Improving the management of colorectal neoplasms in clinical practice

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part IV
SUMMARY AND DISCUSSION

CHAPTER 10

In the first part of this thesis, we focus on the management of hereditary colorectal cancer.

CHAPTER 2 concerns a retrospective observational study in two large hospitals that aimed to evaluate the proportion of individuals with a positive I-FOBT in the Dutch population screening program that fulfil criteria for familial/hereditary CRC. Another goal was to evaluate the proportion of patients that need further genetic analysis based on their personal and family history and/or endoscopic findings.

A total of 657 individuals with a positive I-FOBT test underwent colonoscopy, 120 of whom (18.3%) were found to have a positive family history for CRC, 20 (3.0%) fulfilled criteria for familial colorectal cancer (FCC), 4 (0.6%) the revised Bethesda guidelines and in one case (0.2%) the Amsterdam Criteria. Multiple adenomas (>10) were found in 21 (3.2%) participants. No cases of serrated polyposis were identified. Based on the current guidelines, a total of 35 (5.3%) required referral to a clinical geneticist and the relatives of 20 (3.0%) participants were referred for surveillance colonoscopy.

More (pilot) studies have been performed to identify familial CRC in individuals that participate in a I-FOBT population screening. A study, performed by Dekker et al. in 2011 in the Netherlands, showed that 17% of the participants with a positive I-FOBT in the CRC screening program had a positive family history of CRC.[1] The percentage we found in our study was comparable with the percentage found by Dekker et al. Another pilot study, conducted in 2006 in Australia, reported a positive family history for CRC in 19.6% of subjects that participated in a I-FOBT screening program.[2] This is also similar with the percentage we found of 18,3%. Although both studies showed that a substantial proportion of individuals with a positive I-FOBT result had a positive family history for CRC, detailed information on the family history and the level of CRC risk was lacking. Also, the identification of polyposis syndromes was not addressed.

Making optimal use of the patient contact arising from the screening program is very important to identify high risk groups (patients with familial CRC and their families). Our study demonstrates that a proportion of the patients need further genetic testing and surveillance colonoscopies. Several previous studies have showed that the identification of individuals with familial cancer and Lynch syndrome is suboptimal.[3] A previous Dutch study estimated that in The Netherlands 100.000 individuals are at risk for familial or hereditary colorectal cancer but currently only a small proportion of these individuals has been recognized.[4] The age distribution of CRC in familial CRC (50-75 years) is almost similar as the patients that are invited for the

Dutch population screening program (55-75 years).[5] The prognosis of patient with familial CRC and their families will improve when de identification is more optimal. Earlier detection of advanced adenomas can prevent the evolution into a CRC. Approximately 95% of CRCs will evolve from an adenomatous polyp or sessile serrated lesion. Despite the dysplastic character of the polyp, only 5% of all adenomatous polyps progresses to CRC in "average risk" individuals.[6] But a recent surveillance study among 550 patients with familial CRC showed that the prevalence of advanced adenomas was two-fold higher than reported in "average risk" individuals.[5] Literature showed that colonoscopic surveillance led to a reduction of CRC by 80%.[7]

In this study we demonstrated that a nationwide population screening program, such as the I-FOBT program in the Netherlands, may not only improve the prognosis of patients with CRC and prevent the development of CRC but also may identify high risk individuals by obtaining a detailed family history. Detection of patients with a positive family history improves care for these patients and their family members. It is therefore essential to document family history of CRC during the routine intake before colonoscopy. In the current era of the electronic patient file, making this a standard part of the report should not be a problem.

In **CHAPTER 3** we performed a multicentre, retrospective study to evaluate whether MMR deficiency (dMMR) testing leads to (1) identification of LS, (2) a change in surgical treatment and (3) changes to systemic therapy in patients with dMMR CRC.

Analysing the outcome of dMMR testing in 225 CRCs, we identified 24 (11%) MMR-deficient CRC patients. Of these patients, 18 (75%) were referred to a clinical geneticist and a pathogenic MMR variant was identified in 9 (37%). One (4%) of the 24 patients underwent a subtotal colectomy, while the chemotherapy regimen was adjusted in 7 (35%) of 20 patients with an MMR-deficient tumour.

