Retrospective Cohort Study

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Endoscopic and surgical treatment outcomes of colitis-associated advanced colorectal neoplasia: a multicenter cohort study

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Background: Inflammatory bowel disease (IBD) patients are at increased risk of advanced neoplasia (high-grade dysplasia or colorectal cancer). The authors aimed to (1) assess synchronous and metachronous neoplasia following (sub)total or proctocolectomy, partial colectomy or endoscopic resection for advanced neoplasia in IBD, and (2) identify factors associated with treatment choice.
Material and methods: In this retrospective multicenter cohort study, the authors used the Dutch nationwide pathology databank (PALGA) to identify patients diagnosed with IBD and colonic advanced neoplasia (AN) between 1991 and 2020 in seven hospitals in the Netherlands. Logistic and Fine & Gray's subdistribution hazard models were used to assess adjusted subdistribution hazard ratios for metachronous neoplasia and associations with treatment choice.
Results: The authors included 189 patients (high-grade dysplasia $n=81$; colorectal cancer $n=108$). Patients were treated with proctocolectomy ($n=33$), (sub)total colectomy ($n=45$), partial colectomy ($n=56$) and endoscopic resection ($n=38$). Partial colectomy was more frequently performed in patients with limited disease and older age, with similar patient characteristics between Crohn's disease and ulcerative colitis. Synchronous neoplasia was found in 43 patients (25.0%; (sub)total or proctocolectomy $n=22$, partial colectomy $n=8$, endoscopic resection $n=13$). The authors found a metachronous neoplasia rate of 6.1, 11.5 and 13.7 per 100 patient-years after (sub)total colectomy, partial colectomy and endoscopic resection, respectively. Endoscopic resection, but not partial colectomy, was associated with an increased metachronous neoplasia risk (adjusted subdistribution hazard ratios 4.16, 95% CI 1.64–10.54, $P<0.01$) compared with (sub)total colectomy.
Conclusion: After confounder adjustment, partial colectomy yielded a similar metachronous neoplasia risk compared to (sub)total colectomy. High metachronous neoplasia rates after endoscopic resection underline the importance of strict subsequent endoscopic surveillance.

Keywords: colectomy, dysplasia, colorectal cancer, endoscopic resection, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) patients have a 1.4–1.7-fold increased risk of developing colorectal cancer (CRC) compared with the general population[1,2]. Endoscopic surveillance is recommended to detect and remove colorectal neoplasia, including indefinite for dysplasia, low-grade dysplasia, high-grade

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dysplasia (HGD) and CRC. In case advanced neoplasia (including HGD and CRC) is detected, complete lesion resection is recommended to prevent residual and recurring colorectal neoplasia.

Historically, a proctocolectomy or (sub)total colectomy was recommended for colorectal advanced neoplasia due to the high risk of synchronous and metachronous (non-visible) colorectal advanced neoplasia[3–6]. This surgical approach potentially results in a permanent ileostomy or ileal pouch-anal anastomosis, significantly impacting quality of life[7]. However, advances in surveillance techniques such as high-definition and chromoendoscopy have improved lesion detection, limiting the risk of missed synchronous neoplasia[8,9]. A recent study in Crohn's disease (CD) patients with CRC reported no increased metachronous CRC risk after partial colectomy compared with (sub) total or proctocolectomy, suggesting that a more restrictive surgical approach may be feasible in patients with limited disease[10]. Another study in ulcerative colitis (UC) patients with CRC showed no metachronous CRC after 7 years of follow-up, suggesting that partial colectomy might be feasible in elderly patients[11].

An even more colon-sparing approach for advanced neoplasia is endoscopic resection, which could be considered for unifocal dysplastic lesions that appear endoscopically resectable (visible lesions with clear borders that lift well), or when the risk of surgery outweighs potential oncological benefits[12–14]. For CRC, limited data from case series show the feasibility of endoscopic resection in case of early-stage CRC, in line with studies on early CRC in the non-IBD population[15–17]. In addition, there are limited data on factors associated with treatment choice in clinical practice. International guidelines advocate a tailored treatment strategy for advanced neoplasia, in which (sub)total or proctocolectomy remains the current standard, but endoscopic resection and partial colectomy can be considered in a subgroup of patients. However, these recommendations are based on low-quality evidence[12,13].

In this study, we aimed to (1) compare cumulative incidences of synchronous and metachronous colorectal neoplasia as well as mortality following advanced neoplasia in CD and UC patients who underwent proctocolectomy, (sub)total colectomy, partial colectomy or endoscopic resection, and (2) to determine factors associated with advanced neoplasia treatment choice.

