with low-risk colorectal cancer after surgery

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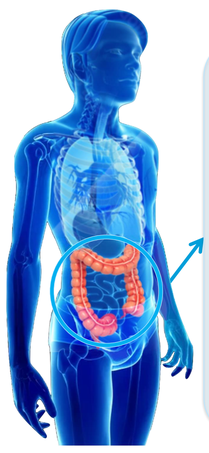
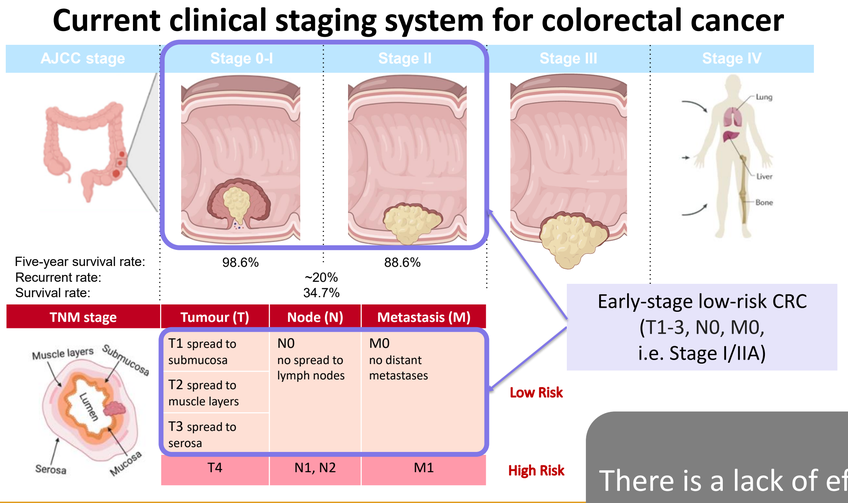
Background



- 3rd — Common cancer worldwide
- 2nd — Deadliest cancer in Australia
- 1.5k — New cases in 2023
- 46% — Diagnosed in the early stages

Current clinical staging system for colorectal cancer



Current surveillance of early-stage low-risk CRC patients is inadequate

Post-surgery management

Risk Assessment						Treatment	
Physical examination	CEA testing	CT scan	ctDNA	Oncotype DX Colon Cancer Assay	Immunoscore	Chemotherapy	Radiotherapy
American Society of Clinical Oncology Resource-Stratified Guideline			Limited sensitivity	Need further investigation and validation	Moderate accuracy	For patients at high-risk	Specific to rectal cancer

Research gap:
There is a lack of effective risk assessment tools capable of accurately predicting recurrence. This is partly due to our limited understanding of the biological mechanisms and biomarkers driving recurrence in this subgroup.

Aims

Identify clinical and molecular factors associated with recurrence by analysing postoperative outcomes from the Cabrini Monash Colorectal Neoplasia Databases (CMCND).

Method

This was a retrospective analysis of 721 patients diagnosed with adenocarcinoma (T1-T3, N0, M0), collected from the CMCND between November 1998 and October 2021, across three tertiary hospitals. Overall survival (OS) and disease-free survival (DFS) were evaluated using both complete case datasets and imputed datasets. Predictive modelling was performed using XGBoost Regression to estimate time to relapse and OS. Variable importance was assessed using both the Mean Decrease in Impurity method and Permutation Feature Importance test.

Results

Following complete case analysis, nine prognostic factors were significantly associated with CRC relapse, including Overall Staging (p<0.001 F), T Stage (p<0.001 F), Tumour Type (p=0.018 F), Lymphovascular Invasion (Yes, p<0.001 F), Mutations (p=0.011 F), Age at diagnosis (p=0.002 MW), Curability (p=0.018 F), Operative urgency (p=0.020 F), and Vasculopathy (Yes, p=0.038 F; Table 1).

Post-Imputation Analysis identified mutational burden as the strongest predictors, contributing to approximately one-third of the model performance. Age at diagnosis, lymph node involvement, were also influential. Classical staging and pathological features contributed to a lesser extent, while many demographic, treatment-related, and additional pathological variables were minimally informative (Figure 1). Permutation importance analysis reinforced the dominance of molecular markers (BRAF and RAS), alongside surgical and staging variables (Figure 2).

