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part II
MANAGEMENT
OF EARLY
COLORECTAL
NEOPLASMS



CHAPTER

5

Referrals for surgical removal of polyps since the introduction of a colorectal cancer screening programme

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ABSTRACT

AIM

Implementation of the national bowel screening program in 2014 led to an increased detection rate of polyps. In general, polyps should be removed endoscopically. However, if the size and location of the polyp makes endoscopic removal technically difficult or if there is a suspicion for early (T1) cancer, surgery is the preferred method for removal. An increasing number of these patients are treated with minimal invasive surgical procedures instead of a segmental resection. The aim of our study was to assess the number of referrals for surgery and the type of surgery for polyps since the introduction of the national bowel screening program.

METHODS

A retrospective cohort study was performed. Patients who underwent surgery for colorectal polyps between January 2012 and December 2017 were included. Exclusion criteria were histologically proven carcinoma prior to surgery. Primary outcomes were number and type of surgical procedures for polyps.

RESULTS

In total, 164 patients were included. An annual increase of procedures for colorectal polyps was observed, from 18 patients in 2012 to 36 patients in 2017. All the procedures before implementation of the screening program were segmental resections and 58.8% of the patients underwent organ preserving surgery after implementation of the screening. Overall complication rate of organ preserving surgery was 16.3%, compared to 44.3% of segmental resections ($p = 0.001$). Overall invasive colorectal cancer was encountered in 23.8% of cases.

CONCLUSION

The number of referrals for surgical resection of colorectal polyps has doubled since the introduction of the CRC screening program with a substantial shift towards organ preserving techniques

INTRODUCTION

Colorectal cancer (CRC) is the second most common malignancy in the Netherlands, with an incidence of 14,258 in 2017.¹ Approximately 95% of CRCs will evolve from an adenomatous polyp or sessile serrated lesion (SSL's).² Adenomatous polyps are the most common polyps and account for approximately two-thirds of all colonic polyps.³ Despite the dysplastic character of the polyp, only 5% of all adenomatous polyps progresses to CRC. Endoscopic screening studies in an asymptomatic population show an overall adenoma prevalence of 25 to 30 percent at the age of 50 years.²⁻⁷

In order to reduce the incidence as well as the mortality rate of CRC, the Dutch National Institute for Health and Environment (RIVM) introduced the national bowel screening program in January 2014. All men and women aged between 55 and 75 years receive a fecal immunochemical test (FIT) biennially, followed by a colonoscopy in case of a positive FIT result.⁸ In a recent systematic review summarizing the results of 6,442 patients, endoscopic resection of large colonic polyps (→ 20 mm) was successful in 92% of the cases. Despite advanced techniques of endoscopic resection, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), colorectal surgery was required in the remaining group.⁹ In certain cases surgery is preferred, for instance if size and location of the polyp makes endoscopic removal technically difficult or if macroscopic inspection implies a suspicion for early (T1). In these cases, an en-bloc resection is the best treatment option.

Colorectal surgery is associated with significant morbidity and mortality. For malignant colorectal resections, all patient and procedure related data are collected in the Dutch Colorectal Audit, however, the data for premalignant lesions are not registered. Literature reporting the number of surgical procedures performed for adenomas or SSL's is lacking. Also, it is unclear whether surgical procedures performed for polyps have the same morbidity and mortality rates as surgical procedures performed for colorectal cancer.

The aim of our study was to investigate the number of referrals for surgical resection of colorectal polyps. Furthermore, the type of surgery and its clinical outcome were studied.

MATERIALS AND METHODS

Study design and population

After approval of the institutional review board, a retrospective cohort study was performed. Written consent from patients was not required.

Patients that underwent surgical removal of colorectal polyps between January

2012 to December 2017 were included. The national bowel screening program started in 2014.

