# Preoperative blood management in colorectal cancer surgery: the controversial role of iron

Wilson, M.J.

# Chapter 1 // **General Introduction**

Anemia, defined by the World Health Organization as hemoglobin <8 mmol/L in males and <7.5 mmol/L in females, is highly prevalent among patients diagnosed with colorectal cancer.[1, 2] Typically, multiple factors contribute to the development of anemia in cancer patients, with iron deficiency as principal cause.[3] Iron deficiency can be induced by chronic tumor-induced blood loss, resulting in an absolute iron deficiency, and impaired iron homeostasis, caused by systemic inflammation with increased hepcidin levels and resulting in functional iron deficiency. Finally, surgery-induced blood loss further aggravates the severity of anemia.

In patients awaiting surgery, anemia is commonly observed and more and more considered as an important health problem.[4, 5] Anemia namely is found to be associated with increased postoperative morbidity and mortality, increased duration of hospitalization, and reduced quality of life.[6, 7] Regarding colorectal cancer patients, preoperative anemia is also an independent prognostic factor for impaired long-term overall and disease-free survival.[8-10] Correcting anemia, notwithstanding the fact that the observed association should not be held equivalent to causality, has therefore become of main interest, not only to improve quality of life but possibly also survival.

Blood transfusions in earlier days were the default therapy to correct such anemia. The overall goal of transfusion is to treat or prevent the deficiency in oxygen delivery to body tissues. The major benefit of blood transfusion, as compared to other treatment modalities for anemia, is a rapid increase in hemoglobin (Hb) levels. Hence, blood transfusion is the only option for patients who require immediate correction of anemia. The first blood transfusions were attempted in the 17th Century, shortly after the English physician William Harvey discovered the circulation of blood. Although successful blood transfusions between animals had been observed, when transfusion of animal blood into humans, mostly to treat psychiatric illnesses, proved fatal, a ban on transfusions was installed by the pope. It was not until 1818 when James Blundell, a British obstetrician, performed the first successful human-to-human blood transfusions for the treatment of postpartum hemorrhage. However, the undiscovered ABO blood group incompatibilities caused these blood transfusions to often show grave hemolytic transfusion reactions with severe morbidity and even mortality. Ever since, several vital discoveries, such as the ABO human blood groups by Karl Landsteiner in 1900, and the ability to anticoagulate and thus test and store blood, contributed largely to the present availability and safety of blood transfusions. Blood transfusions presently save many trauma and obstetric patients from exsanguination and enable complicated surgery and intensive hemato-oncologic treatments.

In modern transfusion medicine in developed countries, the nowadays' high level of safety in the transfusion chain, involving the entire process from donor recruitment to transfusion outcome, is evidenced by the low incidence of adverse events in the transfusion chain.[11] However, aside from this low risk for adverse events, growing evidence suggests that the correction of anemia by blood transfusion is associated with increased postoperative morbidity and mortality.[12, 13] In the

specific context of colorectal cancer surgery, the use of perioperative blood transfusion was not only found associated with increased short-term postoperative morbidity, but, importantly, also with impaired long-term overall and disease-free survival, as already demonstrated by Busch et al in 1993.[14] In a randomized controlled trial, Busch et al. demonstrated that regardless of their type (autologous or allogeneic), transfusions are associated with poor prognosis. Twenty years later, Harlaar et al. studied the long-term outcomes of this randomized controlled trial, demonstrating that the patients did not benefit from autologous as compared to standard allogeneic transfusion. On the contrary, the overall and colorectal-cancer specific survival rates were worse in the patients in the autologous group.[15] The causality of the association between blood transfusions and long-term prognosis in colorectal cancer, as well as the potential causal mechanism, is being questioned and is still a major topic of discussion.[16-18]