Only 4% of all patients selected for MSI analyses or MMR testing were found to have LS which is lower compared with results of a previous study which reported LS in 9.2% of pre-selected patients, using the revised Bethesda criteria.[8] The lack of an adequate referral procedure may be the explanation that in our study 25% of the patients did not receive proper genetic counseling. Literature showed a low compliance with referral of 35,7%, when the surgeon is being responsible to refer the patient. Compliance with the referral was higher when the clinical geneticist was responsible for initiating conversations about further genetic counseling.[9] Further research Is needed to identify possible barriers to visit the clinical geneticist ro finally improve compliance with the referral as also suggested by Irons et al.

In 2011, Parry et al. investigated the risk of developing metachronous CRC in

MMR gene mutation carriers. Cumulative risk of metachronous CRC was 16% (95% CI 10–25%) at 10 years, 41% (95% CI 30–52%) at 20 years and 62% (95% CI 50–77%) at 30 years after segmental colectomy. These risk estimates could help in the decision-making regarding the extent of primary surgical resection.[10] A subtotal colectomy is recommended according to the current guidelines in patients with evidence for LS and age <60 years. In our study only one patient (4%) underwent a subtotal colectomy instead of hemicolectomy based on a suspicion of LS due to MMR deficiency and a young age (42 years) at diagnosis of CRC. After surgery, a MSH2 mutation was identified. This low number is due to the fact that only 4 of 24 patients were under age 60 years. In addition, the majority of MSI/IHC were performed on the resected specimen (139 of total 225 (61.7%)) instead of on the biopsies. Due to the possible consequences on the surgical treatment, it is preferable to perform MMR testing preoperatively on the biopsies.

There is an increasing amount of evidence that adjuvant chemotherapy with 5-FU in patients with a stage II or III CRC with MMR-defective tumours does not improve the prognosis. A study of 754 CRC patients showed an improvement of survival in patients who received adjuvant chemotherapy with 5-FU only in patients with a MMR-competent tumor. Overall survival of patients with MMR-deficient tumors did not improve with adjuvant 5-FU monotherapy.[11] In our study, in 7 (35%) of the 20 patients who had an indication for adjuvant chemotherapy, the initial planned treatment with 5-FU monotherapy was changed due to MMR deficiency. The MMR status of a CRC is becoming increasingly important due to implications regarding the choice of chemotherapy and immunotherapy. Chalabi et al. showed major pathological responses (<5% viable tumour cells) and a 57% complete response rate in patients with dMMR CRC treated with neo-adjuvant ipilimumab and nivolumab.[12] Together with excellent immunotherapy results in dMMR metastatic CRC reported by Overman et al., these are a very promising developments.[13] To ensure optimal treatment decisions in CRC patients, MSI or IHC analysis should be performed in all patients with CRC < 70 yrs and in patients with CRC > 70 yrs in case there might be an indication for (neo-)adjuvant chemotherapy.

In conclusion, MSI and IHC analysis resulted in identification of LS patients, a patient that needed extended colorectal surgery and a substantial number of patients that required adjustment of the chemotherapy protocol. The study also demonstrated that a substantial proportion of the patients (25%) were not referred to the clinical geneticist. A systematic discussion of the result of MSI/IHC should be incorporated in a multidisciplinary meeting and also, who is responsible for the referral to the clinical geneticist, to improve the referral of patients with MMR-deficient tumor.

In **CHAPTER 4** we retrospectively investigated the proportion of LS patients currently tested for *Helicobacter pylori* infection and addressed the question of whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.

Of the 443 (male, 184) proven mutation carriers included, 206 (46%) were screened for *H. pylori* and 42 (20%) were found to be positive. Of the patients ascertained as mutation carriers before 2010, 37% was screened for *H. pylori*. After 2010, this percentage increased to 68%. Family history was available for 356 mutation carriers, 25 of whom had at least one first-degree family member with gastric cancer, while seven had more than one first-degree relative with gastric cancer. The *H. pylori* infection rate in patients with a first-degree relative was 20%.

This is the first study to report the outcome of *H. pylori* screening in a large series of LS mutation carriers. We found a *H. pylori* infection in 20% of the mutation carriers, a proportion that is similar to the general population.[14,15] The recommendation to screen for *H. pylori* has been operative since 2010, and the proportion of patients being tested increased from 37% before 2010 to 68% after 2010. Assuming *H. pylori* is an important risk factor in the development of gastric cancer in Lynch patients, we expected to find a higher infection rate in mutation carriers with a positive family history, as *H. pylori* clusters within families.[16,17] However, the proportion of patients affected with *H. pylori* in this group was similar to the *H. pylori* infection rate in the total group.

