The survival paradox – comparing prognostic outcomes in patients with late-stage II and early-stage III colorectal cancer

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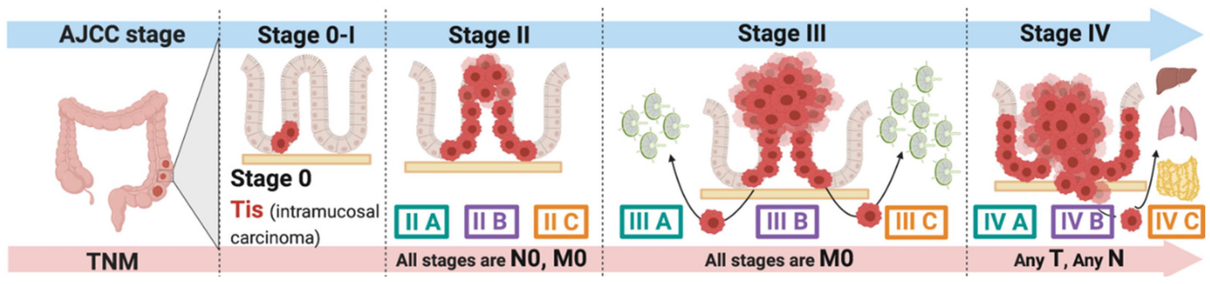
Background

In colorectal cancer staging, nodal disease is highly weighted as a poor prognostic sign, with patients classified as stage III, regardless of the level of cancer invasion into the bowel wall or surrounding structures.

While higher stage cancers are often associated with worse prognosis, with regards to colorectal cancer, there is strong evidence of a 'survival paradox' with early stage III (IIIA) patients, having significantly improved overall survival compared to late stage II (IIB/C) patients.

This paradox has been demonstrated across both colon and rectal cancer, despite significantly differing treatment strategies, specifically with the use of neoadjuvant therapy for rectal cancer.

Adjuvant chemotherapy as well as high risk factors such as lymph node yield, lymphovascular invasion and tumour grade have been suggested as reasons for this paradox, however the evidence in the literature is unclear.



Aims

To address the multifactorial nature of the paradox, we used our prospectively maintained clinical colorectal database to assess whether a survival paradox exists between stage IIB/C and IIIA patients

- Primary aims
  - Overall Survival (OS) and Relapse Free Survival (RFS)
- Secondary aims
  - 30-day mortality; Complications

Methods

Study Design
- Retrospective study of prospectively maintained colorectal neoplasia database
- Period: January 2010 – December 2023
- Centres: Cabrini Health, The Alfred

Inclusion criteria
- Adults receiving colorectal resection for proven malignancy

Exclusion criteria
- Stage I or IV colorectal cancer at diagnosis

Statistical analysis
- Univariate and multivariate Cox proportional hazard regression analysis
- Kaplan-Meier Survival analysis
- Propensity Score Matching (PSM)

Results

A total of 1933 patients were identified from the database, 100 patients with stage IIB/C and 158 patients with stage IIIA.

Demographics
- Stage IIB/C patients were older and had higher ASA scores compared to stage IIIA
- Stage IIB/C patients had significantly higher rates of emergency operations, poorly differentiated tumours and lymphovascular invasion.
- Stage IIIA patients had significantly higher rates of adjuvant chemotherapy compared to IIB/C

Outcomes
- 5-year overall survival (5-OS) was significantly worse in stage IIB/C patients compared to stage IIIA patients (p = 0.011).
- After adjusting for demographics, high risk factors, neoadjuvant therapy and adjuvant chemotherapy, 5-OS continued to be significantly worse in stage IIB/C patients (p = 0.013).
- 5-year relapse free survival (5-RFS) was also significantly worse in stage IIB/C patients compared to stage IIIA and this difference continued after adjustment (p = 0.001; p = 0.005 respectively)

Analysis
- Univariate and multivariate analysis showed significantly worse 30-day mortality, OS and RFS rates in stage IIB/C compared to IIIA.
- No significant difference was seen in complication rates.
- PSM analysis also showed that stage IIB/C patients had worse OS (ATET 3.020, p <0.001) and RFS (ATET 3.030, p <0.001) compared to stage IIIA.

Variables			Univariate		Multivariate	
	No [n (%)]	Yes [n (%)]	RR/HR (95%CI)	P-value	ARR/AHR (95%CI)	P-value
Any complications						
IIIA	126 (6.5)	32 (1.7)	Reference	---	Reference	---
IIB/C	78 (4.0)	22 (1.1)	1.086 (0.663 - 1.779)	0.742	0.857 (0.594 - 1.236)	0.408
30-day mortality						
IIIA	157 (8.1)	0 (0.0)	Reference	---	Reference	---
IIB/C	98 (5.1)	2 (0.1)	**3.012 (1.668 - 5.437)**	**<0.001**	**2.115 (1.110 - 4.028)**	**0.023**
Overall survival						
IIIA	148 (7.7)	10 (0.5)	Reference	---	Reference	---
IIB/C	80 (4.1)	20 (1.0)	**5.597 (2.309 - 13.571)**	**<0.001**	**3.430 (1.975 - 5.956)**	**<0.001**
Relapse-free survival						
IIIA	148 (7.7)	10 (0.5)	Reference	---	Reference	---
IIB/C	80 (4.1)	20 (1.0)	**5.624 (2.342 - 13.503)**	**<0.001**	**3.369 (2.012 - 5.642)**	**<0.001**