Patients were included if they were referred for surgical removal of colorectal polyps that could not be endoscopically removed due to technical reasons (size, position of the endoscope, location) or if upon macroscopic inspection cancer was suspected. If lesions in the left-colon or rectum were suitable for removal by ESD they were referred to another hospital with experience with this. Exclusion criteria were defined as histological proven carcinomas prior to surgery, as well as patients with a genetic predisposition to colorectal cancer (i.e. patients with Lynch syndrome, APC related (attenuated-) adenomatous polyposis coli and serrated polyposis syndrome (SPS). Polyps were defined as lesions histological proven or macroscopically suspicious or (advanced) adenomas, SSL's or early (T1) cancer. Patients who were referred from other hospitals for surgical treatment were excluded.

Primary outcomes were the number and type of surgical procedures. Secondary outcomes were clinical and histological outcome. Clinical outcome was defined as 30-day or in-hospital morbidity and mortality was graded according to the Clavien-Dindo classification (CDG).¹⁰

Procedures and definitions

All endoscopic examinations were carried out by or under the supervision of a certified gastroenterologist. For the national screening program, all endoscopists and proceedings met the national quality requirements. If applicable, the 'lifting' sign was tested by injecting NaCl 0.9% with Indigo Carmine submucosally. Non-optimal lifting of the polyp was stated as a positive non-lifting sign. An attempt, but unsuccessful endoscopic resection of the polyp was defined as partial removal of the polyp. Colonoscopies performed after a positive fecal occult blood test within the national bowel screening program were defined as screening colonoscopies. Colonoscopies for all other reasons (surveillance following removal of adenomas or SSL's in the past or symptomatic patients) were defined as regular colonoscopies.

All patients were discussed at our weekly colorectal multidisciplinary team meeting. All surgical colorectal procedures were performed by or under the supervision of a specialized colorectal surgeon. The different types of surgery included a segmental colon resection, low anterior resection (LAR), transanal endoscopic microsurgery (TEM) and limited endoscopic-assisted wedge resection (LEAWR). LEAWR is a type of combined endoscopic-laparoscopic surgery (CELS) where no anastomosis is created.¹¹ During laparoscopy, the involved part of the colon is mobilized to ensure LEAWR. A suture was placed laparoscopically with intraluminal

endoscopic visualization through the base of the polyp. Traction was given on the suture to enable positioning of the linear stapler. Before stapling off the polyp, the patency of the lumen and total inclusion of the polyp tissue was checked endoscopically. Both TEM and LEAWR were introduced in our hospital in 2015. LEAWR was not suitable if the polyp encompassed more than half of the circumference of the colon, in case of diverticulosis or if polyps were located near or at Bauhin's valve. TEM was not suitable for polyps located more than 15 cm from the anal verge. Complications were graded according to the Clavien-Dindo classification (CDG) of complications.¹⁰ Major complications were defined as grade 3b or higher.

Histological material was obtained preoperatively through endoscopically conducted biopsies and/or postoperatively from the surgically resected specimen. Polyps were categorized as hyperplastic, tubular adenoma (TA), tubulo-villous adenoma (TVA), villous adenoma (VA) or sessile serrated lesions (SSL). Adenomas were further subdivided as low-grade dysplasia (LGD; mild to moderate dysplasia) or high-grade dysplasia (HGD; severe dysplasia). For staging invasive cancer, the TNM 5 classification system was used, according to the latest national guideline. High risk features for lymph node metastasis in case of a T1 colorectal carcinoma were defined as poorly differentiated tumour, (lymph)angio-invasive growth and a resection margin of less than 1mm. A low risk T1 colorectal carcinoma was defined as moderate/good differentiated tumour, no (lymph)angio-invasive growth and a free resection margin of 1mm or more.¹²

