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SHORT COMMUNICATION

Time from colorectal cancer diagnosis to laparoscopic curative surgery—is there a safe window for prehabilitation?

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Abstract

Background There is a growing interest in the adoption of formal prehabilitation programmes prior to elective surgery but regulatory targets mandate prompt treatment following cancer diagnosis. We aimed to investigate if time from diagnosis to surgery is linked to short- and long-term outcomes.

Methods An exploratory analysis was performed utilising a dedicated, prospectively populated database. Inclusion criteria were biopsy-proven colorectal adenocarcinoma undergoing elective laparoscopic surgery with curative intent. Demographics, date of diagnosis and surgery was captured with patients dichotomised using 4-, 8- and 12-week time points. All patients were followed in a standardised pathway for 5 years. Overall survival was assessed with the Kaplan-Meier log-rank method.

Results Six hundred sixty-eight consecutive patients met inclusion criteria. Mean time from diagnosis to surgery was 53 days (95% CI 48.3–57.8). Identified risk factors for longer time to surgery were males (OR 1.92 [1.2–3.1], $p = 0.008$), age ≤ 65 (OR 1.9 [1.2–3], $p = 0.01$), higher ASA scores ($p = 0.01$) stoma formation (OR 6.9 [4.1–11], $p < 0.001$) and neoadjuvant treatment (OR 5.06 [3.1–8.3], $p < 0.001$). There was no association between time to surgery and BMI ($p = 0.36$), conversion (16.3%, $p = 0.5$), length of stay ($p = 0.33$) and readmission or reoperation ($p = 0.3$). No differences in five-year survival were seen in those operated within 4, 8 and 12 weeks ($p = 0.397$, $p = 0.962$ and $p = 0.611$, respectively). Multivariate analysis showed time from diagnosis to surgery was not associated with five-year overall survival (HR 0.99, $p = 0.52$).

Conclusion Time from colorectal cancer diagnosis to curative laparoscopic surgery did not impact on overall survival. This finding may allow preoperative pathway alteration without compromising safety.

Keywords Colorectal cancer · ERAS · Enhanced recovery · Prehabilitation · Optimization · Delay

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Introduction

Perioperative practices have evolved through the widespread uptake of minimally invasive techniques and enhanced recovery after surgery protocols. Despite these successes, laparoscopic colorectal resection remains associated with early co-morbidity which risks poor clinical, functional and long-term survival outcomes [1].

The concept of prehabilitation, where patients undertake physical, psychological, nutritional and lifestyle risk factor assessments to determine their baseline and identify impairments allowing targeted preoperative multimodality interventions to be carried out, aims to reduce perioperative morbidity [2, 3]. There is emerging evidence that patient optimisation can improve postoperative pain, length of stay, early morbidity and physical function following major abdominal surgery including colorectal

cancer resection [4, 5]. This is also likely to bring resource benefits to healthcare providers.

Whilst prehabilitation represents an attractive strategy, prompt cancer treatment is mandated by regulatory guidelines such as the 2007 UK NHS cancer reform strategy. The time from diagnosis to surgery can vary widely as it is subject to a large number of factors relating to both the individual patient and healthcare provider. Incorporating additional prehabilitation strategies into these timeframes can prove challenging [3].

Understandably clinicians and patients may also be concerned about the potential oncological risk that may arise from delayed treatment and may be reluctant to accept prehabilitation programmes. Presently, it is unclear if a safe window for prehabilitation exists for these patients meaning there is insufficient evidence to justify a delay in surgery [6]. The available reports on outcomes following delayed colorectal resection show conflicting results [7–9]. It is noteworthy these studies contained primarily open cases and no use of enhanced recovery protocols limiting their applicability to contemporary practice. Therefore, we aimed to investigate if time from diagnosis to curative laparoscopic colorectal surgery with enhanced recovery care is linked to long-term patient overall survival.

Methods

An observational review of a dedicated colorectal cancer patient database was performed with local research ethics and data governance committee approval.