Red blood cell production is normally controlled by erythropoietin, a cytokine produced in the kidneys. Erythropoiesis-stimulating agents (ESAs) were therefore initially developed for the treatment of anemia in patients with chronic kidney disease. Later, in an attempt to avoid blood transfusion and eliminate the associated risks, ESAs were additionally used in cancer patients undergoing chemotherapy. ESAs indeed increased the Hb level in these patients, and, as a result, decreased the need for blood transfusions.[19, 20] However, aside from these short-term advantageous effects, thromboembolic risks were also found associated with ESA treatment.[21-24] In addition, numerous randomized studies with ESA therapy in various types of cancer have shown a decrease in overall and disease-free survival.[25-28] ESAs therefore are now contraindicated when the anticipated treatment outcome is cure. Hence, only in patients undergoing palliative treatment the use of ESAs may be considered.[29]

New approaches to optimize the preoperative hemoglobin level and thus reduce the blood transfusion requirement, however, remain of large interest and are collectively termed as patient blood management (PBM). In this regard, the effect of iron, and especially intravenous iron, is increasingly being explored.[30-32] While oral iron is the standard treatment for iron deficiency anemia since the 19th century, it also has significant disadvantages. It is known to be slow in terms of absorption rate, to potentially cause constipation, and, due to poor duodenal absorption caused by increased hepcidin production, to be largely ineffective in patients with inflammation and cancer. These side effects have led to the development of parenteral iron compounds, that indeed showed to be more effective in optimization of Hb level and to have less side effects. Presently, ferric carboxymaltose (Ferinject)[33-35] and iron isomaltoside 1000 (Monofer)[36] are most frequently used for intravenous iron administration. In the perioperative setting, the iron preparations can be administered as a single treatment of up to 1000 mg in a relatively short time, and the effect of such iron preparations is mostly studied in orthopedic and cardiac.[37-39] However, presently, also in cancer surgery perioperative intravenous iron therapy is more and more considered while anemia in cancer patients is most frequently associated with iron deficiency.[3] In the specific context of

colorectal cancer surgery, intravenous iron, as compared to oral iron, has been shown to be more effective in treating preoperative anemia and iron deficiency. However, most studies so far did not demonstrate intravenous iron to reduce the blood transfusion requirement and, more importantly, actually improve postoperative outcome.[40, 41] As a result, the advantages and use of preoperative intravenous iron remain matter of debate in colorectal cancer patients.

Whilst the short-term effects and safety of intravenous iron are increasingly reported, strikingly no data on the long-term oncological effects and safety are available. Possible long-term oncological effects of iron therapy, however, are of special interest for several reasons. First, the results of laboratory, epidemiological and animal studies have shown a crucial role of iron in promoting cancer development and cancer growth.[42-47] Second, anemia of inflammation is believed to be a potentially defense strategy of the human body to limit the growth of tumor cells.[48] Anemia of inflammation is characterized by both reduced duodenal iron uptake and the sequestration of iron into the reticuloendothelial system. As a result, there is a disturbance of iron homeostasis with subsequent limitation of the availability of iron for not only erythropoiesis, but also, and importantly, the growth of tumor cells. Third, and finally, corroborating evidence implicates that especially gastrointestinal cancer cells, likely by their original iron-absorbing nature, have an altered iron homeostasis.[49] This altered iron metabolism is characterized by increased iron import and decreased iron export proteins, resulting in enhanced proliferation.

## OUTLINE OF THE THESIS

Against the background described above, the general aim of this thesis was to evaluate the role of iron in anemic patients with solid cancer, with special attention to the long-term oncological effects of iron therapy in the preoperative setting. In this thesis, this role of iron is specifically studied in the context of colorectal cancer.