HIGHLIGHTS

- Synchronous colorectal neoplasia was found in 1 out of 4 patients.
- 1 out of 3 patients developed metachronous neoplasia after a median 27.5 months.
- Endoscopic resection was associated with metachronous advanced neoplasia.
- Partial and (sub)total colectomy yielded similar metachronous neoplasia rates.
- All-cause mortality did not differ between treatment modalities.

Methods

Design and outcomes

We performed a multicenter retrospective cohort study in seven hospitals in the Netherlands and assessed the following outcomes after proctocolectomy, (sub)total colectomy, partial colectomy and endoscopic resection for advanced neoplasia in CD and UC:

(1) Synchronous colorectal neoplasia, defined as co-existence of two or more neoplastic colorectal lesions detected in the initial resection specimen or up to 6 months after treatment of the index lesion, categorized in (a) any neoplasia (independent of grade) and (b) advanced neoplasia (HGD or CRC)[18].
(2) Metachronous neoplasia, defined as colorectal neoplasia detected greater than or equal to 6 months after treatment of index advanced neoplasia, categorized in (a) any neoplasia (independent of grade) and (b) only advanced neoplasia, including the impact of IBD type[19].
(3) All-cause mortality.
(4) Clinical and disease characteristics associated with advanced neoplasia treatment choice.

Patients

The Dutch nationwide pathology databank (PALGA) was searched up to 1 December 2020, to identify patients with IBD and advanced neoplasia in five academic and two peripheral hospitals in the Netherlands. All seven selected centres are high volume IBD centres with accessible electronic patient charts. PALGA has a complete nationwide coverage since 1991. Each report links with an identifier to individual patient records. The search was performed using the following terms: 'ulcerative colitis', 'Crohn's disease', 'indeterminate colitis' and 'chronic idiopathic inflammatory bowel disease' and 'high-grade dysplasia', 'carcinoma in situ' and 'colorectal cancer'. All patients with IBD [UC, CD or IBD-unclassified (IBD-U)] with a histological diagnosis of colorectal advanced neoplasia and available treatment data were included. Exclusion criteria were familial CRC syndrome, advanced neoplasia prior to IBD diagnosis.

Data Collection

We extracted the following data from electronic patient records: Sex, age, IBD type and extent [Limited disease: Montreal classification E1 and E2 (UC)[20], or less than 50% colonic involvement (CD); Extensive disease: Montreal classification E3 (UC), or more than 50% colonic involvement (CD)], IBD duration, CRC family history, smoking, primary sclerosing cholangitis (PSC), post-inflammatory polyps, and CRC risk stratification according to the BSG guideline[21].

In addition, data regarding colorectal neoplasia were collected, including date, grade (indefinite for dysplasia, low-grade dysplasia, HGD or CRC), type (polypoid, non-polypoid, invisible[13]) and location. Index advanced neoplasia was defined as the first colorectal lesion with HGD or CRC. In case of co-existence of two or more advanced lesions, we scored the highest grade. Only for CRC, TNM stage[22] and all-cause mortality were derived using the national cancer registry of the Netherlands (NCR), with nationwide coverage since 1989[23].

The treatment modality of index advanced neoplasia was collected and categorized as (1) endoscopic resection [snare polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal resection (ESD)], (2) partial colectomy (ileocecal resection, segmental resection, right or left hemicolectomy) or (3) (sub)total or proctocolectomy. Endoscopic

Table 1

Baseline characteristics of $n = 189$ advanced neoplasia patients.

