

Comparison of Non-operative Versus Operative Management of Resectable Colorectal Cancer in Elderly Patients: A Systematic Review

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Protocol

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Abstract

Background: In 2010, 1.3 million Canadians were aged 80 and older. This number is expected to more than double to 3.3 million by 2036. Colorectal cancer (CRC) is the third most common cancer in both men and women, with its highest incidence rate in septu- and octogenarians. As clinicians encounter a growing number of very elderly patients (80 years and older) with resectable colorectal cancer, justifying major surgery in a comorbid population with limited life expectancy is difficult. Therefore, this study aims to systemically review the available literature to compare non-operative management to surgical resection with respect to overall survival and quality of life.

Method: A systematic review will be conducted, in accordance with the PRISMA guideline. We will search MEDLINE, EMBASE and the Cochrane Database of Controlled Trials from 2000 to 2020 with the assistance of a health information specialist and clinical expert in the field of colorectal surgery.

Discussion: The goal of this review is twofold: to synthesize the existing data on management of colorectal cancer in the very elderly patients, and identify the gap in the literature for potential future research. More specifically, we aim to streamline non-operative outcome data on resectable colorectal cancers to aid clinicians' decision making with respect to survival outcomes and quality of life. We foresee challenges with this study, for example, we expect a lack of outcome data with regards to non-operative management of resectable, as well we also envision large degrees of heterogeneity with retrospective data and suboptimal study designs. In addition, outcomes such as quality of life and change of level of care lack widely recognised assessment tools, which will render comparisons difficult. Ultimately, despite these challenges, this review will serve to synthesize the existing data and lay the groundwork for future research.

Systematic review registration: PROSPERO. Registration number: CRD42020199509

Background

In 2010, 14% of the Canadian population were senior (65 years and older), totalling 4.8 million individuals. Amongst those, 1.3 million were aged 80 and older. This number is expected to more than double to 3.3 million by 2036 according Statistics Canada. (1) Meanwhile, it is estimated that 6.25% of Canadians develop colorectal cancer (CRC) during their lifetime (2), with its incidence rising steeply from around the age of fifty to reach the highest rates in septu- and octogenarians (3). With an aging population, combined with increased incidence in the elderly, the prevalence of CRC will continue to rise in this population.

Treatment algorithms for CRC are well established in today's literature. However due to increased co-morbidity and frailty concerns, in addition to higher postoperative morbidity and mortality rates than their younger counterparts, treatment decisions in the elderly population has become more complex. (4, 5) To address this issue, the International Society of Geriatric Oncology (SIOG) 2013 task force performed an overview of recent data on epidemiology and geriatric of assessments of CRC patients. (6) As part of the

overall conclusions and recommendations, they urged the development of a separate treatment guideline for elderly patients with CRC as they identified a gap in the literature for this special population.

As clinicians encounter a growing number of very elderly patients (80 years and older) with resectable colorectal cancer, justifying major surgery in a comorbid population with limited life expectancy is difficult. In fact, there is a paucity of literature around the natural disease progression without surgical intervention to guide the treatment discussions. A limited number of small series, observational studies published in recent years compared these two treatment arms in attempt to answer this question, (7–9) with early results favouring operative management. However, these data have not been synthesized. In addition, with decreased physiologic reserve in elderly patients (10), little is known in respect to the impact of major colorectal surgery on their postoperative quality of life and functional status. Therefore, we aim to systemically review the available literature to compare non-operative management of resectable colorectal cancer to surgical resection in patients 80 years and older to assess for overall survival and quality of life.

Review Methods

This systematic review will be conducted based on a review protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO registration CRD42020199509). The protocol for this review has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P) Guidelines.(11) (Table 1, additional file 1) The aim of this study is to compare the non-operative management of resectable colorectal cancer in elderly patients to surgical resection in respect to patient survival and quality of life through a systematic review of literature including randomized control trials, prospective and retrospective cohort studies, consecutive series, and cross-sectional studies.

