Improving the management of colorectal neoplasms in clinical practice

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INTRODUCTION

CHAPTER 1

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent cancers in the Western world, with an incidence of 12,000 and annual mortality rate of 5,000 in the Netherlands.[1] Forty-five percent of symptomatic patients have metastatic disease.[2]

The overall prevalence of adenoma in an asymptomatic population is 25-30% at the age of 50 years and approximately two-thirds of all colonic polyps are adenomatous.[3] Around 95% of CRCs evolve from an adenomatous polyp or sessile serrated lesion (SSL). However, despite its dysplastic character, only 5% of all adenomatous polyps progress to CRC.[3-8]

To reduce both the incidence and mortality rate of CRC, the Dutch Minister of Health, Welfare and Sport (VWS) decided to implement a national bowel screening program in January 2014.[1,9] Individuals aged between 55 and 75 years are now offered biennial colorectal testing using an immuno-faecal occult blood test (I-FOBT) and participants with a positive I-FOBT are referred for colonoscopy.[9-11]

In 10 to 15% of cases, CRC is caused by a combination of hereditary and environmental factors. In 3 to 5%, CRC is due to a hereditary CRC syndrome such as Lynch syndrome (LS) or one of the polyposis syndromes. Around 100,000 people in the Netherlands are thought to have familial CRC but unfortunately most of these patients remain unrecognized.[12,13]

A mismatch repair deficiency (dMMR) is present in more than 95% of Lynch syndrome (LS)-associated colorectal carcinomas and in 15% of sporadic colorectal cancer (CRC).[14-16] LS patients have a lifetime CRC risk of approximately 50%, depending on the underlying gene defect, even with active preventative measures such as surveillance colonoscopy and polypectomy.[17] In LS, a pathogenic germline mutation in one of the DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6* or *PMS2*) causes genomic instability in the tumour. This is referred to as microsatellite instability (MSI) and is the hallmark of LS.[18,19] Tumours with either MSI or loss of MMR protein expression are designated MMR-deficient. Besides identification of LS patients and their families, MMR deficiency testing has additional implications. The outcome of MMR deficiency testing can be important in surgical decision making, as extended colectomy is recommended in young LS patients with CRC.[20] Tumours with MMR deficiency are associated with better overall survival.[21] Moreover, dMMR status has consequences for the choice of adjuvant chemotherapy as MMR-deficient CRC is resistant to 5-fluorouracil (5-FU) monotherapy.[22-26]

Patients with Lynch syndrome (LS) also show increased risk for other LS-associated tumours, including gastric cancer.[27-29] The Prospective Lynch Syndrome Database (PLSD) shows a cumulative incidence of 5.3% to 7.7% for gastric cancer at the age of 75, depending on the underlying gene defect. When diagnosed under the age of 65 years, the 5-year survival rate for gastric cancer is only 61%.[30] In 2013, a group of European experts (the Mallorca group) published revised guidelines for the clinical management of Lynch syndrome.[31] Due to the low risk of gastric cancer and the lack of established benefits, endoscopic surveillance of the upper gastrointestinal (GI) tract was not recommended. However, screening MMR mutation carriers for the presence of *H. pylori* infection was recommended, as *H. pylori* is an important risk factor for gastric cancer in the general population and eradication reduces risk.[32] A recommendation that Dutch physicians screen for *H. pylori* has been in place since 2010.[33]

Since the implementation of a nationwide colorectal screening program in the Netherlands in 2014, the detection of advanced neoplasms (advanced adenomas and early-stage colorectal cancer (CRC)) as well as the number of patients referred for endoscopic or surgical treatment for these lesions has increased.[34-36]

The majority of advanced polyps can be safely removed with standard polypectomy, a well-established procedure for non-invasive colonic neoplasms.[37] For more challenging neoplasms, advanced endoscopic techniques such as endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (eFTR) have improved complete en-bloc local resectability compared with standard polypectomy.[38-43] However, large sessile neoplasms situated at difficult locations in the colon can still be technically challenging to remove endoscopically and may require surgical removal.[44] In a large population study, endoscopic resection of large colonic polyps (→ 20 mm) was successful in 92% of cases, while the remaining 8% required surgery.[8] Segmental colectomy is associated with significant morbidity (24%) and mortality (2%), independent of tumour stage.[45] In the case of benign lesions, surgical treatment results in an overall complication rate of 25.5%, re-intervention rate of 8.1% and a mortality rate of 0.9%.[46] Fortunately, several methods can bridge the gap between endoscopic resection and major surgery.

