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Review

The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: A systematic review☆

C. Hangaard Hansen*, M. Gögenur, M. Tvilling Madsen, I. Gögenur

Centre for Surgical Science, Department of Surgical Gastroenterology, Zealand University Hospital, Denmark

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ABSTRACT

Many countries have implemented cancer pathways with strict time limits dictating the pace of diagnostic testing and treatment. There are concerns that prehabilitation may worsen long-term oncological outcomes if surgery is delayed. We aimed to systematically review the literature investigating the association between increased time between diagnosis of colon cancer and surgical treatment, with special focus on survival outcomes.

Methods: Through a systematic search and analysis of the databases PubMed (1966–2017), EMBASE (1974–2017), CINHAL (1981–2017), and The Cochrane Library performed on June 7th, 2017, the effect of treatment delays on overall survival in colon cancer patients was reviewed. Treatment delay was defined as time from diagnosis to initiation of surgical treatment. All patients included were diagnosed with colon cancer and treated with elective curative surgery without neoadjuvant chemotherapy. This review was prospectively registered on the PROSPERO database of systematic review protocols with registration number CRD42017059774.

Results: Five observational studies including 13,514 patients were included. The treatment delay intervals ranged from 1 to ≥56 days. Four of the five studies found no association between time elapsed from diagnosis to surgery and reduced overall survival. One study found a clinically insignificant association between longer treatment delays and overall survival. Three studies investigated the effect on disease specific survival and found no negative associations.

Conclusion: The available data showed no association between treatment delay and reduced overall survival in colon cancer patients.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide. In 2014 the global incidence was estimated to be 1,360,602 cases [1]. The only curative treatment for CRC is primary surgical removal, but despite surgery, up to 30% of patients with potentially curable disease relapse [2].

Efficient diagnosis and accelerated treatment of cancer have been major research areas in the last decades. Surgical techniques, neoadjuvant, and adjuvant chemotherapy have improved postoperative mortality and morbidity significantly [3]. However, approximately one third of patients undergoing CRC surgery still suffer from postoperative complications [4].

Quality-improvement such as enhanced recovery programs (ERAS) have been implemented to decrease length of stay (LOS), complication rates and morbidity after surgery [2,4]. A novel area of research, which can be seen as a natural extension of ERAS, is preoperative optimisation also known as prehabilitation [5]. Preliminary studies show that prehabilitation programs with exercise, dietary interventions and correction of anaemia may provide additional benefits in the postoperative period leading to reduced morbidity and complications [6]. This has already been tested in e.g. cardiovascular [7], abdominal [8] and orthopaedic surgery [9] and has shown promising results regarding reduced LOS and postoperative complication rates [8]. However, a combination of patient expectations and legislation may prevent implementation in patient groups with cancer who probably would benefit most from the programs [10].

☆ **What does this paper add to the literature:** We investigated the effect of time from diagnosis to surgery in colon cancer patients to determine whether reasonable wait-time is detrimental to the patients' survival, and whether there is potential for patient optimisation preoperatively, and thereby possible improvement on postoperative results. This has to our knowledge not been done before.

* Corresponding author. Department of Surgery, Zealand University Hospital, Køge-Roskilde, Lykkebækvej 1, 4600, Køge, Denmark.
E-mail address: chhah@regionsjaelland.dk (C. Hangaard Hansen).

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From the patient perspective and a pathophysiological point of view, early diagnosis and quick treatment is rational. Many malignancies have linear or exponential growth models [10,11]. Early diagnosis means lower tumour stage, which followed by immediate treatment would be expected to lead to a better prognosis. However, the natural development of cancers should be taken into consideration. In colon cancer where the adenoma adenocarcinoma sequence [12] may take 10–15 years to develop [13] the time from diagnosis to surgery may not be instrumental.

With the implementation of cancer patient pathways (CPPs) in several countries the world over, diagnostics and treatment have sped up, however little to no research have been done investigating which psychological effects this acceleration has on the patients.

The aim of this review was to investigate studies reporting on effects of time between diagnosis of colon cancer and surgical treatment. Outcomes of interest where both based on short term and long-term outcomes.

Method

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] and was prospectively registered in the open access PROSPERO database of systematic review protocols [15] with registration number CRD42017059774.

The PICO model [14] was used for constructing the eligibility criteria and search strategy; the Patient population was adults – 18 years of age or older – who had been diagnosed with colon cancer. The Intervention was elective surgical treatment. Controls in this study was set to be “time to surgery” – short vs. long – and the Outcomes of interest were: overall survival, disease free survival, 5-year survival, postoperative complications, and recurrence. No fixed limits were set for follow-up periods. No minimum or maximum timeframe was defined as “treatment delay” or “time to surgery”, only that the period of interest should be the time from diagnosis to initiation of surgical treatment.