Characteristics	(Sub)total and proctocolectomy, $n = 78$	Partial colectomy, $n = 56$	Endoscopic resection, $n = 38$	Total sample[a] ($n = 189$)
Male sex, *n* [%]	47 [60.3]	32 [57.1]	21 [55.3]	110 [58.2]
Disease, *n* [%]				
Ulcerative colitis	54 [68.4]	28 [50.9]	25 [65.8]	119 [63.0]
Crohn's disease	23 [29.1]	25 [45.5]	12 [31.6]	65 [34.4]
IBD-unclassified	2 [2.5]	2 [3.6]	1 [2.6]	5 [2.6]
Age at time of IBD diagnosis, median [IQR]	28 [19.0–40.0]	34 [24.0–52.5]	37 [24.0–48.0]	31 [22.0–44.5]
Family history of colorectal cancer, *n* [%]	8 [14.5]	8 [20.0]	6 [21.4]	22 [11.6]
Smoking, *n* [%]				
Current	2 [2.5]	3 [5.5]	4 [10.5]	10 [5.3]
Past	10 [12.7]	17 [30.9]	13 [34.2]	42 [22.2]
None	51 [64.6]	25 [45.5]	17 [44.7]	102 [54.0]
PSC, *n* [%]	17 [21.5]	1 [1.8]	3 [7.9]	23 [12.2]
Post-inflammatory polyps, *n* [%]	35 [44.3]	24 [43.6]	16 [42.1]	86 [45.5]
Maximal endoscopic extent (Montreal), *n* [%]				
E1 (ulcerative colitis)	0	2 [6.7]	0	2 [1.0]
E2 (ulcerative colitis)	7 [12.5]	13 [43.3]	5 [19.2]	26 [13.8]
E3 (ulcerative colitis)	49 [87.5]	15 [50.0]	21 [80.8]	96 [50.8]
L1 (Crohn's disease)	0	0	3 [25.0]	3 [1.6]
Colon <50% (Crohn's disease)	3 [13.6]	12 [46.2]	5 [41.7]	22 [11.6]
Colon >50% (Crohn's disease)	19 [86.4]	14 [53.8]	4 [33.3]	40 [21.2]
CRC risk classification[b], *n* [%]				
Low risk	3 [3.8]	12 [21.8]	10 [26.3]	32 [16.9]
Intermediate risk	47 [59.5]	28 [50.9]	18 [47.4]	76 [40.2]
High risk	25 [31.6]	7 [12.7]	6 [15.8]	55 [29.1]
No indication for surveillance	4 [5.1]	8 [14.5]	4 [10.5]	26 [13.8]
Index AN, *n* [%]				
High-grade dysplasia	33 [42.3]	12 [21.4]	35 [92.1]	81 [42.9]
Colorectal cancer	45 [57.7]	44 [78.6]	3 [7.9]	108 [57.1]
Lesion characteristics, *n* [%]				
Polypoid	16 [23.2]	16 [39.0]	27 [71.1]	60 [31.7]
Non-polypoid	46 [66.7]	21 [51.2]	11 [28.9]	83 [43.9]
Invisible	7 [10.1]	4 [9.8]	0	11 [5.8]
Tumour stage[c], *n* [%]				
I	8 [17.8]	6 [13.6]	3 [100.0]	19 [17.6]
II	15 [33.3]	17 [38.6]	0	34 [31.5]
III	15 [33.3]	13 [29.5]	0	29 [26.9]
IV	5 [11.1]	7 [15.9]	0	22 [20.4]
Multifocal neoplasia, *n* [%]	22 [28.9]	7 [13.5]	8 [21.1]	37 [19.6]
Prior dysplasia, *n* [%]	26 [32.9]	9 [16.4]	14 [36.8]	50 [26.5]
Indefinite for dysplasia	6 [7.6]	0 [0.0]	2 [5.3]	8 [4.2]
Low-grade dysplasia	24 [30.4]	8 [14.5]	14 [36.8]	47 [24.9]
Age at time of index AN in years, median [IQR]	48 [39.8–59.0]	62 [51.0–70.0]	58 [51.0–67.3]	55 [45.0–64.5]
IBD duration until index AN in years, median [IQR]	18.0 [11.0–24.0]	19.0 [13.0–31.0]	19.0 [13.0–30.0]	19.0 [12.0–26.0]
Endoscopic follow-up after index AN in months, median [IQR]	30.0 [0.0–61.0]	20.5 [1.0–40.5]	48.5 [13.0–104.5]	27.0 [7.0–69.0]
Endoscopies after index AN, median [IQR]	2 [0–4]	1.5 [0–3]	4 [2–6]	2 [1–4]

AN indicate advanced neoplasia; CRC, colorectal cancer; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis.

[a]Including 17 patients without treatment of index AN.

[b]Risk classification prior to index AN, according to the BSG guidelines[20].

[c]For index CRC only, based on TNM classification[21].

and surgical follow-up was recorded until the most recent available procedure.

Statistical analysis

Categorical and continuous variables were reported as proportions with percentages and medians with interquartile range (IQR), respectively. Categorical variables were compared with chi-square or Fisher exact tests (for groups with $n \leq 5$) and continuous variables with Mann–Whitney U tests. We performed competing risk analyses with Fine & Gray's subdistribution hazard model to assess metachronous neoplasia, using subdistribution hazard ratios (sHR) with a 95% CI. Death and proctocolectomy were considered competing events. We censored patients at the end of follow-up if no event (metachronous neoplasia, death, or proctocolectomy) occurred. The cumulative metachronous neoplasia and

mortality incidence were displayed with cumulative incidence functions. Incidence curves were compared using Gray's test. Considering the long inclusion period of our study and the fact that endoscopic surveillance an treatment techniques have advanced over time, we performed a time-frame analysis excluding all patients with an index lesion less than 2010. The cut-off point was set on 2010 because of the implementation of high-definition devices around this time, and the publication of the first studies on EMR and ESD in IBD in 2007 and 2008, making endoscopic resection a more widely accepted modality in the subsequent years[24,25]. Associations with treatment modalities were assessed with a multinomial logistic regression model and presented as (adjusted) odds ratios ((a)OR) with 95% CI. Confounder selection for multivariable models was based on clinical relevance and univariable $P < 0.1$. The inflammatory pattern (continuous vs. segmental) of UC/IBD-U vs. CD could potentially result in different effectiveness of partial and (sub)total) colectomy between IBD types. Therefore, we explored the modifying effect of IBD type on the metachronous (advanced) neoplasia risk. Statistical analyses were performed with SPSS v25 and R v3.6.3 (package "*cmprsk*").