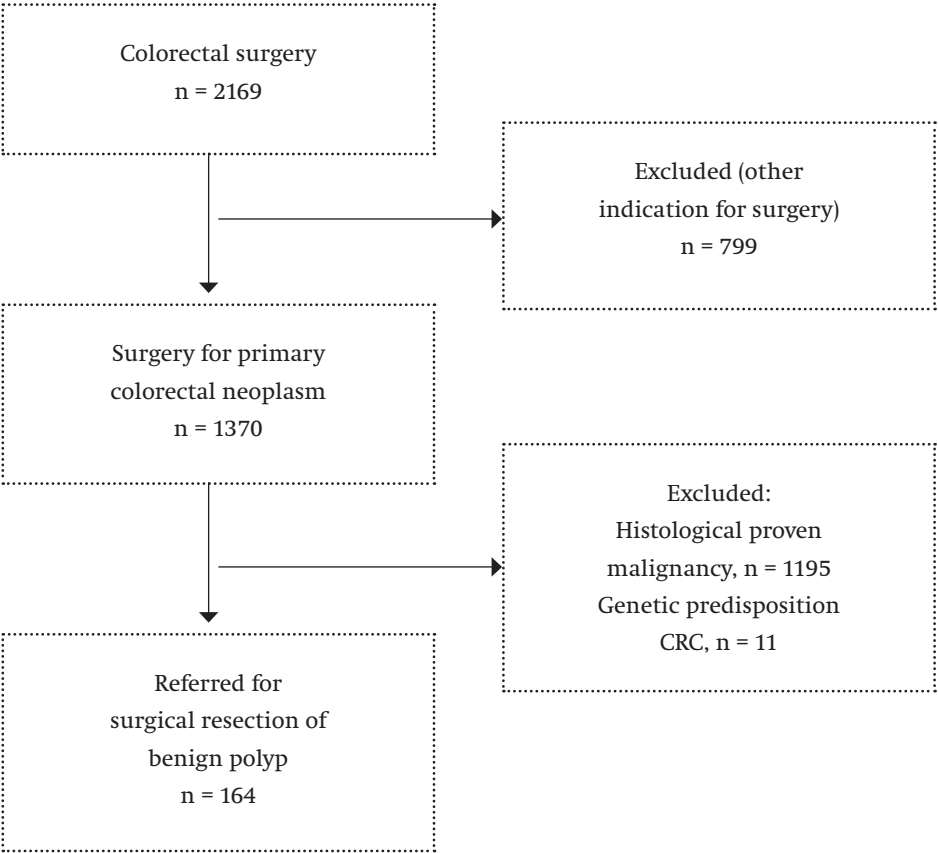
Data management and analysis

For data collection and analysis, both ResearchManager® (Cloud9 Software, Deventer, the Netherlands) and IBM SPSS Statistics, Version 25.0 (IBM Corp. Armonk, NY, USA) were used. Continuous variables were presented, according to the distribution, as median values with the interquartile range (IQR). Continuous data were compared between groups using the Mann-Whitney-U test and categorical data were compared using the Fisher's exact or Fisher-Freeman-Halter Test. P-values of < 0.05 were considered statistically significant.

RESULTS

A total of 2,169 patients were identified who underwent a colorectal surgical procedures between January 2012 and December 2017. Out of this group, 2,005 cases were excluded and 164 patients who were operated for benign polyps were included. (Figure 1)

Figure 1.
Flowchart of the patient selection process



The total number of conducted colonoscopies after implementation of the screening program ranged between 5.141 to 5.517 colonoscopies per year, in comparison to 5.555 colonoscopies in 2012 before implementation of the screening program.

The majority of patients were male (57.3%) with a median (IQR) age of 69 (range 63-74) years. (Table 1) The majority (76.2%) of patients were referred for surgery because of polyps that were technically endoscopically unresectable due to size,

Table 1.
Baseline characteristics

	Total N = 164 (%)
Age (years)	
Median	69
IQR	63-74
Gender	
Female	70 (42.7)
Male	94 (57.3)
BMI (kg/m2)	
Median	26.6
IQR	24.3-29.5
CCI (score)	
Median	3
IR	2-4.8
Morphology	
Sessile	51 (31.1)
Flat	43 (26.2)
Pedunculated	18 (11)
Unknown	52 (31.7)
Size (cm)	
Median	3.5
IQR	2.5-4.5
Location	
Right colon	90 (54.9)
Transverse colon	9 (5.5)
Left colon	37 (22.6)
Rectum and rectosigmoid	28 (17.1)
Preoperative histology	
No dysplasia	4 (2.4)
LGD	90 (54.9)
HGD	50 (30.5)
Unknown	20 (12.2)
Non-lifting sign	
Positive	31 (18.9)
Negative	22 (13.4)
Not performed	111 (67.7)
Endoscopic resection attempts	
One or more attempts	33 (20.1)
No attempts	131 (79.9)
Gastroenterologist's assessment	
Suspect malignant	55 (33.5)
Not suspect	109 (66.4)