Study Eligibility Criteria/ Outcomes

The study selection criteria have been established according to the PICOS (Population – Intervention – Comparator- Outcomes – Study design)

- Population: Elderly population, 80 years and older, with surgically resectable (with intent to cure) colorectal cancer
- Intervention: Surgical resection with curative intent, excluding palliative procedures such as bypass or diverting stomas, including metastatic tumors provided surgery is with curative intent
- Comparison: Non-operative management/ Palliation, including patients who undergo palliative procedures (such as stenting or diverting stomas)
- Outcome:
- Primary outcome: life expectancy, survival

- Secondary outcomes: quality of life, need for future treatments (e.g palliative surgery, emergency surgery, radiation, etc.), resource utilization, change in level of care (e.g need of nursing home, etc)

Covariates thought to be associated with disease outcomes will also be collected such as tumor factors (TNM staging, location of the tumor), patient factors (comorbidities, ASA score, smoking status, functional status, etc.), treatment factors (chemotherapy, radiation therapy, type of surgical treatment, postoperative hospital stay and morbidity)

- Study designs: We will include randomized control trials, prospective and retrospective cohort studies, consecutive series, cross-sectional studies, case series. Case reports editorial letters and review articles will be excluded.

Search Strategy and Data Sources

We will search MEDLINE, EMBASE and the Cochrane Database of Controlled Trials from 2000 to April 2020 (inclusively) using a predetermined search strategy developed with the assistance of a health information specialist with expertise in systematic reviews and clinical expert in the field of colorectal surgery (R.M). The search strategy will be comprised of Medline subject headings and key words. The search strategy will be peer reviewed by a second health information specialist using the PRESS framework to ensure robust capture. (12) We will also search grey literature to include abstracts presented at relevant society meetings from the past three years and ongoing key websites (clinicaltrials.gov, etc.) to explore ongoing and upcoming studies relevant to our review.

Study Selection and Data Collection

Two authors (R.H and R. S) will complete abstract screening independently and in duplicate using Mendeley systematic review manager software. Full text screening will be completed in duplicate by two authors (R.H and R.S). To ensure consistent application of selection criteria, the two reviewers (R.H and R.S) will carry out a pilot exercise comparing their study selection. This will be done during each stage of selection, after review of the first 50 abstracts at stage 1 and the review of the 20 full texts at stage 2. All disagreements will be settled by a third party reviewer (R.M). The study selection process will be summarized in a PRISMA flow chart.

Two authors (R.H and R.S) will complete data extraction independently and in duplicate using a standardized data extraction form implemented in Excel. A pilot extraction exercise of three studies will be performed to ensure consistency in approach between reviewers. Data elements to be collected will include those related to basic publication characteristics (including year, journal, authorship list and country), study methods (including design and elements necessary for risk of bias appraisal), population studied (enrollment criteria and key demographic measures including age, gender, BMI, comorbidities, ASA, preoperative nutritional status, anemia, frailty index, smoking, TNM stage of the cancer, tumor location), intervention compared (non-operative – observation and palliative procedures, chemotherapy, radiation therapy, surgical intervention – laparoscopic or open) and outcome data (survival/ life

expectancy, quality of life, need for future treatment, change in care needs, postoperative morbidity and mortality). Binary outcomes will be collected as n(%) and continuous outcomes will be collected as mean (SD).

Risk of Bias Assessment

The Methodological Index for Non- Randomized Trials (MINORS) criteria will be used to assess the risk of bias of all included studies. (13)The MINORS criteria is a validated bias assessment tool for non randomized studies. Comparative studies are evaluated on twelve criteria (Table 2) and each item is assigned a score between 0 to 2 (0 = not reported, 1 = reported by inadequate, 2 = reported and adequate). Studies are then scored out of a global ideal of 24. Two authors (R.H and R.S) will complete risks of bias assessments using the MINORS criteria. Disagreements will be settled by a third party reviewer (R.M). Findings will be narratively summarized in the text of the final study with full assessments available in an appendix. Sensitivity analyses based upon findings from the assessments (e.g focused upon high methodologic quality studies) will be considered in the event that studies are pooled for analysis.