Ethical considerations

This study was approved by the institutional review board of the Radboud University Medical Center (2017-3219) and the scientific committee of PALGA (lzv-2019-87). Our work has been reported in line with the STROCSS criteria and was registered in clinicaltrials.gov (NCT05674773)[26], Supplemental Digital Content 1, http://links.lww.com/JS9/A670.

Results

Patients

We included 189 IBD patients with advanced neoplasia (supplementary figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A671), including 81 patients with HGD and 108 patients with CRC as index AN, of whom 172 underwent treatment. Of these, 110 (58.2%) were male, 119 (63.0%) had UC, 23 (12.2%) had PSC and 136 (72.0%) had extensive disease. Median IBD duration at time of index AN was 19 years (IQR 10.5–25.0) (Table 1 and supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A671).

Treatment of AN

Index advanced neoplasia was treated with (sub)total or proctocolectomy in 78 (41.3%; CD $n = 22$, 33.8%; UC/IBD-U $n = 56$, 45.2%) patients and with partial colectomy in 56 (29.6%; CD $n = 26$, 40.0%; UC/IBD-U $n = 30$, 24.2%) patients (Table 2 and supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/A671). Endoscopic resection was performed in 38 (20.1%; CD $n = 12$, 18.5%; UC/IBD-U $n = 26$, 21.0%). There were no significant differences in patient characteristics between CD and UC/IBD-U, except for more frequent PSC in the (sub)total or proctocolectomy group and more extensive disease in the endoscopic resection group with UC (supplementary table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A671). In 17 (9.0%; CD $n = 5$, 7.7%; UC/IBD-U $n = 12$, 9.7%) patients, the index advanced neoplasia was left untreated due to comorbidity or metastatic disease. Lesions were located in (previously) inflamed colonic mucosa in 76 (97.4%), 50 (89.3%) and 30 (78.9%) of patients who were treated with (sub)total or proctocolectomy, partial colectomy or endoscopic resection, respectively. Indications for surgery are reported in supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/A671.

Synchronous CRC

Synchronous neoplasia (any grade) was found in 43 (22.8%, indefinite/low-grade dysplasia $n = 33$, HGD $n = 9$, CRC $n = 1$), without a significant difference between CD ($n = 16$, 13.9%) and UC/IBD-U ($n = 27$, 29.4%, $P = 0.43$). Synchronous neoplasia was observed in 22 (28.2%) patients who underwent (sub)total or proctocolectomy, 8 (14.3%) who underwent partial colectomy, and 13 (34.2%) who underwent endoscopic resection ($P = 0.06$). Synchronous advanced neoplasia was found in 10 (5.3%) patients without a significant difference between CD ($n = 5$, 3.4%) and UC/IBD-U ($n = 5$, 6.6%, $P = 0.29$). Synchronous advanced neoplasia was detected in 5 (6.4%) patients who underwent (sub)total or proctocolectomy, one (1.8%) who underwent partial colectomy and four (10.5%) who underwent endoscopic resection (Fig. 1).

Metachronous neoplasia

Median endoscopic follow-up after treatment of index advanced neoplasia was 27 months (IQR 7.0–69.0), with a median of two (IQR 1–4) endoscopies. Forty-two patients (30.2%, CD $n = 16$, 24.6%; UC $n = 26$, 21.0%) developed metachronous neoplasia (indefinite/low-grade dysplasia $n = 26$, HGD $n = 9$, CRC $n = 7$) after median 27.5 months (IQR 14.0–46.0) (Fig. 2A). Overall metachronous (advanced) neoplasia rates and cumulative incidences for each treatment modality are displayed in Figure 1. For CD, we found a metachronous neoplasia rate of 3.5, 9.2 and 16.9, and for UC/IBD-U of 7.8, 13.6 and 12.4 per 100 patient-years after (sub)total colectomy, partial colectomy and endoscopic resection, respectively (supplementary Figure 2, Supplemental

Table 2

Treatment of index advanced neoplasia.