IQR = interquartile range; BMI = body mass index; CCI = Charlson comorbidity index

location, and/or non-lifting sign. (Table 2) In total, 45.5% of encountered polyps were sessile, with a median size of 3.5 cm. The majority of polyps (54.9%) were located in the right colon and showed low grade dysplasia preoperatively (62.5%). In 33 cases (20.1%) one or more attempts were made for endoscopic removal. (Table 1) In 29 of these 33 patients no malignancy was suspected. Out of 55 polyps suspicious for an

Table 2.
Surgery characteristics

	Total N = 164 (%)
Indication for surgery	
Endoscopically unresectable	125 (76.2)
Non-radical polypectomy	20 (12.2)
Recurrence in scar tissue	11 (6.7)
Multiple polyps	5 (3.0)
Other	3 (1.8)
Duration of surgery (minutes)	
Median	95
IQR	70-129
Type of surgery	
Ileocecal resection	9 (5.5)
Right hemicolectomy	63 (38.4)
Left hemicolectomy	9 (5.5)
Transverse colon resection	4 (2.4)
Sigmoid resection	18 (11.0)
LAR	12 (7.3)
TEM	22 (13.4)
LEAWR	27 (16.5)
Approach	
Open	23 (14.0)
Laparoscopic/transanal	135 (80.5)
Conversion*	6 (4.3)

IQR = interquartile range; LAR = low anterior resection; TEM = transanal endoscopic micro-surgery; LEAWR = limited endoscopic-assisted wedge resection.
 * Percentage of total amount of intended laparoscopic surgeries

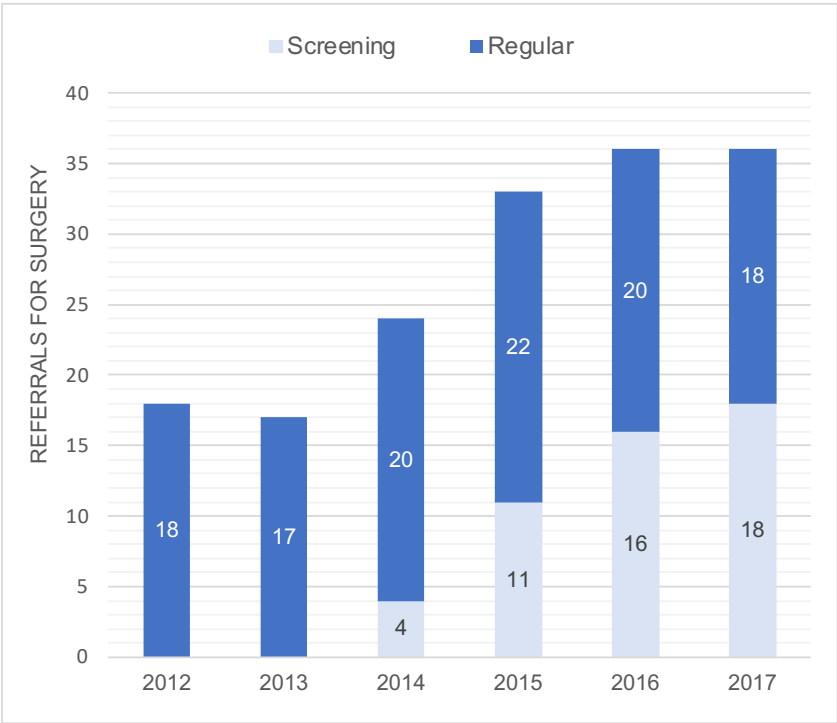
invasive tumor, 20 polyps were malignant (positive predictive value 36.3%). Of the 109 suspected benign polyps, 19 polyps were carcinomas (negative predictive value 82.6%). Of the 49 patients who underwent organ preserving surgery, 15 patients (30.6%) were suspected to have a malignancy. Of the 115 patients who underwent

major surgery, 18 (15.7%) patients had a polyp who was suspicious for an invasive tumor. In 51 out of 55 suspect malignant cases (92.7%) no endoscopic resection attempts were performed.