Table 1 | Patients profile in Disease free and Recurrence cohorts

Variables	*Disease free n= 573, 79.3% n %*	*Recurrence n= 150, 20.7% n %*	*P-value*
Age at diagnosis [Median (P25-P75)]	68.0 (61.0-76.0)	72.0 (62.0-81.0)	0.002 MW
Tumour Type			0.018 F
Adenocarcinoma	443 (77.3)	133 (88.7)	
Adenocarcinoma mucinous	62 (10.8)	9 (6.0)	
Other Tumour	3 (0.5)	1 (0.7)	
No residual	65 (11.3)	7 (4.7)	
T Stage			<0.001 F
T1	159 (27.8)	23 (15.3)	
T2	146 (25.5)	24 (16.0)	
T3	268 (46.8)	103 (68.7)	
Overall Staging			<0.001 F
1	305 (53.2)	47 (31.3)	
2	268 (46.8)	103 (68.7)	
Mutations			
IHC Results			0.011 F
Normal	162 (74.0)	67 (88.2)	
Mismatch Repair Proteins Absent	57 (26.0)	9 (11.8)	
RAS Wildtype	2 (7.1)	13 (28.3)	0.037 F
RAS Mutated	0 (0.0)	15 (32.6)	0.001 F
BRAF Wildtype	0 (0.0)	13 (28.3)	0.001 F
BRAF Mutated	6 (21.4)	2 (4.4)	0.047 F
Curability			0.018 F
Curative	565 (99.3)	146 (97.3)	
Palliative due to metastasis	0 (0.0)	2 (1.3)	
Palliative due to local invasion	0 (0.0)	1 (0.7)	
Curative-Gross resections of Stage	4 (0.7)	1 (0.7)	
Operative urgency (BM)			0.020 F
Emergency	14 (2.5)	11 (7.3)	
Urgent	18 (3.2)	6 (4.0)	
Elective	537 (94.4)	133 (88.7)	
Lymphovascular Invasion (Yes)	68 (12.0)	36 (24.0)	<0.001 F
Vasculopathy (Yes)	106 (18.5)	17 (11.3)	0.038 F

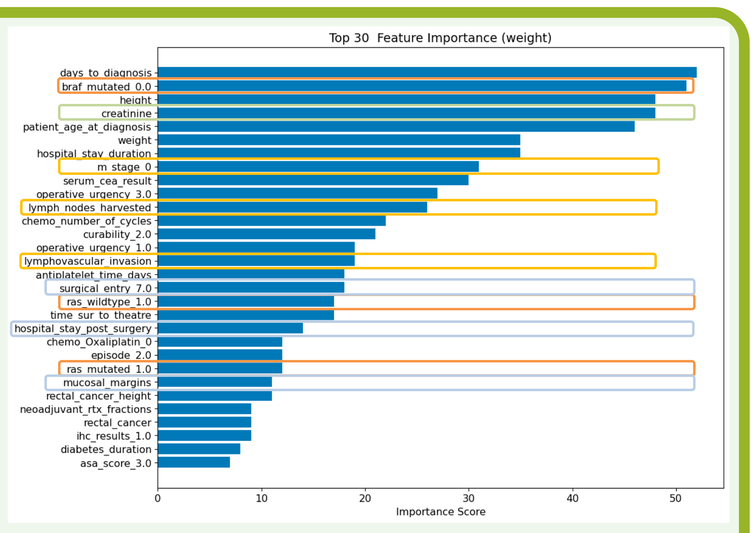


Figure 1. Feature importance plot (using the Mean Decrease in Impurity) from a XGB Regression model. Each line corresponds to one feature used in the model. The longer the bar, the more influential that feature was in the model's predictions.

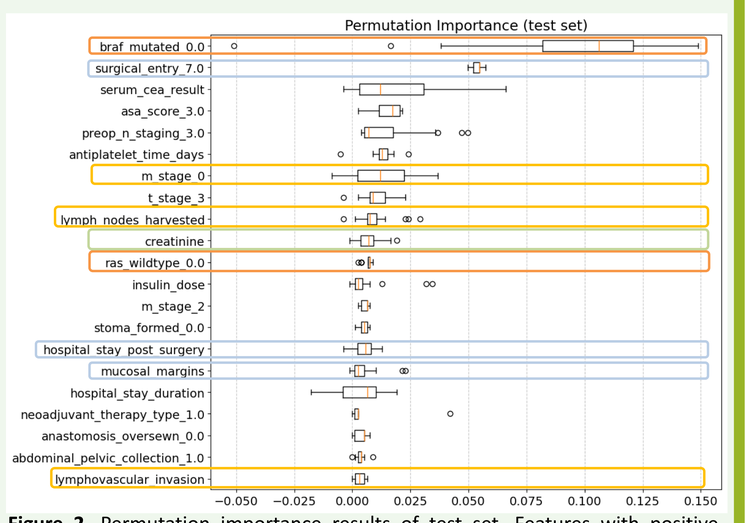


Figure 2. Permutation importance results of test set. Features with positive importance values (e.g. BRAF mutation, RAS wild-type status, surgical entry, and TNM stage) had the greatest impact on predictive accuracy, while many demographic, treatment-related, and pathological variables clustered around zero, indicating minimal contribution.

Conclusion

Machine-learning models applied to high-quality, prospectively collected clinical data can effectively identify predictors of recurrence in low-risk CRC, potentially improving postoperative surveillance strategies and personalised follow-up care.

With special thanks to the patients who generously donate their tissue

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