Treatment	HGD ($n = 81$)	CRC ($n = 108$)	Total sample ($n = 189$)
(Sub)total or proctocolectomy, *n* [%]	33 [40.7]	45 [41.7]	78 [41.3]
Proctocolectomy	14 [17.3]	19 [17.6]	33 [17.5]
(Sub)total colectomy	19 [23.5]	26 [24.1]	45 [23.8]
Partial colectomy, *n* [%]	12 [14.8]	44 [40.7]	56 [29.6]
Left hemicolectomy	1 [1.2]	3 [2.8] 3	4 [2.1]
Right hemicolectomy	5 [6.2]	14 [13.0]	19 [10.1]
Segment resection	5 [6.2]	24 [22.2]	29 [15.3]
Ileocecal resection	1 [1.2]	3 [2.8]	4 [2.1]
Endoscopic resection, *n* [%]	35 [43.2]	3 [2.8]	38 [20.1]
Polypectomy	21 [25.9]	1 [0.9]	22 [11.6]
EMR	6 [7.4]	0 [0.0]	6 [3.2]
ESD	6 [7.4]	0 [0.0]	6 [3.2]
Unknown	2 [2.5]	2 [1.9]	4 [2.1]
No resection, *n* [%]	1 [1.2]	16 [14.8]	17 [9.0]

CRC, colorectal cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia.

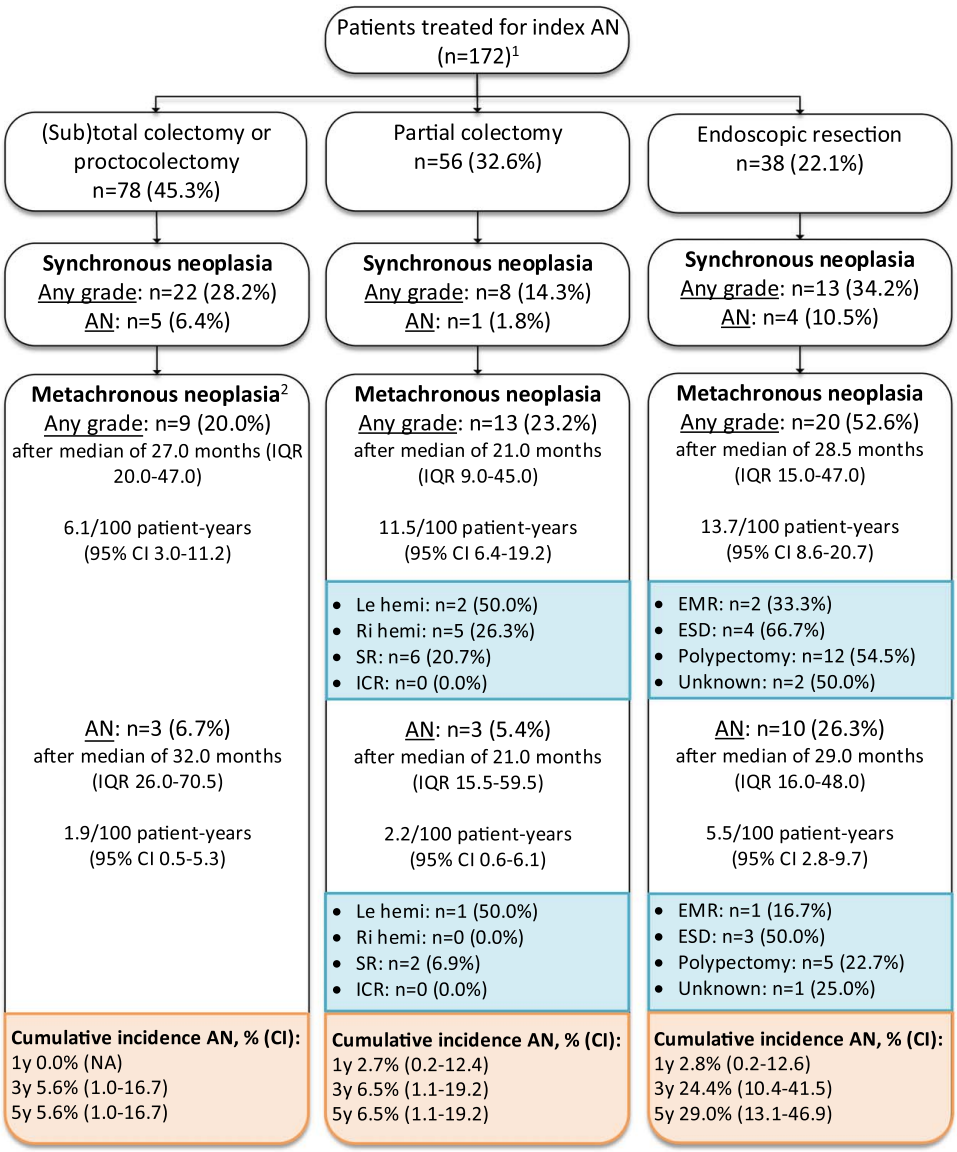

Figure 1. Synchronous and metachronous neoplasia per treatment modality. [1]Seventeen patients who did not undergo treatment for index AN were excluded from analysis. [2]Patients who were treated with proctocolectomy were excluded from analysis of metachronous neoplasia. AN indicate advanced neoplasia; CRC, colorectal cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ICR, ileocecal resection; IQR, interquartile range; Le hemi, left hemicolectomy; NA, not applicable; Ri hemi, right hemicolectomy, SR, segmental resection.