Thus, the inclusion criteria were that the study population should have a diagnosis of colon cancer before inclusion and that the planned surgical intervention should be elective surgery. The only exclusion criteria was planned neoadjuvant chemotherapy before elective surgery. This exclusion was chosen because neoadjuvant treatment would constitute a prolongation of time from diagnosis to surgical treatment and not serve as a meaningful comparison to no neo-adjuvant therapy studies. All study types were eligible for inclusion – no language restrictions and no restrictions regarding publication year were used in the literature search for this review.

No attempts to include ongoing studies were made. All reference lists of included studies were scanned for additional relevant studies. No separate manual search of journals or conference abstracts was performed.

A systematic search of the databases PubMed (1966–2017), EMBASE (1974–2017), CINHAL (1981–2017), and The Cochrane Library was performed on June 7th, 2017, using the following search words:

- Colon cancer OR colonic cancer OR colon neoplasms OR colorectal cancer OR cancer OR rectal cancer OR colonic neoplasms OR malignancy OR tumour OR adeno carcinoma AND elective surgery OR surgical treatment OR tumour resection OR resection OR cancer operation OR surgical intervention OR cancer resection OR colonic surgery AND “time to surgery” OR “waiting period” OR “therapeutic delay” OR “treatment delay” OR “provider delay” OR “wait-time" OR “cancer treatment delay” OR “surgery delay” OR “prehabilitation” AND perioperative outcomes OR length of stay OR postoperative complications OR disease free survival OR long term outcomes OR short term outcomes OR 5-year survival OR oncological outcomes Or survival. The search terms were adapted to each search engine – no filters were applied.

Title and abstracts were screened by two independent authors (CHH and MG) using the covidence.org data tool. Any disagreements were discussed until consensus within the author group was reached. In the full text screening, the articles were assessed for their eligibility independently by two authors. Disagreements were again discussed until consensus was reached. Reference lists were manually screened for eligible studies and relevant studies were included into the review. Finally, data extraction was performed independently by two authors (CHH and MG), using a defined extraction form. The plan was to perform a meta-analysis on the following outcomes: overall survival (OS), disease free survival (DFS), disease specific survival (DSS) or cancer specific survival (CSS), and 5-year survival, according to the *Cochrane Handbook for Systematic Reviews of Interventions*, if possible. Review Manager Version 5 would be used for this purpose.

Quality assessment of the included studies was performed by using the Down's and Black quality and bias assessment tool [16] which evaluates 27 separate items of the studies. Each assessment item was evaluated using a score of 0 or 1, with one exception where the score was 0, 1 or 2. The assessment items were further subdivided into five domains: Reporting (max 11), External validity (max 3), Internal validity – bias (max 7), Internal validity – confounding (max 6), and Power (max 1). The total score was obtained through the addition of each domain, thereby making the maximum score 28.

Results

The four predefined database searches yielded 3259 records – three additional studies were identified from other sources. After the removal of 567 duplicates, and subsequent screening of titles and abstracts, a further 2534 studies were excluded leaving 30 articles for full text evaluation. After full text evaluation according to eligibility criteria, 25 studies were excluded for the reasons listed in the PRISMA flow diagram (Fig. 1). A total of five studies were eligible for inclusion in this review [10,17–20].

The included studies were published between 2006 and 2017, and the sample size ranged from 458 to 7989 patients. Two studies were observational cohort studies, one was a population-based retrospective cohort study, another was a retrospective cohort study, and the last was a prospective observational cohort study. The five studies varied in both size and geographical origin. The smallest was a regional Danish study [10], followed by an American single centre study [19], two state wide Canadian studies (Ontario) [17,20], and one national South Korean study [18]. The characteristics of the included studies are shown in Table 1. The delay periods investigated ranged from 1 to 14 days to >60 days and were structured differently in each of the studies. The specific intervals, as well as inclusion and follow-up periods are shown in Table 2.

Four of the included studies found no association between treatment delay and reduced OS regardless of the time intervals investigated. The fifth study [17] showed a clinically insignificant association between treatment delay and reduced OS, but found no association between treatment delay and reduced DSS. On the contrary, the American study found that longer wait time resulted in better OS [19]. The 741 patients included in the study were distributed into quartiles (Q1-4) determined by the period from diagnosis to surgery. The median treatment delay for each quartile being: 8, 19, 29, and 55 days respectively, for Q1 through 4. The patients in Q4 showed a higher survival rate than Q1 even after adjustment for tumour stage. A subgroup analysis of high risk patients (tumour positive lymph nodes, metastatic disease, extramural vascular

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