Inclusion criteria were patients with biopsy proven colorectal adenocarcinoma undergoing elective laparoscopic surgery with curative intent between 2002 and 2015. Those with metastatic disease, unfit for resection or received open surgery, were excluded. Date of diagnosis (defined as date of multidisciplinary meeting where diagnosis was confirmed), patient demographics, date of surgery and conversion (defined as the inability to complete the dissection including the vascular ligation laparoscopically and usually, but not always, requiring an incision larger than that required to remove the specimen) was captured. Since 2002, all patients were managed within a previously described 16 element enhanced recovery programme and cared for by a specialist multi-disciplinary team [10]. No patient was intentionally delayed for any reason as our centre did not employ any formal prehabilitation programme during the study timeframe. The date of surgery offered represented the earliest time where patient choice, completion of investigations, preoperative assessments and operating room and surgeon availability were successfully met.

Postoperative data included length of stay, unplanned hospital readmission, histopathological tumour staging, 90-day mortality and five-year overall survival. The primary endpoint of this study was five-year overall survival by time from diagnosis. For this exploratory analysis, patients were dichotomised using 4-, 8- and 12-week time points. All patients entered a standard five-year clinical, radiological and endoscopic follow-up.

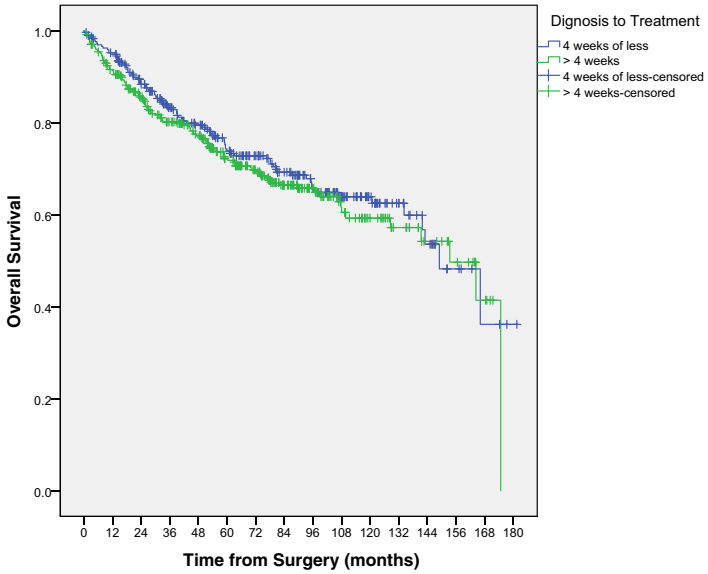
The data was analysed using SPSS (v24; SPSS Inc., Chicago, IL, USA). For categorical data, analysis included the use of cross tabulation, odds ratios and chi-squared to test the difference or association between groups. Fisher's exact test was used when indicated. The Pearson's chi-squared test of association was used to examine the relationship between each variable and outcome. The effect magnitude was quantified using the odds ratio (OR) with 95% confidence interval. A multivariate cox regression analysis was performed to investigate time for diagnosis to surgery with overall survival. Data is displayed as medians with interquartile ranges unless specified. *T* test, Mann-Whitney *U* and Kruskal-Wallis testing were used to compare medians from normal and non-normally distributed populations. The Kaplan-Meier log-rank test method was applied to compare survival curves.

Results

Six hundred sixty-eight consecutive patients met inclusion criteria and underwent laparoscopic resection with curative intent. Mean cohort age was 71 (range 25–96, SD 11), BMI 26.0 (17.1–39.6, SD 7.3), 57% males. Four hundred seven (61%) had colonic tumours (207 right, 44 transverse, 151 left or sigmoid, 5 total colectomy) with 57 (22%, 8.5% overall cohort) of the 261 rectal cancers underwent neoadjuvant chemoradiotherapy. Histopathologically defined tumour UICC stages were 0 (pathological complete response and adenomas—42, 6.3%), 1 (138, 20.7%), 2 (220, 32.9%), 3 (208, 31.1%), 4 (36, 5.4%) and unknown (24, 3.6%).