The main surgical procedure was a segmental colectomy (70.1%), the remaining group of 49 patients (29.9%) underwent a TEM (n = 22) or LEAWR (n = 27). Procedures were performed laparoscopically or transanally in 80.5% (n = 132) with a conversion rate of 4.3% (n = 6). (Table 2)

Before implementation of the national screening program in 2014, the annual number of patients who underwent surgical removal of polyps was 18 (2012) and 17 (2013). (Figure 2) Since the implementation, the absolute number of surgical procedures increased annually to 36 procedures in 2017. The percentage of patients who

Figure 2.
Annual volume of surgical procedures



'Regular' = number of patients who were referred for surgery after colonoscopy due to other reasons than a screening colonoscopy
'Screening' = number of patients who were referred or surgery after colonoscopy in case of national screening program

were referred for surgery after a positive FIT result increased from 16.7% in 2014 to 50% in 2017.

From 2012 to 2014, all surgical procedures were major surgical procedures. In the following years the number of organ preserving surgery increased to 21 out of 36 (58.3%) procedures in 2017, resulting in an average of 41.2% organ preserving surgeries after implementation of the screening program.

Clinical and pathological outcome

The overall complication rate was 36.0%, which were mostly minor complications. Only 8 out of 164 patients (4.9%) presented with one or more major complications, of which 7 patients were post-segmental resection. One patient presented with a major complication after an organ preserving procedure, a post-TEM hemorrhage treated surgically. There were no serious complications after LEAWR. In 4 out of 115 segmental resections (3.5%) an anastomotic leakage occurred. Postoperative mortality was zero. A significant lower overall complication rate (16.3%) was seen after organ preserving surgery compared to a segmental resection (44.3%) ($p = 0.001$). (Table 3)

Table 3. Clinical outcomes

	Total N = 164 (%)	Organ preserving N = 49 (%)	Segmental resections N = 115 (%)	p value
Overall complication rate	59 (36.0)	8 (16.3)	51 (44.3)	.001**
CDG				1.000**
≤ 3a	51 (31.1)	7 (14.3)	44 (38.3)	
≥ 3b	8 (4.9)	1 (2.0)	7 (6.1)	
Anastomotic leakage	4 (3.5*)	-	4 (3.5)	a
Mortality	-	-	-	a
(Re)laparotomy	7 (4.3)	-	7 (6.1)	.200**
Stoma creation at re-intervention				a
Temporary	2 (1.2)	-	2 (1.7)	
Permanent	1 (0.6)	-	1 (0.9)	
Days of admission				< .001***
Median	5	2	5	
IQR	3-6	2-3	4-8	
Readmission	11 (6.7)	2 (4.1)	9 (7.8)	.508**
Days of readmission				.808***
Median	6	6	6	
IQR	5-21	5-7	5-22.5	

CDG = Clavien-Dindo classification; IQR = interquartile range. A Statistical analysis could not be performed.

* Percentage of total primary anastomoses (n = 115).

** Fisher's Exact Test

*** Mann-Whitney U Test

Overall invasive colorectal cancer was encountered in 23.8% of the referred polyps. Fifty percent of the resected polyps appeared to contain high-grade dysplasia, 45% of the resected polyps contained low-grade dysplasia. (Table 4)

In 8 patients that underwent organ preserving treatment for a polyp a colorectal carcinoma was found. An additional oncological resection was indicated in 4 out of the 8 patients due to high risk features for lymph node metastases; this number represents only 8.2% of all patients who received organ preservation. The remaining four patients had a low risk pT1 CRC carcinoma. No major complications occurred within 30 days after additional oncological surgery.