Recently, Lin et al. reported a CELS-full thickness excision (CELS-FT) procedure for the removal of challenging colonic polyps which combines endoscopic and laparoscopic treatment. A circumferential incision is made in the seromuscular layer over the polyp using laparoscopy, which is subsequently marked with indigo carmine solution. The dissected area is then invaginated into the bowel lumen and a snare is

endoscopically introduced and looped around the polyp. Three patients underwent CELS-FT for problematic benign polyps with minimal blood loss and no perioperative complications. The average surgical time was 179 minutes.[47]

With the development of laparoscopic surgery, laparoscopic-assisted or laparoscopic -monitored colonoscopic polypectomy for the treatment of complex colon polyps has also been described. [48-50] In 2011, Yan et al. reported that colonoscopic-assisted laparoscopic wall excision to remove polyps is also an important combined approach. In this procedure colonoscopy is used to locate the polyp and to monitor the surgical margin. A laparoscopic Endo-GIA stapler is then placed to excise a full-thickness resection of the colonic wall. Colonoscopy is also helpful when assessing the bowel lumen for adequacy and patency.[51] To date, wedge resection has mainly been used in the caecum or ascending colon, a favourable location for use of a linear stapler.[47,52] In 2015, we began performing colonoscopy-assisted wedge resection in the entire colon, using a linear stapler without forming an anastomosis. We modified the technique described by Yan et al. by placing a suture close to the polyp base to provide traction on the colon, enabling better positioning of the stapler. A year later we published our first case series of 8 patients.[52]

In more than half of diagnosed CRCs, the tumour is located in the left part of the colon.[2] Around 1 to 7% of patients with CRC have a synchronous tumour, two thirds of which are located in the same surgical segment.[53-56] Furthermore, 15 to 20% of all patients with CRC present with bowel obstruction. In these patients, colonoscopy might fail to diagnose synchronous tumours proximal to an obstructive cancer that requires secondary surgery.[57-61]

Computed tomographic colonography (CTC) was developed as a non-invasive alternative to colonoscopy for the detection of CRC and polyps. In patients with obstructive CRC, Park et al. reported a 100% sensitivity of CTC in the detection of proximal synchronous CRC and moderate sensitivity (88.6%) in detecting proximal synchronous adenomas, including advanced adenomas.[60] In patients with stenosing CRC, most authorities recommend CTC before surgery to exclude synchronous CRC.[62-65] Two studies reported a change in primary surgical plan due to additional information from CTC (14 and 16%, respectively) in patients with stenosing CRC due to location errors, synchronous adenomas or synchronous carcinomas.[66,67] However, in most cases of stenosing CRC the synchronous tumour is at an advanced stage (T-stage 3 or 4) and therefore visible with regular staging CT, which is now performed in all CRC patients prior to surgery.

Chemotherapy is used to treat colorectal carcinoma at multiple disease stages. It is considered a primarily neoadjuvant therapy in patients with locally advanced colon cancer (cT4bN0-2M0|), an adjuvant treatment in stage III disease and as a component of chemoradiotherapy in patients with advanced rectal carcinoma. The goals are downstaging to enable an R_0 resection in patients with locally advanced cancer, or an increase in disease-free survival in cases with high-risk stadium II-III or low-risk stadium III colon carcinoma. Chemotherapy also has a place in the treatment of metastatic disease.[68]

Fluoropyrimidine monotherapy is the recommended chemotherapeutic treatment for patients with metastatic colorectal cancer (mCRC) who may not tolerate more aggressive therapy.[69-71] Oral capecitabine provides a convenient alternative to standard intravenous fluoropyrimidine and in clinical trials oral capecitabine monotherapy was shown to be as effective as intravenous 5-fluorouracil as a first-line treatment for mCRC. Oral capecitabine is generally associated with an improved safety profile, with lower rates of stomatitis, alopecia, diarrhoea, nausea and grade 3/4 neutropenia.[72-75] However, rates of hand-foot syndrome (HFS) are higher[72,74-76] and data regarding adverse events following oral capecitabine monotherapy for mCRC are limited.