Mean time from diagnosis to surgery was 53 days (95%CI 48.3–57.8). Two hundred ninety-six (44%) patients received surgery in under 4 weeks, 537 (80.4%) within 8 weeks, 578 (86.5%) within 12 weeks. There were no difference in the distribution of tumour stages between patient groups ($p = 0.3$). Identified risk factors for longer time to surgery were males (OR 1.92 [1.2–3.1], $p = 0.008$), age ≤ 65 (OR 1.9 [1.2–3], $p = 0.01$), increased American Society of Anaesthesiologists score (ASA I mean 32 days, II 41, III 47 and IV 52, $p = 0.018$), stoma formation (OR 6.9 [4.1–11], $p < 0.001$) and neoadjuvant rectal cancer treatment (OR 5.06 [3.1–8.3], $p < 0.001$). There was no association between time to surgery and BMI ($p = 0.36$), length of stay ($p = 0.33$) and readmission or reoperation ($p = 0.3$).

Mean operative time was 213 min (95% CI 206–221). One hundred nine (16.3%) patients were converted to open surgery. Median length of stay was 7 days (IQR 5–10). Compliance with our ERAS protocol has previously been reported to be 93% (range 53–100%) for this group [10]. Ninety-day mortality was 1.9%. There were no differences in five-year survival in the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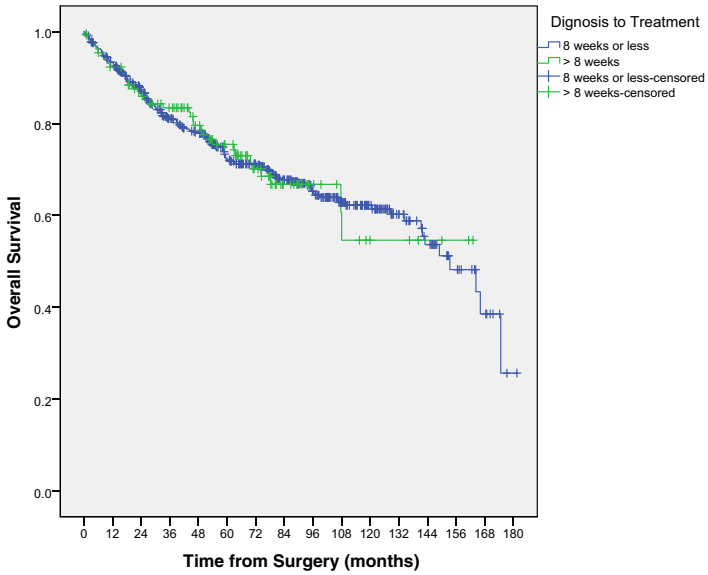
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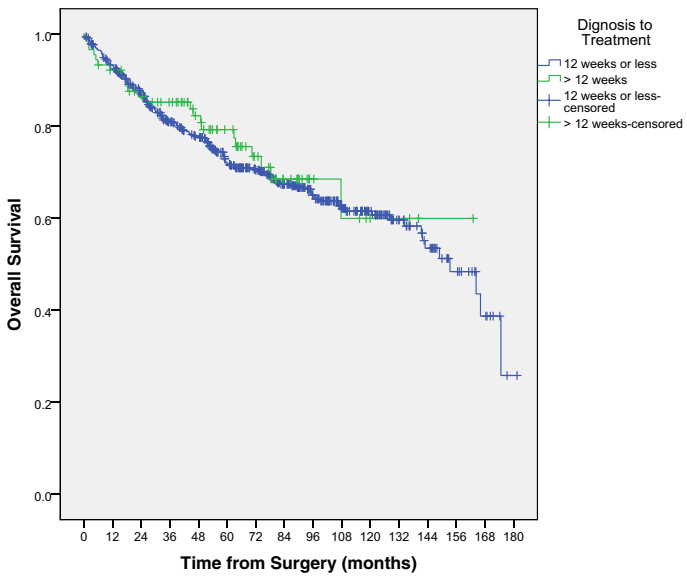
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Time from Surgery (months)

Fig. 1 Five-year overall survival displayed using 4 (**a**), 8 (**b**), and 12 (**c**) weeks from diagnosis to surgery to divide the cohort. Blue curves represent patients where the time to surgery was below each timepoint with green showing those who waited longer than each chosen timepoint. No differences in long-term overall survival was seen ($p = 0.397$, $p = 0.962$, and $p = 0.611$, respectively)

4-, 8- and 12-week diagnosis to surgery groups ($p = 0.397$, $p = 0.962$ and $p = 0.611$, respectively, Fig. 1). Cox regression modelling incorporating all variables reported above showed time from diagnosis to surgery was not associated with five-year overall survival (HR 0.99, $p = 0.52$).