H. pylori is a proven carcinogen in the general population, but it's role in the pathogenesis of gastric cancer in Lynch syndrome is still unknown. The fact that gastric cancer in mutation carriers occurs more frequently in countries with a higher prevalence of *H. pylori* infection coupled with fact that the incidence of gastric cancer in the general population in Western countries has decreased parallel to the decline of *H. pylori* infection, strongly suggest an important role for this bacterium in the carcinogenesis.

The recommended screening for *H. pylori* is increasingly followed. To prove the effectiveness of this guideline, a large prospective randomized study in LS families would be necessary. However, a meta-analysis showed that even in low-prevalence countries (America, Canada, UK, and Finland), screening the general population for *H. pylori* was cost-effective in the prevention of gastric cancer.[18] Taking into consideration the results of this meta-analysis and the high risk of developing of gastric cancer in LS families, screening of LS patients would also be beneficial.

In the second part of this thesis, we focus on the treatment of early colorectal neoplasms.

CHAPTER 5 concerns the level of referrals for surgical resection of colon polyps and the type of surgery following the introduction of the national bowel screening program in the Netherlands in 2014. The included patients underwent surgery for colorectal polyps between January 2012 and December 2017 in Isala in Zwolle, The Netherlands. The exclusion criterion was histologically proven carcinoma prior to surgery. Primary outcomes were number and type of surgical procedures for polyps.

In total, 164 patients were included. An annual increase in the number of referrals for surgical resection for colorectal polyps was observed, rising from 18 patients in 2012 to 36 patients in 2017. We divided the included patients into two subgroups, (1) patients who underwent an segmental resection and (2) patients who underwent organ preserving surgery. The following surgical procedures felt into the latter group: transanal endoscopic microsurgery (TEM), limited endoscopic-assisted wedge resection (LEAWR). Procedures performed before the implementation of the screening program were exclusively segmental resections, whereas after implementation 58.8% of procedures were organ-preserving surgical procedures. The overall complication rate for organ-preserving surgery was 16%, compared to 44% for segmental resections (p = 0.001). Only in the group with segmental resections there were reinterventions, in 6.1% (n = 7/115). A readmission rate of 6.7% (n = 11/164) was found, in the subgroup with organ-preserving surgery the readmission rate was 4.1% (n = 2/49) and in the group with segmental resection this rate was 7.8% (n = 9/115). Invasive colorectal cancer was encountered in 24% of cases overall.

Data about surgical referrals for complex polyps are scarce. In one cohort study the number of patients referred for laparoscopic colorectal resection for non-malignant polyps almost tripled after the introduction of the national screening program.[19]

Substantial morbidity related to segmental colon resections of polyps was found in our study, comparable with results in large cohort studies reporting a reoperation rate of 7.8% and readmission rate of 3.6% after surgery for nonmalignant colorectal polyps.[20,21] In the organ preserving group, 7 patients (14.3%) had a minor complication. Only 1 out of 49 patients (2.0%) who underwent minor surgery presented with a major complication, this concerned a post-TEM haemorrhage, which required surgery. LEAWR did not lead to major complications. A recent study reporting on short- and long-term results of TEM observed similar rates of minor complications in 12 patients (8.8%) and major complications in 2 out of 135 patients (1.5%).[22] Three retrospective studies investigating postoperative complications after different types of combined endoscopic and laparoscopic surgery (CELS) observed no complications.[23-25] These studies were limited by their small sample sizes, ranging from 3 to 23 patients which makes comparison difficult. A prospective study by

Wilhelm et al. analyzed 146 patients who underwent CELS, of which 82% underwent local excision and 18% received endoscopy-assisted segmental colon resection. The overall complication rate was 25% and major complication rate was 3%.[26] These results are very comparable to our overall complication rate of 36.0% and occurrence of major complications in 4.9% of patients, especially when considered that in our study 70% of surgeries were segmental resections.

