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# Peri-operative blood transfusion for resected colon cancer: Practice patterns and outcomes in a population-based study

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ABSTRACT

*Background & objectives:* Literature suggests that peri-operative blood transfusion among patients with resected colon cancer may be associated with inferior long-term survival. The study objective was to characterize this association in our population.

*Methods:* This is a retrospective cohort study using the population-based Ontario Cancer Registry (2002–2008). Pathology reports were obtained for a 25% random sample of all cases and constituted the study population. Log binomial regression was used to identify factors associated with transfusion. Cox proportional hazards model explored the association between transfusion and cancer specific survival (CSS) and overall survival (OS).

*Results:* The study population included 7198 patients: 18% stage I, 36% stage II, 40% stage III, and 6% stage IV. Twenty-eight percent of patients were transfused. Factors independently associated with transfusion included advanced age ($p < 0.001$), female sex ($p < 0.001$), greater comorbidity ($p < 0.001$), more advanced disease ($p < 0.001$) and open surgical resection ($p < 0.001$). Transfusion was associated with inferior CSS (HR 1.51, 95% CI 1.38–1.65) and OS (HR 1.52, 95% CI 1.41–1.63), after adjusting for important confounders.

*Conclusions:* Peri-operative transfusion rates among patients with colon cancer have decreased over time. Transfusion is associated with inferior long-term CSS and OS.

## 1. Introduction

Colorectal cancer is the third most common newly diagnosed cancer in Ontario, Canada and is responsible for the second highest proportion of cancer deaths in this province [1].

Patients undergoing surgery for colon cancer are transfused frequently [2]. Population level studies appear to show large variations in the rates of transfusion by surgeon (2–59%) and institution (3–33%) [3].

Blood transfusion was noted to have immunologic effects in renal transplant patients in a number of early reports [4]. Shortly thereafter, concerns were raised regarding the potential negative association between blood transfusion and colorectal cancer survival [5]. Since these earlier publications, a number of studies have assessed the long term effects of blood transfusion on colorectal cancer survival. A Cochrane review [6] included 36 studies published over a 20 year period (1985–2001) and found that red blood cell (RBC) transfusion was associated with an increased risk of cancer recurrence. This review included a large number of studies with significant heterogeneity, limited sample size, and many of the included studies did not adjust for comorbidities, disease stage or other pathologic risk features. Most of the included publications were conducted prior to the standardization and use of modern 5-Fluorucil based chemotherapy regimens.

The objective of this paper was to describe transfusion rates among patients with resected colon cancer in routine practice, identify factors associated with transfusion and evaluate the association between transfusion and long-term survival.

## 2. Methods

### 2.1. Study design and population

This is a retrospective population-based cohort study to describe the effect of *peri*-operative red blood cell transfusion in colon cancer patients in the province of Ontario, Canada. Ontario (population 13.5 million) has a single-payer universal health care system. Patients with

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resected colon cancer were included in this study. Study dates were from 2002 − 2008. The Ontario Cancer Registry (OCR) was used to identify all incident cases of colorectal during this period. We then identified cases with primary tumour resection within 6 months of diagnosis. We identified a random sample of 25% of all surgical cases in the OCR for whom we obtained surgical pathology reports. Reports were not available for patients with surgery in 2005; as such, the study cohort was restricted to patients who had surgery in 2002–2004 and 2006–2008. The study was approved by the Research Ethics Board of Queen's University Kingston, Canada, and by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

### 2.2. Data sources

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information for greater than 98% of all incident cases of cancer in the province [7]. This registry also provides information about vital status and cause of death. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical procedures; these records are known to have a very high level of completeness for colorectal cancer surgery [8]. Provincial physician billing records from the Ontario Health Insurance Plan, treatment records from regional cancer centres and provincial records of chemotherapy delivery were used to identify chemotherapy utilization. A trained team of data abstractors reviewed the pathology reports and entered information about extent of disease into an electronic database. These datasets were linked using unique encoded identifiers and analyzed at the Institute of Clinical and Evaluative Sciences.