Table 1: Univariate and Multivariate analysis

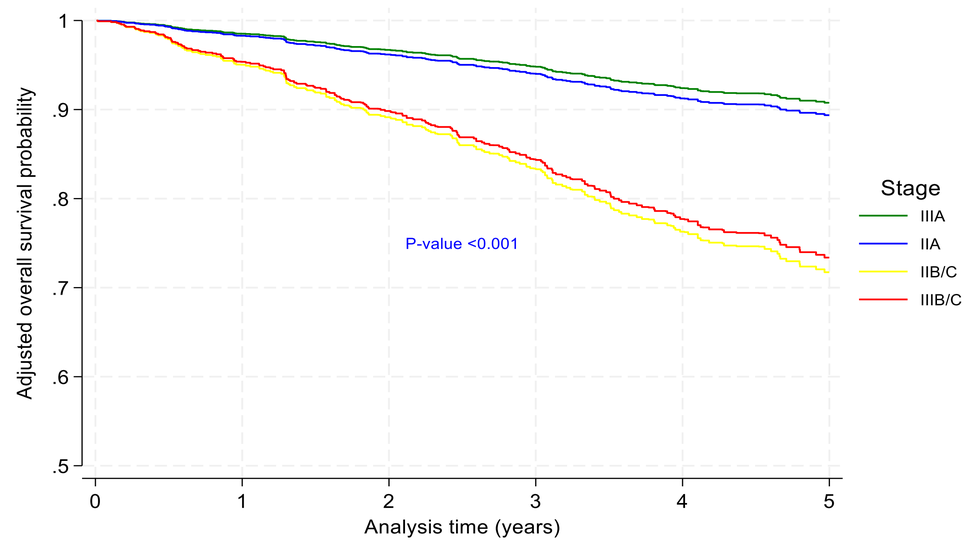


Figure 1: Adjusted overall survival across stages

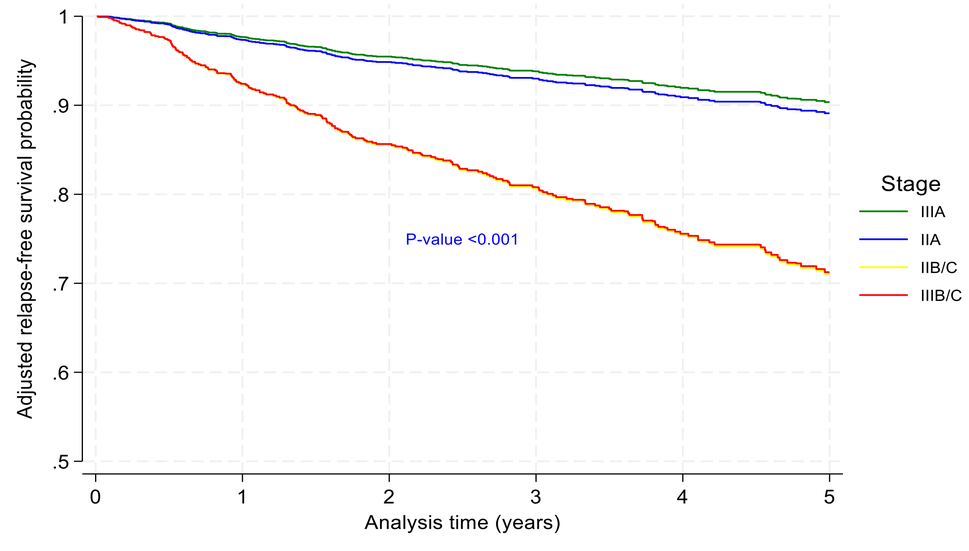


Figure 2: Adjusted relapse free survival across stages

Discussion

Why is there a difference?
- High-risk factors in colorectal cancer such as lymphovascular invasion and lymph node yield have been suggested as reasons for worse outcomes, however the literature is inconclusive on whether these factors directly contribute to this.
  - Our data, which accounted for these risk factors in the multivariate analysis, suggests that these are unlikely to impact the survival paradox in meaningful way
- The higher use of adjuvant chemotherapy in stage IIIA compared to IIB/C is also thought to play a role in improved survival.
  - Our data again accounted for this and showed that stage IIB/C cancers still have worse outcomes regardless of adjuvant treatment.
- A potential explanation for the paradox may be due to understaging of patients from unidentified micrometastases.
  - A recent study suggests that with new techniques, stage II patients may be upstaged by up to 30%
  - Upstaging of this magnitude may explain the survival paradox and may explain why stage IIB/C patients performed closer to the stage IIIB/C patients in the survival curve results.

Conclusion

The survival paradox between stage IIB/C and IIIA colorectal cancer patients persists even after accounting for high-risk factors and adjuvant chemotherapy.

Revision of the AJCC guidelines should acknowledge this, and more aggressive treatment of stage IIB/C patients may be warranted.

In addition, further investigations into micrometastasis diagnosis may be required to ensure patients are not understaged.

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