In the majority of the included patients in our study, no attempt was made for an endoscopic removal. This was mainly due to unfortunate polyp characteristics, such as large size; difficult location; non-lifting sign and/or the suspicion of early (T1) carcinoma. In these cases, an en-bloc resection is advised, which is not always possible by endoscopy.[27-30] In recent years, endoscopic treatment options are expanding, where the introduction of ESD and endoscopic full thickness resections have enabled local excision of pT1 tumors. The use of these techniques may reduce the referrals for surgery. Prior to referral for surgical excision, it is recommended to consult experts for endoscopic treatment. Repeated colonoscopy before surgery in an expert center can also reduce the rate of surgical referrals by 71%.[31]

A clear definition of an unresectable polyp was difficult to establish, and this definition changed over time with the development of endoscopic expertise in our clinic. The therapeutic strategies were based on the endoscopic assessment by different gastroenterologists, which can lead to interobserver variability. The increasing number of referrals for surgical resection due to the implementation of the screening program led to the development of a less invasive technique (LEAWR). This technique, in which laparoscopy and endoscopy are combined, was developed in 2015. One of the great benefits of this minimally invasive technique is that no anastomosis is created. In a pilot study, no complications were observed.[32] This new technique may have led to a lower threshold to refer the patient for a surgical resection. Despite increasing endoscopic possibilities and techniques over time, an increase in referrals for surgery was still observed.

This study reflects the consequences of a bowel screening program for daily clinical practice in a large teaching hospital. It revealed a doubling of the referral rate for surgical resection of colorectal polyps since the introduction of the CRC screening program, but with a substantial shift towards organ-preserving techniques. The low complication rate of organ-preserving techniques makes these procedures an attractive option in cases where endoscopic techniques fail. This therapy should be first choice if surgical treatment of colon polyps is necessary.

In **CHAPTER 6** we report our experience with limited endoscopy-assisted wedge resections (LEAWR) in the entire colon.

Eight patients were treated (mean age 74.5 years; range 68-82 yrs). The main indications for LEAWR were size and difficult location of the polyp. The mean operative time was 132 minutes and there were no complications. Five patients were discharged the day after surgery and remaining 3 patients were discharged 2 days after surgery, with no complications found.

In this pilot study, we found that LEAWR is feasible and allows easy removal of colonic polyps and residual adenomatous tissue in scars inaccessible to endoscopic removal. Due to traction provided by the suture through the base of the polyp, the linear stapler can be easily used for wedge resections of polyps, even for those in unfavourable positions.

In the literature we did not find an earlier publication of using traction on a suture to perform a wedge resection.

We performed a limited EAWR for polyps with sessile as well as (semi-) pedunculated morphology. Indication for limited EAWR was difficult location of the polyp and thereby an unstable position of the endoscope. Even with laparoscopic assistance, endoscopic removal is not always possible or may not be effective in cases where a snare cannot be placed over the polyp because of size, location or scarring from previous biopsies. This may lead to piecemeal resection and subsequent inadequate histopathological assessment of the specimen as well as a higher risk of recurrence.[33,34] Endoscopic submucosal dissection (ESD) is a well-established technique that facilitates an en-bloc excision of large polyps. However, there are several disadvantages to ESD that limit its use in routine clinical practice, including the need for specialized equipment, procedure length and a long learning curve.[35] Many patients now indicated for ESD can also easily be treated with limited EAWR.

Caution is taken when polyps are situated in a sigmoid with multiple diverticula, in these patients endoscopic wedge resection might be challenging. A possible concern of a limited EAWR could be narrowing of the bowel. We prefer to place the stapler in a transverse direction, this is however not always possible. In our patients there was no evidence for possible narrowing of the colon.

Due to the encouraging results, in collaboration with the Dutch T1 colorectal working group we initiated a multicentre trial to evaluate this technique in broader clinical practice.

CHAPTER 7 focuses on the results of a large prospective multicentre study in 13 Dutch hospitals conducted between January 2017 and December 2019. The aim of this study was to prospectively evaluate the short-term safety and efficacy of our modified colonoscopic assisted laparoscopic wedge resection (CAL-WR), also known as limited endoscopic assisted laparoscopic wedge resection (LEAWR) as described in **CHAPTER 6**. And also, to assess whether this new technique can replace segmental colectomy in routine clinical practice.