Digital Content 2, http://links.lww.com/JS9/A671). Sixteen (11.5%, CD $n=6$, 9.2%; UC/IBD-U $n=10$, 8.1%) patients developed metachronous advanced neoplasia after median 28.0 months (IQR 17.5–55.0) (Fig. 2B). We observed a metachronous advanced neoplasia rate of 3.2, 1.6 and 2.9 for CD and 1.1, 2.9 and 7.0 per 100 patient-years for UC/IBD-U after (sub) total colectomy, partial colectomy and endoscopic resection, respectively (supplementary Figure 3, Supplemental Digital Content 2, http://links.lww.com/JS9/A671).

Predictors of metachronous neoplasia

Our competing risk model showed that endoscopic resection was an independent predictor of metachronous neoplasia after adjustment for type of index advanced neoplasia, synchronous neoplasia and strictures or fistulas [asHR 3.56 (95% CI 1.50–8.43), $P<0.01$] in contrast to partial colectomy [asHR 2.00 (95% CI 0.82–4.89), $P=0.13$, Table 3]. Endoscopic resection was a predictor for metachronous advanced neoplasia [sHR 5.79 (95% CI 1.62–20.70), $P<0.01$, Table 4]. IBD type was not a significant effect modifier for the metachronous (advanced) neoplasia risk (data not shown). A time-frame analysis, excluding patients with advanced neoplasia <2010, showed a statistically significant sHR in line with the main analysis (sHR 7.10, 95% CI 1.92–26.30, $P<0.01$). Of note, 12 (75.0%) metachronous lesions detected after endoscopic resection of index advanced neoplasia were located in the same colon segment where the index advanced neoplasia was found. Fifteen (35.7%) patients underwent additional surgical resection for metachronous neoplasia

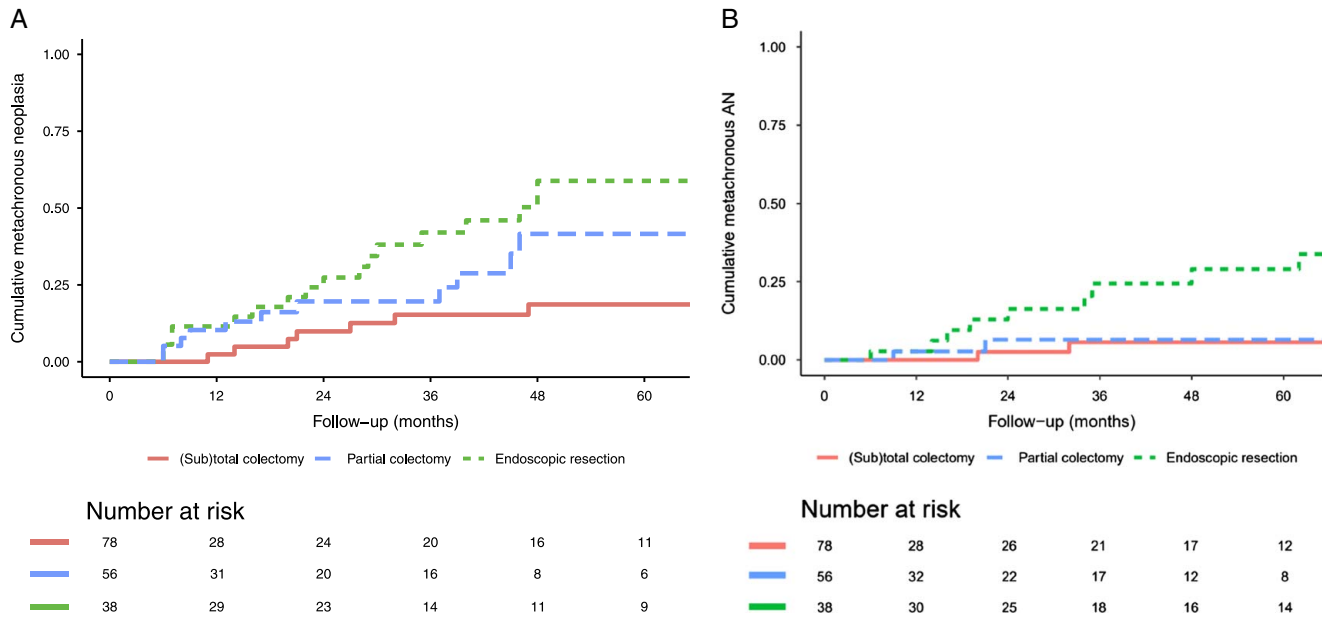

Figure 2. (A) Cumulative incidence of metachronous neoplasia by treatment modality. (B) Cumulative incidence of metachronous advanced neoplasia by treatment modality.