OUTLINE OF THE THESIS

Part I – Management of hereditary colorectal cancer

In up to 15% of CRCs, hereditary and environmental factors play an important role. Lynch syndrome (LS) is responsible for 3 to 5% of cases and familial colorectal cancer (FCC) and other polyposis syndromes for the remaining cases. Identification of individuals at risk for LS or FCC is important because preventative strategies may improve the prognosis or even avert cancer development.

In **CHAPTER 2** we describe a retrospective multicentre study. The aims of the study were to evaluate the proportion of individuals in the Dutch bowel screening program with a positive I-FOBT that fulfil criteria for LS and familial colorectal cancer (FCC) and to evaluate the proportion of participants that require genetic counselling or colonoscopic surveillance.

In **CHAPTER 3** we present the results of a retrospective study of the consequences in clinical practice of testing for mismatch repair deficiency in colorectal cancer. The aims of the study were to evaluate whether MMR deficiency testing leads to (1) identification of Lynch syndrome, (2) a change in surgical treatment and (3) adjustment of systemic therapy in patients with dMMR CRC.

In **CHAPTER 4** we present the results of a retrospective multicentre observational cohort study. We aimed to assess the proportion of LS patients that was tested for *H. pylori* infection and address the question of whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.

Part II – Management of early colorectal neoplasms

The implementation of the national bowel screening program in 2014 led to an increased detection rate of polyps, which are generally removed endoscopically. However, if size and location of the polyp makes endoscopic removal technically difficult or if there is a suspicion for early (T1) cancer, surgical removal is preferred. An increasing number of patients are now treated with minimally invasive surgical procedures rather than segmental resection. To preserve as much of the colon as possible, we recently introduced a modified laparoscopic endoscopic-assisted wedge resection (LEAWR) for advanced polyps that are endoscopically challenging to remove.

In **CHAPTER 5** we discuss a retrospective study to assess the number of referrals for surgery, the type of polyp surgery since the introduction of the national bowel screening program and the morbidity and mortality of conducted surgeries.

In **CHAPTER 6** we present the results of the first cohort treated with limited endoscopy-assisted wedge resection (LEAWR). The aim of this cohort study was to report our experience with this new technique.

In **CHAPTER 7** we describe the results of a prospective multicentre LEAWR study in The Netherlands. The aim of this study was to evaluate the safety and efficacy of our modified endoscopy-assisted laparoscopic wedge resection procedure.

Part III – Management of advanced colorectal neoplasms

As a synchronous tumour is reported in 1 to 7 % of CRC patients, CT colonography is recommended in patients with a stenosing colorectal tumour in order to exclude the presence of a CRC proximal to the primary tumour. In patients with metastatic CRC, palliative chemotherapy can be considered. Capecitabine monotherapy is a treatment option for selected patients with metastatic colorectal cancer (mCRC) and is administered in up to 17% of patients.

In **CHAPTER 8** we present a retrospective single-centre study focussed on the yield and additional clinical implications of CT colonography in patients with stenosing CRC.

In **CHAPTER 9** we describe a single-centre, retrospective study of patients treated at a large community hospital for mCRC. The aim was to provide data on adverse event rates and dose adjustments/discontinuations associated with capecitabine monotherapy in patients with mCRC.

REFERENCES

1. Committed to health and sustainability [Internet]. Bilthoven: RIVM (NL); 2012 Jul 13. Bowel cancer screening programme; [date unknown, cited 2018 May 24]. Available at: http://www.rivm.nl/en/Topics/B/Bowel_cancer_screening_programme
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):104-117.
3. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR (2009) Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. Dec;7(12):1272-8.
4. Fearon ER, Vogelstein B (1990) A genetic model for colorectal tumorigenesis. Cell. Jun 1;61(5):759-67.
5. Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, Helper DJ, Wiersema MJ, Langefeld CD, Li W (1993) Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. Am J Gastroenterol. Jun;88(6):825-31.
6. Rex DK (1995) Colonoscopy: a review of its yield for cancers and adenomas by indication. Am J Gastroenterol. Mar;90(3):353-65.
7. Pendergrass CJ, Edelstein DL, Hylind LM, Phillips BT, Iacobuzio-Donahue C, Romans K, Griffin CA, Cruz-Correa M, Tersmette AC, Offerhaus GJ, Giardiello FM (2008) Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. Clin Gastroenterol Hepatol. Sep;6(9):1011-5.
8. Hassan C, Repici A, Sharma P, Correale L, Zullo A, Bretthauer M, Senore C, Spada C, Bellisario C, Bhandari P, Rex DK (2016) Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut. May;65(5):806-20.
9. Health Council of the Netherlands. A national colorectal cancer screening programme. The Hague: Health Council of the Netherlands, 2009; publication no. 2009/13E. ISBN 978-90-5549-780-5.
10. Inadomi JM, Vijan S, Janz NK, Fagerlin A, Thomas JP, Lin YV et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 2012;172(7):575-582 doi: 10.1001/archinternmed.2012.332.
11. Binefa G, Rodriquez-Moranta F, Teule A, Meidna-Hayas M. Colorectal Cancer: From prevention to personalized medicine. World J Gastroenterol 2014;20(22):6786-808 doi: 10.3748/wjg.v20.i22.6786.