Table 4.
Postoperative pathology

	Total N = 164 (%)	Organ preserving N = 49 (%)	Major surgery N = 115 (%)
Benign	125 (76.2)	41 (83.7)	84 (73.0)
High grade dysplasia	61	16	45
Low grade dysplasia	55	20	2
No dysplasia	5	3	2
Unknown	4	2	2
Malignant	39 (23.8)	8 (16.3)	31 (27.0)
Low risk pT1	4	4	-
High risk pT1	4	4	-
TNM > pT1	31	-	31

DISCUSSION

Since the introduction of the Dutch CRC screening program in 2014 the number of referrals for the surgical resection of polyps have doubled in our hospital. Thirty percent of these patients were treated using an organ preserving technique. Colorectal cancer was found in 24% of these patients.

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.¹³ The conducted screening colonoscopies after a positive FIT resulted in a higher number of surgical resections compared to the conducted colonoscopies in symptomatic patients. This is related to a higher number of endoscopically detected polyps during screening colonoscopies, which is consistent with results of earlier research in which adenoma prevalence in the screening population was higher than in symptomatic patients.¹⁴

In our hospital, the increase in surgical referrals for removal of colorectal polyps led to the development of a less invasive surgical technique. This technique (LEAWR), 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.¹¹

Our study shows a substantial morbidity related to segmental colon resections of polyps. These results are comparable with large cohort studies reporting an reoperation rate of 7.8% and readmission rate of 3.6% after surgery for nonmalignant colorectal polyps.^{15,16} Over time, there is a reduction of surgery related morbidity. [16] Morbidity rates for benign lesions are comparable to surgery for colorectal cancer.¹⁷

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%). [18] Three retrospective studies investigating postoperative complications after different types of CELS observed no complications.^{11, 19, 20} 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 seg-

mental colon resection. The overall complication rate was 25% and major complication rate was 3%.²¹ 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. Considering a significant lower overall complication rate was encountered in the organ preserving group, this therapy should be first choice if surgical treatment of colon polyps is necessary.

The overall postoperative malignancy rate of 23.8% is in line with malignancy rates between 6.9 and 44.3 percent of surgically resected colorectal polyps reported in the literature.²²⁻²⁷ A plausible explanation for the differences in percentages,, is selection bias, as polyps that were endoscopically deemed suspicious for early cancer were included in several studies.

In our study we observed a high percentage of right-sided polyps. According to multiple retrospective studies colorectal polyps predominantly exhibit a proximal colonic distribution.^{30,31} Another explanation for the high proportion of right-sided polyps referred for surgery is due to higher risk for complications such as perforation and bleeding associated with the removal of right-sided polyps.³⁰

In the majority of the included patients, 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 51 out of the 55 patients where no endoscopic attempt to remove the polyp was made, there was a suspicion of a malignancy with deep invasion. In these cases, an en-bloc resection is advised, which is not always possible by endoscopy.³¹⁻³⁴

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. Our hospital participates in a network with in which all these endoscopic techniques are available. A French study showed a reduction of referrals after the implementation of a regional referral network, however, all included patients were screen detected. [35] Therefore, the influence of a national bowel screening program on referral numbers was not investigated. 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%.³⁶ For rectal lesions, the choice for ESD or TEM has still to be established by a multicenter study (TRIASSIC-study) which is currently still including patients.³⁷

There were a few limitations in our study, mainly due to its retrospective design.

At first, 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. In the final years of the study period, complex polyps were extensively discussed with experienced endoscopists. Furthermore, total numbers and success rates of endoscopic treatments (polypectomies) and referrals for ESD to other hospitals during the studied time interval were not available. The increase in surgical referrals due to the implementation of the screening program led to the development of a less invasive technique (LEAWR) which may have reduced the threshold for surgical referrals. In addition, if all referred patients, despite complexity were discussed with more experienced endoscopists, the number of patients who underwent surgery could possibly have been lower. Despite increasing endoscopic possibilities and techniques over time, an increase in referrals for surgery was still observed. However, this study might reflect the consequences of a bowel screening program for daily clinical practice in a large teaching hospital.

In conclusion, the number of referrals for surgery for colorectal polyps has doubled since the introduction of the CRC screening program with a substantial shift towards organ preserving techniques.

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