### 2.3. Measures and outcomes

Indicators of the socioeconomic status (SES) of the community in which patients resided at diagnosis were linked as described previously [9]. Quintiles (Q) of the median household income were based on the household income distribution for the full province of Ontario. Q1 represents the communities where the poorest 20% of the Ontario population resided. Geographic regions reflect the catchment areas for Ontario's regional cancer centres [9]. Co-morbidity was classified using the Charlson Index modified for administrative data based on all non-cancer diagnoses recorded during any hospital admission within 5 years prior to surgery [10]. Each case was assigned a surgeon volume index based on the total number of colon cancer resections performed in the 12 months prior to surgical date. The surgeons were divided into quartiles of annual hospital volume. Adjuvant chemotherapy was defined as chemotherapy initiated within 16 weeks after surgery. Our primary exposure, red blood cell transfusion, was identified through the CIHI database. This information was only available as a binary variable. We were unable to determine the number of units transfused or whether other blood products were transfused. In addition, the timing of transfusion during the admission was not known (i.e. preoperative, intraoperative, postoperative).

Overall (OS) and cancer-specific survival (CSS) were determined from date of primary tumour resection. To account for possible cause of death miscoding, CSS included death from any cancer. Complete information about vital status in the OCR was available up to December 31, 2012; cause of death was available up to December 31, 2010. The primary end-point was CSS. CSS was prioritized over OS as it was felt likely to be less vulnerable to bias from unmeasured prognostic factors.

### 2.4. Statistical analysis

Comparisons of proportions between study groups were made using the chi-square test. Survival was determined from date of surgery using the Kaplan-Meier technique and comparisons between groups were made using the log-rank test. Factors associated with transfusion were evaluated by log binomial regression. The association between patient-, disease-, and treatment-related factors with CSS and OS was evaluated using the Cox proportional hazards regression model.

The primary model included all cases; stratified analyses were subsequently conducted for each stage of disease. To control for confounding variables when exploring the association between RBC transfusion and survival, we also employed the propensity score technique in the Cox proportional hazards model. We created five propensity strata with balanced confounding variables between RBC transfusion patients and non-transfused patients. Survival of transfused patients was compared to those without transfusion within each stratum using a Cox proportional hazards model; a summary HR combining the results across quintiles was calculated [11]. Finally, we also undertook a pre-specified sensitivity analysis in which cases that died within 90 days of surgery were removed from the exploratory survival analysis. Results were considered statistically significant at p-value $< 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## 3. Results

### 3.1. Study population

Linked administrative data-sets identified 25,613 potentially eligible patients who underwent resection of primary colon cancer in 2002–2004 and 2006–2008 (Supplemental eFig. 2). Surgical pathology reports were reviewed for 7519 randomly selected cases. The age, sex, SES, co-morbidity, and survival of these randomly selected cases did not differ substantially from the 18094 unselected cases (Supplemental eTable 1 and eFig. 1). Among the 7519 randomly selected cases, 321 cases (4%) were excluded due to variant histology (56/321), rectal primary (134/321), inconsistent dates between surgical record and pathology (87/321), delivery of pre-operative chemotherapy (44/321) (Supplemental eFig. 2). Of the 7198 patients included in our study, a total of 2009 (28%) received transfusion.

Characteristics of the study population are shown in Table 1. Patients with transfusion were older (mean age 74 vs. 69), female (53% vs. 46%), and with greater co-morbidity. They were also more likely to have right-sided cancer and an open resection.

### 3.2. Transfusion in routine practice

Transfusion rate decreased substantially over the study period from 31% (259/823) in 2002 to 24% (253/1054) in 2008 ($p < 0.001$). Factors associated with transfusion are shown in Table 2. In adjusted analyses, advanced age ($p < 0.001$), female sex ($p < 0.001$), greater comorbidity ($p < 0.001$), advanced stage ($p < 0.001$) and open operation ($p < 0.001$) were associated with increased rate of transfusion (Table 2).

### 3.3. Outcomes

Short term and long term outcomes by transfusion status are shown in Table 3. This univariate analyses showed that patients who were transfused had longer length of stay, greater post-operative mortality, and inferior long-term survival.

Factors associated with long-term survival are shown in Table 4. After adjusting for important confounders, we found that RBC transfusion was associated with inferior CSS [HR 1.51 (95% CI 1.38-1.65)] and OS [HR 1.52 (95% CI 1.41–1.63)]. These results were consistent with the propensity score analysis [CSS HR 1.51 (95% CI 1.38-1.65); OS HR 1.52 (95% CI 1.41-1.63)] (Supplemental eTable 2).

We conducted a test for interaction between stage and transfusion in the original Cox model. This showed evidence of interaction in both the OS model ($p < 0.001$) and CSS model ($p = 0.015$). In an exploratory analysis, we repeated the Cox model stratified for stage of disease