12. De Jong AE, Vasen HF. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64(10):367-70.
13. Ijspeert JE, Bevan R, Senore C, Kaminski MF, Kuipers EJ, Mroz A et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut 2016. pii: gutjnl-2015-310784. doi: 10.1136/gutjnl-2015-310784.
14. Vasen HF. Review article: The lynch syndrome (hereditary nonpolyposis colorectal cancer). *Aliment Pharmacol Ther.* 2007;26 Suppl 2:113-126.
15. Bonnet D, Selves J, Toulas C, et al. Simplified identification of lynch syndrome: A prospective, multicenter study. *Dig Liver Dis.* 2012;44(6):515-522.
16. Niv Y. Microsatellite instability and MLH1 promoter hypermethylation in colorectal cancer. *World J Gastroenterol.* 2007;13(12):1767-1769.
17. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Med in Gen.* 2020;22(1);15-25.
18. Liu B, Parsons R, Papadopoulos N, et al. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nat Med.* 1996;2(2):169-174.
19. Peltomaki P, Vasen H. Mutations associated with HNPCC predisposition -- update of ICG-HNPCC/INSiGHT mutation database. *Dis Markers.* 2004;20(4-5):269-276.
20. de Vos tot Nederveen Cappel,W.H., Buskens E, van Duijvendijk P, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. *Gut*. 2003;52(12):1752-1755.
21. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology.* 2010;138(6):2073-2087.e3.
22. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med.* 2003;349(3):247-257.
23. Jover R, Zapater P, Castells A, et al. Mismatch repair status in the prediction of benefit from adjuvant fluorouracil chemotherapy in colorectal cancer. *Gut*. 2006;55(6):848-855.
24. He EY, Hawkins NJ, Mak G, et al. The impact of mismatch repair status in colorectal cancer on the decision to treat with adjuvant chemotherapy: An australian population-based multicenter study. *Oncologist*. 2016.

25. Boland CR, Lynch HT. The history of lynch syndrome. *Fam Cancer.* 2013;12(2):145-157.
26. Diaz LA,Jr, Le DT. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;373(20):1979.
27. Capelle LG, Van Grieken NC, Lingsma HF et al (2010) Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 138:487–492
28. Renkonen-Sinisalo L, Sipponen P, Aarnio M et al (2002) No sup- port for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol 37:574–7
29. Correa P (1992) Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 52: 6735–6740
30. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in *path_MMR carriers* by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018; 67:1306–1316. doi:10.1136/gutjnl-2017-314057
31. Vasen HF, Blanco I, Aktan-Collan K et al (2013) Revised guide- lines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 62:812–23
32. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (1994) Schistosomes, liver flukes, and Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum June 61:1–241
33. www.oncoline.nl, erfelijke tumoren, Lynch syndrome, consensus based, 1-7-2010
34. Elferink M.A.G., Toes-Zoutendijk E., Vink G.R., et al. National population screening for colorectal carcinoma in the netherlands: Results of the first years since the implementation in 2014. *Ned Tijdschr Geneeskd.* 2018;162:D2283.
35. Marres C.C.M., Buskens C.J., Schriever E., et al. The impact of the national bowel screening program in the netherlands on detection and treatment of endoscopically unresectable benign polyps. *Tech Coloproctol.* 2017;21(11):887-891. Accessed Dec 10, 2020. doi: 10.1007/s10151-017-1705-x.
36. Bosch D., Leicher L.W., Vermeer N.C.A., et al. Referrals for surgical removal of polyps since the introduction of a colorectal cancer screening programme. *Colorectal Dis.* 2020. Accessed Dec 10, 2020. doi: 10.1111/codi.15413.