Of the 138 eligible patients, 118 were included in the analysis following assessment by the expert panel and review of the histological specimen, if indicated. The main indication for CAL-WR was an endoscopically unresectable colonic neoplasm (56%). Almost half of the neoplasms were in the caecum. Successful CAL-WR was performed in 110 of the 118 patients (93%). In the case of lesions found in the caecum the technical success rate was 96%, and in twenty-seven of the fifty (54%) successfully performed CAL-WR procedures the neoplasms showed ingrowth into the appendix. The patients who underwent a successful CAL-WR (n = 110) had an overall complication rate of 6%, all of which were minor (Clavien-Dindo grade I-II) and neither reintervention nor mortality was observed. Radical resection was performed in 91% of patients who successfully underwent a CAL-WR (n = 100/110), and an additional oncologic segmental resection was performed in 12 cases (11% (n = 12/110)) of the patients who successfully underwent a CAL-WR. Residual tissue at the scar was observed in 5% (n = 4) of patients who successfully underwent a CAL-WR during endoscopic follow-up.

To date, few studies have described the use of various combined endoscopic laparoscopic surgery (CELS) techniques.[23,32,36-38] Reported technical success rates from available literature range from 95% to 100%[23,32,37,38], comparable to our technical success rate of 93%. A recent systematic review of CELS involving 101 patients showed no intra- or postoperative complications.[36] Another recent retrospective cohort study (n = 115 patients) showed Clavien-Dindo grade I-II complications in 13% of patients after CELS.[39] In that study, both CAL-WR and another form of CELS such as laparoscopy-assisted endoscopic resection (LAER) was performed. Therefore, the reported 6% morbidity rate in our study appears acceptable, especially in a multicentre design.

Our overall rate of radical resection (91%) of a CAL-WR is comparable to the mentioned percentage in the available literature, radical resections rates in other studies range from 75% to 100%.[23,32,36-38] Recurrent adenomatous tissue was detected at follow-up colonoscopy in 5% (n = 4) of cases. In one case the pathologist found loose adenomatous cells in the staple margin, while the primary resection margin

was free of adenomatous tissue. We hypothesize that manipulation of the lesion in this case, either by placing of the suture and/or closure with the stapler, caused adenomatous cells to become embedded in the staple margin. Careful manipulation of the lesion during CAL-WR as well as follow-up endoscopy is therefore strongly recommended. None of the previous CAL-WR studies reported recurrence at follow-up endoscopy.[1,23,32,36-38]

Endoscopic full-thickness resection (eFTR) using an over the scope clip is another relatively new technique for the treatment of complex colonic neoplasms. The overall technical success rate of eFTR varies between 84% to 94%[40-44], while the complication rate ranges from 9.3% and 14%. In 2% to 3.5% of cases surgical reintervention is needed to treat complications.[40-44] The reported complication rate of eFTR is higher (9.3% – 14%) compared to CAL-WR (6%), as demonstrated by our study. A relatively common complication after eFTR is a secondary appendicitis close to the appendiceal orifice, which requires surgical reintervention. CAL-WR is particularly suitable for these cases, as 27 patients in our study (25%) had a lesion with ingrowth into the appendix, all of which could be treated without complication.

The radical resection rates for eFTR and CAL-WR are similar and vary from 72% to 90% and from 72% to 100%, respectively.[32,37,38,40-44] The recently described Dutch eFTR colorectal registry reported residual/recurrent lesions in 6.4% of patients,[40] while other eFTR studies reported a recurrence/residual rate of between 5.8% and 13.5%.[40-44] In our study we found a recurrence/residual adenomatous tissue at follow-up colonoscopy in 5% (n = 4) of cases. Which is similar to the reported percentages of the eFTR. Unfortunately, details on whether the primary resection in these cases was complete (R_0 resection) was not provided in these studies.[40,43,44] The use of eFTR is restricted to lesions of less than 20 mm by the size of the cap.[40,41,43,44] In our study, the median size of lesions was 20 mm [range 5 – 50 mm], indicating that lesion size is less of a limitation compared to eFTR.

In conclusion, in our prospective study we found that CAL-WR is an effective, organ-preserving approach that results in minor complications and circumvents the need for more advanced surgical procedures, which are accompanied by higher morbidity (24%) and mortality (2%) rates.[45] In the present study only 11% of patients underwent additional oncological segmental resection, indicating that segmental colectomy could be prevented in all other cases. CAL-WR therefore deserves consideration when endoscopic excision of circumscribed lesions is impossible or incomplete. In addition, indications for this technique may expand to patients with T1 CRC diagnosed during colonoscopy. If this procedure is considered for these patients, they should be informed that an additional oncologic resection might be necessary,

depending on the presence of high-risk histological factors for lymph node metastasis.