Data Synthesis and Statistical Analysis

The literature search for this review may identify both comparative studies and single group studies. Single group studies will be focused upon reporting experience with either operative or non-operative treatment, whereas comparative studies will be assessed and analyzed separately from the latter. If multiple comparative studies are identified that directly compared (i.e simultaneously collected and compared endpoints) curative resection to non-operative management of colorectal cancer in the elderly, whether prospective or retrospective, a meta-analysis will be performed using random-effects, inverse variance approach. For group of studies presenting single arm study data related to outcomes for either operative or conservative management, random effects meta-analyses will be performed to assess the median survival of the individual study arm, in addition to evidence of benefits and harm; narrative summaries of these findings will be prepared with the realization that comparisons based on these data are weaker based upon the nature of the data. Clinical and methodologic heterogeneity will be assessed by the research team for the set of included studies to establish their degree of similarity in terms of patient populations and study methods. Statistical heterogeneity will be assessed for meta-analyses using the I^2 statistic, with a value of 50% or higher suggesting the presence of important heterogeneity. Forest plots will be presented for all syntheses, and pooled estimates will be removed from these plots in cases where the presence of high statistical heterogeneity cannot be addressed.

Discussion

The goal of this review is two folds: synthesize the existing data on management of colorectal cancer in the very elderly patients, and identify the gap in the literature for potential future research. A systematic review published in *Lancet* in 2000 pooled 34 194 patients from 28 independent studies, reported that despite increased incidence of postoperative morbidity and mortality with advancing age, cancer specific survival showed little difference between the studied age groups (65–74, 74–84, 85+), suggesting the

likely benefit of surgical resection regardless of patients age. (14) However, most data were retrospective, with an inherent risk of selection bias. The very elderly patients chosen for surgical resection were likely result of a careful selection of physiologically fitter patients by the surgical team. This review also had no data on patients' postoperative functional status and quality of life, an important factor to be considered when offering an elderly patient surgical treatment, and it did not include any data on non-operative management for very elderly patients with curative disease.

Therefore, there is a need to gather more recent data comparing operative to non-operative management (2000 and onward), with the goal of determining the role of surgical resection in the very elderly patients with colorectal cancer. In addition to survival outcomes, this review will also focus on the impact of surgery on patient quality of life and functional outcomes. Ultimately, this review aims to streamline information to help clinicians with treatment decisions and facilitate discussions with elderly patients using evidence-based findings.

There is an expected paucity of data in this field, which the authors believe will pose certain challenges to this review. For example, we expect a lack of outcome data with regards to non-operative management of resectable disease as these patients may not require a rigorous surgical follow-up. We also envision large degrees of heterogeneity with retrospective data and suboptimal study designs. In addition, outcomes such as quality of life and change of level of care lack widely recognised assessment tools, which will render comparisons difficult. Ultimately, despite these challenges, this review will serve to synthesize the existing data and potentially help identify the gap in literature to lay the groundwork for future research.

Abbreviations

ASA score: American society of anesthesiologists

BMI: body mass index

CRC: colorectal cancer

MINORS: Methodological Index for Non- Randomized Trials

SIOG: International Society of Geriatric Oncology

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta- Analysis for Protocols

Declarations

Ethics approval and consent to participate:

N/A

Consent for publication:

N/A

Availability of data and material:

All Data generated or analyzed during this study are included in this published article and its supplementary information files

Competing interests:

The authors declare that they have no competing interests

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Authors contribution:

All authors have made substantial contributions to the conception of the work. RH and RS performed the acquisition and analysis of data. All authors contributed to draft or revise the work. All have approved the submitted version.

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Conflicts of Interest:

The authors declare that they have no conflicts of interest

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Supplementary Files

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- [Appendix.docx](#)
- [PRISMAPchecklist.docx](#)