Discussion

Through the alteration of the preoperative patient management, prehabilitation aims to reduce perioperative morbidity and promote rapid recovery following major surgery. Before application to oncological cases, clinicians and patients require reassurance that the potential limited extension of the time from diagnosis to curative surgery for patient optimisation does not compromise outcomes. As available reports are contradictory and contain mainly open cases [7–9], we aimed to investigate if there was an association between waiting times and long-term survival in patients that received exclusively laparoscopic surgery and enhanced recovery care which is currently advocated as best practice [11].

This exploratory analysis utilising a large, prospective, mature cohort that did not receive any formal prehabilitation interventions did not identify any difference in short- or long-term outcomes including when patients were dichotomised by 1-, 2- or 3-month periods. This suggests that, where indicated, clinical cancer pathways could safely evolve to incorporate patient optimisation and prehabilitation programmes. Patient focused perioperative medicine based upon a personalised risk stratification presents a logical care evolution rather than non-evidenced based inflexible time-based pathways [3].

Patients with higher American Society of Anaesthesiology scores were seen to have longer times to surgery which presents an opportunity to formalise their preoperative care without significantly altering our practice. Understandably, neoadjuvant rectal cancer treatment requires prolongation of the preoperative timeframe. We included these patient as chemoradiotherapy has been shown to negatively impact patient fitness as quantified with cardiopulmonary exercise testing although importantly, this deficit was rapidly restored with a preoperative structured training programme [12]. It is unclear why younger patients, who are less likely to have significant co-morbidity had longer waiting times for surgery at our institution.

Given cancer treatment regulatory guidelines and patient and clinician desire for prompt treatment, presently, there is insufficient justification to extend times from diagnosis to colorectal cancer resection outside of research settings [6]. A number of prehabilitation randomised clinical trials are now recruiting (*Prepare-ABC* ISRCTN82233115, *EMPOWER* NCT01914068, *pERAS* NCT02746731, *PHYSSURG-C* NCT02299596 and *LIPPSMAckPOP* ACTRN12613000664741). Patient-centred studies appear indicated to explore the acceptability of prehabilitation, maximise protocol compliance and explore whether a short delay in curative treatment is justified by potential recovery benefits.

This study is subject to a number of limitations. Although our pragmatic study is the first to explore time to surgery in a laparoscopic and enhanced recovery cohort, our findings should be interpreted with caution given it was not possible to control for the large number of confounding factors that could influence this result. Date of surgery can be influenced by many factors and as the decision making behind each surgical approach choice was not available, selection bias cannot be fully excluded. However, our findings are likely to generalisable to units that do not have formal prehabilitation programmes. Time to surgery and long-term survival may not represent a direct causative link. We aimed to investigate overall survival as our interventions were surgically based. Whilst both cancer-specific and disease-free survival data is of interest, this was not routinely captured in these patients and prevents direct comparison with previous reports.

Conclusion

Time from colorectal cancer diagnosis to curative laparoscopic surgery did not impact on overall survival. This finding may allow preoperative pathway alteration for patient optimisation without compromising safety.

Author contribution The project was conceived by NC, ES and NKF. Study design was led by NKF and NJC. Data acquisition was performed by NJC and NKF and managed by ES. Surgery and patient care was performed by all authors except ES. Statistical analysis and data interpretation were performed by ES and NJC. The manuscript was drafted by NJC and MA and critically revised by all authors. All authors approved the final version.

Compliance with ethical standards

Ethical approval For this retrospective study, formal approval was not required. However, initial database creation and review of already held, anonymised data was approved by our local research ethics and data governance committees.

Competing interests The authors declare that they have no competing interests.

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