37. Winawer S.J., Zauber A.G., Ho M.N., et al. Prevention of colorectal cancer by colonoscopic polypectomy. *New England Journal of Medicine.* 1993;329(27):1977-1981. https://doi.org/10.1056/NEJM199312303292701. Accessed Jan 14, 2021. doi: 10.1056/NEJM199312303292701.
38. Zwager L.W., Bastiaansen B.A.J., Bronzwaer M.E.S., et al. Endoscopic full-thickness resection (eFTR) of colorectal lesions: Results from the dutch colorectal eFTR registry. *Endoscopy*. 2020;52(11):1014-1023. Accessed Dec 10, 2020. doi: 10.1055/a-1176-1107.
39. Byeon J.-S., Yang D.-H., Kim K.-J., et al. Endoscopic submucosal dissection with or without snaring for colorectal neoplasms. *Gastrointest Endosc.* 2011;74(5):1075-1083. Accessed Jan 14, 2021. doi: 10.1016/j.gie.2011.03.1248.
40. Bergmann U., Beger H.G., Endoscopic mucosal resection for advanced non-polypoid colorectal adenoma and early stage carcinoma. *Surg Endosc.* 2003;17(3):475-479. Accessed Jan 14, 2021. doi: 10.1007/s00464-002-8931-6.
41. Conio M,, Repici A,, Demarquay J,-F., et al., EMR of large sessile colorectal polyps. *Gastrointest Endosc.* 2004;60(2):234-241. Accessed Jan 14, 2021. doi: 10.1016/s0016-5107(04)01567-6.
42. Saito Y., Uraoka T., Yamaguchi Y., et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest Endosc.* 2010;72(6):1217-1225. Accessed Jan 14, 2021. doi: 10.1016/j.gie.2010.08.004.
43. Yokota T., Sugihara K., Yoshida S., Endoscopic mucosal resection for colorectal neoplastic lesions. *Dis Colon Rectum.* 1994;37(11):1108-1111. Accessed Jan 14, 2021. doi: 10.1007/BF02049812.
44. Puli S.R., Kakugawa Y., Gotoda T., et al., Meta-analysis and systematic review of colorectal endoscopic mucosal resection. *World journal of gastroenterology : WJG.* 2009;15(34):4273-4277. https://www.ncbi.nlm.nih.gov/pubmed/19750569. doi: 10.3748/wjg.15.4273.
45. Vermeer N.C.A., Backes Y., Snijders H.S., et al. National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer. *BJS Open.* 2019;3(2):210-217. Accessed Dec 10, 2020. doi: 10.1002/bjs5.50125.
46. Vermeer N.C.A., de Neree tot Babberich M.P.M., Fockens P., et al., Multicentre study of surgical referral and outcomes of patients with benign colorectal lesions. *BJS open.* 2019;3:687-695.