Moreover, combining CAL-WR with a sentinel node procedure might be considered in the future. If technically possible, CAL-WR may also be suitable in cases with a T1 CRC with less favourable characteristics. Future research should include a cost-effectiveness analysis of CAL-WR and a prospective trial comparing CAL-WR with eFTR and/or ESD.

In the third part of this thesis, we focus on the management of advanced colorectal neoplasms.

CHAPTER 8 concerns the clinical relevance of CT colonography for patients with stenosing CRC. At the time of our study, most guidelines recommend preoperative CTC in patients with stenosing CRC.[46-49] The aims of the study were to evaluate the yield and added clinical implications of CTC in stenosing CRC.

One hundred sixty-two patients with stenosing CRC were included. Nine (5.6%) synchronous cancers proximal to the stenosing tumour were suspected based on CTC. While in four of the nine patients CTC did not change the primary surgical plan because the tumours were in the same surgical segment, the surgical treatment plan in the remaining five patients was changed by CTC. Three of these five patients underwent an extended resection, and the presence of synchronous tumours was confirmed. However, two of the three synchronous CRCs were also visible on abdominal staging CT. In the other two patients, the CTC result was false positive, which led to an unnecessarily extended resection in one patient.

Previous studies reported stenosing CRC in 15–20 % of the cases and synchronous tumors in 1–7 %.[50-57] CT colonography has similar sensitivity as colonoscopy in detecting CRC and has moderate sensitivity in detecting advanced adenomas.[58-60] Park et al. demonstrated a high sensitivity of CTC for detection of proximal synchronous tumors, but limited capability of CTC in differentiating advanced adenomas from CRC in patients with stenosing CRC.[61]

Preoperative CTC has some advantages when compared to colonoscopy performed 3 months after primary surgery: (1) CTC could prevent the need of secondary surgery in case of a synchronous tumor and (2) it could prevent growing of secondary tumors into a more advanced stage when detection and treatment are delayed.

Two previous studies described a change in surgical plan in 14–16 %, due to location errors, synchronous CRC, or synchronous adenomas revealed by performing CTC.[62,63] In these studies, the primary surgical plan was changed in 4 and 11% due to location errors. However, tattooing colorectal tumors during endoscopy is

currently standard of care, which limits the role of CT scan in determination of the location. Moreover, most stenosing tumors are at stage T3 or T4 (in our study in 90 % of the patients) and might therefore likely have been visible on abdominal staging CT, which is performed nowadays in all patients prior to surgery. The presence of a previous performed abdominal CT was not mentioned in these studies. In the abovementioned studies, the detection of synchronous CRC or adenomas changed the surgical plan in 7.3% and 4.1% of the patients, respectively. The stage of the synchronous tumors was not mentioned in above-described studies. In our study, in one of the four patients with suspected synchronous CRC but no change in the primary surgical treatment plan, the postoperative histology showed no synchronous CRC but a proximal 35-mm tubulovillous adenoma.

We demonstrated the clinical value of CTC seems to be very limited. In 3 out of 162 patients, CTC was meaningful in terms of detection of a second primary CRC that changed the primary surgical treatment strategy. In two patients, the CTC was false positive and even leading to an unnecessary extended resection in one patient. Based on our research, our recommendations at the time of the article was to perform active screening for synchronous carcinomas using abdominal staging CT and not CTC for the detection of synchronous tumours. Several years have passed since our article and in the current Dutch Colorectal Cancer Guideline, a CTC does not have a place in the preoperatively full imaging of the colon at diagnosis, only when a colonoscopy is contraindicated.

In **CHAPTER 9** we describe the outcomes of a retrospective study that analysed data from CRC patients scheduled to receive up to 8 planned cycles of capecitabine monotherapy. Patients were treated between 2009 and 2013 at a single large community hospital in the Netherlands. The aim of this study was to provide real-world data on adverse event rates and dose adjustments/discontinuations associated with capecitabine monotherapy in patients with metastatic CRC (mCRC). Adverse events we defined as: (1) hand-foot syndrome (HFS), (2) gastrointestinal events (GIE), (3) hematological adverse events and (4) cardiotoxicity. We chose to analyze only patients receiving capecitabine monotherapy to reduce unwanted interactions and influence by other anticancer drugs in the treatment.