(supplementary Figure 4, Supplemental Digital Content 2, http://links.lww.com/JS9/A671).

Mortality after CRC diagnosis

No significant difference in all-cause mortality between treatment modalities was observed after a median 70.0 months (IQR 32.8–98.5) follow-up (CRC: $P = 0.546$, Fig. 3). All 17 patients who did not undergo treatment for index AN died within 3 years after index AN diagnosis.

Associations with treatment modalities

Compared to (sub)total or proctocolectomy, endoscopic resection and partial colectomy were more frequently performed in patients with limited disease extent [adjusted odds ratio (aOR) 4.52, 95% CI 1.77–11.57, $P = 0.04$ and aOR 3.49, 95% CI 1.09–11.24, $P < 0.01$, respectively) and older age at time of index advanced neoplasia (annual aOR 1.06, 95% CI 1.02–1.09, $P < 0.01$ and annual OR 1.08, 95% CI 1.03–1.13, $P < 0.01$, respectively). Partial colectomy was associated with CD rather than UC/IBD-U (OR 2.21, 95% CI 1.07–4.53, $P = 0.03$) and absence of PSC (aOR 8.94, 95% CI 1.09–73.5, $P = 0.04$). Endoscopic resection was associated with HGD rather than CRC diagnosis (aOR 27.26, 95% CI 6.79–109.43, $P < 0.01$, Table 5).

Discussion

In this multicenter study, including 189 IBD patients with advanced neoplasia, both partial colectomy and endoscopic resection were frequently performed in CD and UC/IBD-U. Synchronous neoplasia was detected in one-fourth of patients without significant differences between treatment modalities or IBD types. After confounder adjustment, partial colectomy did not result in an increased metachronous neoplasia risk compared to (sub)total colectomy. By contrast, endoscopic resection was associated with metachronous neoplasia and advanced neoplasia. IBD type did not impact metachronous (advanced) neoplasia rates. All-cause mortality after CRC diagnosis did not differ between treatment modalities. Both endoscopic resection and partial colectomy were associated with limited disease extent and older age at time of index advanced neoplasia.

Current guidelines recommend (sub)total or proctocolectomy for advanced neoplasia in both CD and UC/IBD-U based on high synchronous and metachronous advanced neoplasia rates in previous studies[13,21,27]. We found synchronous advanced neoplasia in 3.4% of CD patients and 6.6% of UC patients treated with (sub)total or proctocolectomy. A recent Italian study in CD patients reported a higher advanced neoplasia rate of 9% after (sub)total or proctocolectomy[10]. Another observational UC study observed a higher synchronous advanced neoplasia rate of 14%[18]. Our study yielded a cumulative metachronous advanced neoplasia incidence of 6.7% after median 32.0 months following (sub)total colectomy and 5.4% after median 21.0 months following partial colectomy. Conflicting evidence regarding metachronous lesions after advanced neoplasia treatment in IBD is available. As such, one study in CD patients ($n = 64$) reported a cumulative metachronous CRC incidence of 40% following partial colectomy and 35% after (sub)total colectomy after median 7 years[19]. Another CD study ($n = 99$) reported 1.3% and 0.0% CRC rates after median 3.5 years, respectively[10]. A UC study ($n = 59$) did not detect any metachronous CRC after (sub)total or partial colectomy for CRC with a median follow-up of 7 years[11]. These conflicting results might be explained by analysis without risk adjustment for proctocolectomy, differences in follow-up duration and CRC risk profiles of included patients.

One could hypothesize that the segmental inflammation of CD permits a more limited resection compared to the continuous inflammatory pattern of UC. Consequently, partial colectomy in UC might result in an increased metachronous neoplasia risk due to residual inflamed colonic mucosa compared to CD.

Table 3

Univariable and multivariable hazard ratios for metachronous neoplasia (any grade).