47. Anthony T. Lin, et al, Dynamic Article: Full-Thickness Excision for Benign Colon Polyps Using Combined Endoscopic Laparoscopic Surgery, Dis Colon Rectum 2016; 59: 16–21
48. Franklin ME Jr, Leyva-Alvizo A, Abrego-Medina D, et al. Lapa- roscopically monitored colonoscopic polypectomy: an estab- lished form of endoluminal therapy for colorectal polyps. *Surg Endosc.* 2007;21:1650 –1653.
49. Ommer A, Limmer J, Mo llenberg H, Peitgen K, Albrecht KH, Walz MK. Laparoscopic-assisted colonoscopic polypectomy: indications and results. *Zentralbl Chir.* 2003;128:195–198.
50. Prohm P, Weber J, Bonner C. Laparoscopic-assistedcoloscopic polypectomy. *Dis Colon Rectum.* 2001;44:746 –748.
51. Jun Yan, et al. Treatment for right colon polyps not removable using standard colonoscopy: combined laparoscopic-colonoscopic approach. Dis Colon Rectum. 2011;54:753–758
52. Leicher LW, de Vos Tot Nederveen Cappel WH, van Westreenen HL (2017) Limited Endoscopic-Assisted Wedge Resection for Excision of Colon Polyps. Dis Colon Rectum. Mar;60(3):299-302.
53. Lam AK, Chan SS, Leung M. Synchronous colorectal cancer: Clinical, pathological and molecular implications. *World J Gastroenterol*. 2014;20(22):6815-6820.
54. Mulder SA, Kranse R, Damhuis RA, et al. Prevalence and prognosis of synchronous colorectal cancer: A dutch population-based study. *Cancer Epidemiol*. 2011;35(5):442-447.
55. Adloff M, Arnaud JP, Bergamaschi R, Schloegel M. Synchronous carcinoma of the colon and rectum: Prognostic and therapeutic implications. *Am J Surg*. 1989;157(3):299-302.
56. Latournerie M, Jooste V, Cottet V, Lepage C, Faivre J, Bouvier AM. Epidemiology and prognosis of synchronous colorectal cancers. *Br J Surg*. 2008;95(12):1528-1533.
57. Billingsley KG, Morris AM, Dominitz JA, et al. Surgeon and hospital characteristics as predictors of major adverse outcomes following colon cancer surgery: Understanding the volume-outcome relationship. *Arch Surg*. 2007;142(1):23-31; discussion 32.
58. Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. *Br J Surg*. 1994;81(9):1270-1276.
59. Serpell JW, McDermott FT, Katrivessis H, Hughes ES. Obstructing carcinomas of the colon. *Br J Surg*. 1989;76(9):965-969.

60. Ascanelli S, Navarra G, Tonini G, et al. Early and late outcome after surgery for colorectal cancer: Elective versus emergency surgery. *Tumori*. 2003;89(1):36-41.
61. Ohman U. Prognosis in patients with obstructing colorectal carcinoma. *Am J Surg*. 1982;143(6):742-747.
62. AGA Clinical Practice and Economics Committee. Position of the american gastroenterological association (AGA) institute on computed tomographic
63. Hong N, Park SH. CT colonography in the diagnosis and management of colorectal cancer: Emphasis on pre- and post-surgical evaluation. *World J Gastroenterol*. 2014;20(8):2014-2022.
64. Cash BD, Rockey DC, Brill JV. AGA standards for gastroenterologists for performing and interpreting diagnostic computed tomography colonography: 2011 update. *Gastroenterology*. 2011;141(6):2240-2266.
65. Spada C, Stoker J, Alarcon O, et al. Clinical indications for computed tomographic colonography: European society of gastrointestinal endoscopy (ESGE) and european society of gastrointestinal and abdominal radiology (ESGAR) guideline. *Endoscopy*. 2014;46(10):897-915.
66. Flor N, Ceretti AP, Mezzanzanica M, et al. Impact of contrast-enhanced computed tomography colonography on laparoscopic surgical planning of colorectal cancer. *Abdom Imaging*. 2013;38(5):1024-1032.
67. Kim JH, Kim WH, Kim TI, et al. Incomplete colonoscopy in patients with occlusive colorectal cancer: Usefulness of CT colonography according to tumor location. *Yonsei Med J*. 2007;48(6):934-941.
68. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/gemetastaseerd_colorectaalcarcinoom_crc/inductiebehandeling_bij_niet_lokaal_behandelbare_metastasen_bij_crc.html
69. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow- up. Ann Oncol. 2014;25(Suppl 3):iii1–9.
70. National Comprehensive Cancer Network (NCCN) Guidelines. Colon Cancer. v2.2016. Available at: http://www.nccn.org. Accessed 24 Mar 2016.
71. National Comprehensive Cancer Network (NCCN) Guidelines. Rectal Cancer. v1.2016. Available at: http://www.nccn.org. Accessed 24 Mar 2016.
72. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, et al. First-line oral capecitabine therapy in metastatic col- orectal cancer: a favorable safety profile compared with intra- venous 5-fluorouracil/leucovorin. Ann Oncol. 2002;13:566–75.

73. Van Cutsem E, Hoff PM, Harper P, Bukowski RM, Cunningham D, Dufour P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer. 2004;90:1190–7.
74. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001;19:4097–106.
75. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluo- rouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol. 2001;19:2282–92.
76. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14:1077–85.