We included data from 86 patients (45 females, mean age at start of treatment 69 years). HFS was experienced by 46.5% of patients and 44.2% experienced a GIE at some time during treatment. Neutropenia as haematological adverse event was found in one patient (1.1%). Cardiotoxicity was found in 5%. Most patients (77%) started with a dose lower than recommended and patients at the lowest dose also

had the lowest median relative dose intensities. Dose reductions and discontinuations occurred in 15 to 25% of patients who experienced HFS or GIE over the course of 8 cycles.

Comparison with the available literature shows us similar adverse events rates of capecitabine monotherapy. The rate of HFS in our study (46.5% overall) is consistent with rates observed in phase III clinical trials of 30–53.5% and with the rate of 42% reported in an observational study that included patients who received capecitabine as monotherapy or in combination treatment.[64-67] The rate of GIE in our study was 44.2%; previous studies have reported that between 11 and 50% of patients experience one gastrointestinal event, including diarrhea, vomiting, nausea, or abdominal pain, while receiving capecitabine monotherapy.[64-66] Our results are consistent with these findings. The haematological adverse events were rare in our study, 1.1%, comparable to the previous reported 1% in the available literature.[64-66] In our study the cardiotoxicity was observed in 5% of the patients. Previous studies reported 1% cardiotoxicity, or it was not reported at all, due to occurring at lower than the 5% threshold for reporting in previous studies.[64-66] It was not possible to establish if this difference could be explained by the current population being more frail than those described in previous controlled trials.

Most patients in this study (77%) started under the approved dose of 1250 mg/m^2 twice daily. The reduced starting doses used here are not the recommended reduced starting doses for special populations (75% of starting dose for renal impairment),and phase III trials evaluated a starting dose of 1250 mg/m^2 twice daily or used 1000 mg/m^2 twice daily in elderly patients >70 years of age.[64-66,68] Patients in this study who received the 1000 mg/m^2 twice-daily dose had a mean age of 71.5 years, consistent with age as an explanation for the use of this reduced dose. However, patients in the study who received 750 mg/m^2 twice daily had a mean age of 64.4 years, suggesting that this population was considered frail by their physician. Although this suggests that physicians are reducing the starting dose of capecitabine in anticipation of adverse events, our real-world data did not provide an explicit explanation for these treatment decisions.

Dose reductions and treatment discontinuations were common in this study, occurring in 17–24% of patients who experienced HFS and 15–25% of patients who experienced a GIE. Cassidy et al. reported that 34% of patients starting treatment at 1250 mg/m^2 twice daily required a dose reduction for adverse events, while Cunningham et al. reported that 15% of elderly patients who started capecitabine treatment at 1000 mg/m^2 twice daily discontinued due to adverse events.[64,65] On this point, a comparison between our found percentage and the percentages mentioned

in the literature is difficult duo to different therapy regims (different adjusted starting dose). In our analysis, the occurrence of HFS and GIE was not related to the dose of capecitabine, which may suggest that lower starting doses and dose reductions do not improve adverse event rates, nor do they prevent them from occurring. In an observational study by Stein et al., the incidence of HFS increased with duration of treatment and was higher in younger patients than in older patients (46 vs. 37%; p = 0.0014) despite similar median daily doses of capecitabine.[66]

The tolerability of chemotherapeutic drugs is an ongoing point of attention influencing treatment outcomes for cancer. This is even more important in the palliative setting. The most frequently occurring adverse events were HFS and GI toxicity. These adverse events often led to dose reductions or even termination of treatment in our study, possibly impairing the benefit of fluoropyrimidines in these patients. These results should be taken in consideration when treating patients with mCRC, particularly older or frail patients. Therefore, it is becoming more important to select appropriate patients who may benefit from this treatment. Growing evidence indicates that adjuvant chemotherapy with 5-FU monotherapy in patients with a stage II or III CRC with MMR-deficient tumours does not improve prognosis and seems to confer no improvement in overall survival.[69] Therefore, to identify such patients, MSI or IHC analysis should be considered in all patients with CRC before starting chemotherapy.

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