Colorectal cancer is the second most common malignancy in the Western world after non-melanoma skin cancer.[50] Patients with TNM stage I-III colorectal cancer (i.e. no distant metastases) are considered for curative treatment by surgical resection of the primary tumor.[51] Partly because of advances in surgical techniques, coupled with effective (neo)adjuvant therapy), the five-year survival rate of colorectal cancer has increased to 64%.[52] The main reason to study the role of iron in the specific context of colorectal cancer is because the effects of both anemia and blood transfusion are already extensively studied in this patient group. As anemia and blood transfusion appear to be strongly associated with adverse short and long-term outcome following surgery, the use of iron therapy has gained increased attention in this patient group.[30, 40] Specifically in colorectal cancer patients awaiting elective surgery, this has led to an increased administration of iron, and specifically intravenous iron, with the aim of optimizing patient's condition and improving the postoperative outcome.

In **Chapter 2** the long-term prognostic value of preoperative anemia in colorectal cancer patients is assessed in a systematic review and meta-analysis. In **Chapter 3** data on the prevalence and type of iron deficiency are reported. In addition, the prognostic value of iron deficiency is presented. **Chapter 4** includes a national survey among gastroenterologists, surgeons, and anesthesiologists to assess the current preoperative blood management strategies in the Netherlands, and to identify preferences of different physicians in the treatment of preoperative anemia. In **Chapter 5**, the short-term effects of preoperative intravenous iron therapy, including change in hemoglobin level and postoperative complication and blood transfusion rate, are studied. In **Chapter 6** the hypothesis that iron therapy, as treatment of anemia, may impair long-term tumor prognosis is discussed. The effect of preoperative intravenous iron therapy on long-term survival and tumor prognosis is presented in **Chapter 7. Chapter 8** presents a general discussion of the overall results together with perspectives for further research. Finally, **Chapter 9 and 10** contain the respective English and Dutch summary of the main findings in this thesis.

## REFERENCES


1. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med* 2004; 116 Suppl 7A:11S-26S.
2. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anemia in cancer patients. *Eur J Cancer* 2004; 40(15):2293-306.
3. Ludwig H, Muldur E, Endler G, et al. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. *Ann Oncol* 2013; 24(7):1886-92.
4. Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology* 2009; 110(3):574-81.
5. Butcher A, Richards T. Cornerstones of patient blood management in surgery. *Transfus Med* 2017.
6. Fowler AJ, Ahmad T, Phull MK, et al. Meta-analysis of the association between preoperative anemia and mortality after surgery. *Br J Surg* 2015; 102(11):1314-24.
7. Leichtle SW, Mouawad NJ, Lampman R, et al. Does preoperative anemia adversely affect colon and rectal surgery outcomes? *J Am Coll Surg* 2011; 212(2):187-94.
8. An MS, Yoo JH, Kim KH, et al. T4 stage and preoperative anemia as prognostic factors for the patients with colon cancer treated with adjuvant FOLFOX chemotherapy. *World J Surg Oncol* 2015; 13:64.
9. Lee H, Park HC, Park W, et al. Negative impact of pretreatment anemia on local control after neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Radiat Oncol J* 2012; 30(3):117-23.
10. van Halteren HK, Houterman S, Verheij CD, et al. Anemia prior to operation is related with poorer long-term survival in patients with operable rectal cancer. *Eur J Surg Oncol* 2004; 30(6):628-32.
11. TRIP (Transfusion and Transplantation Reactions in Patients) *Annual Report Hemovigilance*. 2015.
12. Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. *Vox Sang* 2009; 97(3):185-97.
13. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; 113(15):3406-17.
14. Busch OR, Hop WC, Hoynck van Papendrecht MA, et al. Blood transfusions and prognosis in colorectal cancer. *N Engl J* Med 1993; 328(19):1372-6.
15. Harlaar JJ, Gosselink MP, Hop WC, et al. Blood transfusions and prognosis in colorectal cancer: long-term results of a randomized controlled trial. *Ann Surg* 2012; 256(5):681-6; discussion 686-7.
16. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006(1):CD005033.
17. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. *Blood Rev* 2007; 21(6):327-48.
18. Vamvakas EC. Allogeneic blood transfusion and cancer recurrence: 20 years later. *Transfusion* 2014; 54(9):2149-53.
19. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001; 19(11):2865-74.
20. Ludwig H, Aapro M, Bokemeyer C, et al. Treatment patterns and outcomes in the management of anemia in cancer patients in Europe: findings from the Anemia Cancer Treatment (ACT) study. *Eur J Cancer* 2009; 45(9):1603-15.
21. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *Jama* 2008; 299(8):914-24.
22. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010; 102(2):301-15.
23. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to

cancer: a meta-analysis. *Cmaj* 2009; 180(11):E62-71.

24. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012; 12:CD003407.
25. Hedenus M, Adriansson M, San Miguel J, et al. Efficacy and safety of darbepoetin alfa in anemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. *Br J Haematol* 2003; 122(3):394-403.
26. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003; 362(9392):1255-60.
27. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005; 23(25):5960-72.
28. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007; 25(9):1027-32.
29. NCCN. *Cancer- and chemotherapy-induced anemia*. 2014.
30. Borstlap WA, Buskens CJ, Tytgat KM, et al. Multicentre randomized controlled trial comparing ferric(III)carboxymaltose infusion with oral iron supplementation in the treatment of preoperative anemia in colorectal cancer patients. *BMC Surg* 2015; 15:78.
31. Froessler B, Palm P, Weber I, et al. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. *Ann Surg* 2016.
32. Richards T, Clevenger B, Keidan J, et al. PREVENTT: preoperative intravenous iron to treat anemia in major surgery: study protocol for a randomised controlled trial. *Trials* 2015; 16:254.
33. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361(25):2436-48.
34. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; 103(5):1182-92.
35. Van Wyck DB, Mangione A, Morrison J, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion* 2009; 49(12):2719-28.
36. Jahn MR, Andreasen HB, Futterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm* 2011; 78(3):480-91.
37. Cuenca J, Garcia-Erce JA, Martinez F, et al. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. *Transfusion* 2006; 46(7):1112-9.
38. Investigators I, Litton E, Baker S, et al. Intravenous iron or placebo for anemia in intensive care: the IRONMAN multicentre randomized blinded trial : A randomized trial of IV iron in critical illness. *Intensive Care Med* 2016; 42(11):1715-1722.
39. Theusinger OM, Leyvraz PF, Schanz U, et al. Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits: a prospective study. *Anesthesiology* 2007; 107(6):923-7.
40. Keeler BD, Simpson JA, Ng O, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anemic patients with colorectal cancer. *Br J Surg* 2017.
41. Edwards TJ, Noble EJ, Durran A, et al. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anemic patients after colorectal cancer surgery. *Br J Surg* 2009; 96(10):1122-8.
42. Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. *Cancer Epidemiol Biomarkers Prev* 2014; 23(1):12-31.
43. Ilsley JN, Belinsky GS, Guda K, et al. Dietary iron promotes azoxymethane-induced colon tumors in mice. *Nutr Cancer* 2004; 49(2):162-9.
44. Stevens RG, Jones DY, Micozzi MS, et al. Body iron stores and the risk of cancer. *N Engl J Med* 1988; 319(16):1047-52.
45. Torti SV, Torti FM. Iron and cancer: more ore to be mined. *Nat Rev Cancer* 2013; 13(5):342-55.
46. Xue X, Shah YM. Intestinal iron homeostasis and colon tumorigenesis. *Nutrients* 2013; 5(7):2333-51.
47. Zhang C, Zhang F. Iron homeostasis and tumorigenesis: molecular mechanisms and therapeutic opportunities. *Protein Cell* 2015; 6(2):88-100.

48. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352(10):1011-23.

49. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144(5):646-74.

50. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017; 67(3):177-193.

51. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. *Cancer* 1997; 80(9):1803-4.

52. Edge S, Byrd, DR, Compton, CC, et al. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th edition. Vol. 7th edtion. *New York: Springer*, 2010.