Characteristics	Univariable sHR [95% CI]	*P*	Multivariable[a] asHR [95% CI]	*P*
Treatment				
Endoscopic	4.38 (2.01–9.56)	< 0.01	3.56 (1.50–8.43)	< 0.01
Partial colectomy (ref. (sub)total colectomy)	1.70 (0.74–3.93)	0.22	2.00 (0.82–4.89)	0.13
IBD type (ref: UC/IBD-U)	0.84 (0.44–1.58)	0.58		
Index AN (HGD)	2.29 (1.25–4.21)	< 0.01		
Tumour stage[b] (ref: I)				
II	1.09 (0.33–3.59)	0.89		
III	0.50 (0.12–2.15)	0.35		
IV	0.19 (0.03–1.60)	0.13		
Synchronous neoplasia	2.29 (1.22–4.30)	< 0.01		
Polypoid index AN[c] (ref non-polypoid or invisible)	0.80 (0.42–1.55)	0.52		
Prior dysplasia	1.00 (0.49–2.04)	0.99		
Extensive disease[d]	0.93 (0.48–1.77)	0.81		
Strictures or fistulas	0.57 (0.30–1.09)	0.09		
PSC	1.04 (0.41–2.66)	0.93		
Family history of CRC	1.64 (0.74–3.64)	0.23		
Age at time of index AN	1.00 (0.98–1.02)	0.97		
Disease duration at time of index AN	0.99 (0.97–1.02)	0.63		

AN indicate advanced neoplasia; asHR, adjusted subdistribution hazard ratio; CD, Crohn's disease; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IBD-U, IBD-unclassified; PSC, primary sclerosing cholangitis; sHR, subdistribution hazard ratio; UC, ulcerative colitis.

[a]Multivariable model with adjustment for type of index AN, synchronous neoplasia and strictures or fistulas.

[b]For index CRC patients only.

[c]Thirty-four patients with missing values were not included in analysis

[d]UC: E3 colitis (Montreal classification), CD: > 50% inflamed colonic mucosa

Table 4

Univariable hazard ratios for metachronous advanced neoplasia.

Characteristics	Univariable sHR [95% CI]	*P*
Treatment		
Endoscopic	5.79 (1.62–20.70)	< 0.01
Partial colectomy (ref: (sub)total colectomy)	1.11 (0.28–5.40)	0.90
IBD type (ref: UC/IBD-U)	0.77 (0.27–2.20)	0.62
Index AN (HGD)	4.34 (1.40–13.40)	0.01
Synchronous neoplasia	1.62 (0.57–4.58)	0.37
Polypoid index AN[a] (ref non-polypoid or invisible)	1.33 (0.47–3.80)	0.60
Prior dysplasia	1.50 (0.52–4.30)	0.45
Extensive disease[b]	6.66 (0.89–49.70)	0.06
Strictures or fistulas	0.30 (0.09–1.05)	0.06
PSC	1.10 (0.25–4.86)	0.90
Family history of CRC	2.74 (0.89–8.45)	0.08
Age at time of index AN	1.00 (0.96–1.03)	0.80
Disease duration at time of index AN	1.01 (0.98–1.05)	0.50

AN indicate advanced neoplasia; CD, Crohn's disease; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IBD-U, IBD-unclassified; PSC, primary sclerosing cholangitis; sHR, subdistribution hazard ratio; UC, ulcerative colitis.

[a]Thirty-four missing values were not included in analysis

[b]UC: E3 colitis (Montreal classification), CD: > 50% inflamed colonic mucosa

Interestingly, we observed that partial colectomy was frequently performed in UC patients (24.2%) without an increased risk of metachronous neoplasia compared with CD. Moreover, CD and UC patients that underwent partial colectomy had similar disease characteristics, including a similar disease extent and age. It could be suggested that historically non-inflamed or mildly inflamed colonic segments do not harbour an increased metachronous neoplasia risk, which might explain the comparable metachronous neoplasia rates between patients with (sub)total colectomy and partial colectomy in both UC and CD. The comparable metachronous neoplasia and advanced neoplasia rates between partial colectomy and (sub)total colectomy suggest that treatment with partial colectomy seems safe. Importantly, patients who received partial colectomy were older and had limited disease extent compared to those who underwent (sub)total colectomy, indicating that partial colectomy could be considered in case of a lower residual CRC risk after colectomy and in absence of other CRC risk factors. In addition, older patients may have more comorbidities or a limited life expectancy, justifying more restricted resection.

A significantly higher metachronous (advanced) neoplasia rate was found in patients who underwent endoscopic resection compared with those who underwent (sub)total colectomy. This might be explained by the risk of incomplete endoscopic resection of index advanced neoplasia and by more residual colon at risk for advanced neoplasia development. Indeed, 75.0% of metachronous neoplasia after endoscopic resection developed in the same colon segment as the index advanced neoplasia. Only one cohort study reported on endoscopic treatment of HGD with EMR and ESD, showing a metachronous neoplasia rate of 17% and a metachronous advanced neoplasia rate of 9–13% after a follow-up of 40–68 months[28]. The higher rate in our study (26.3% after median 29.0 months) could be explained by our

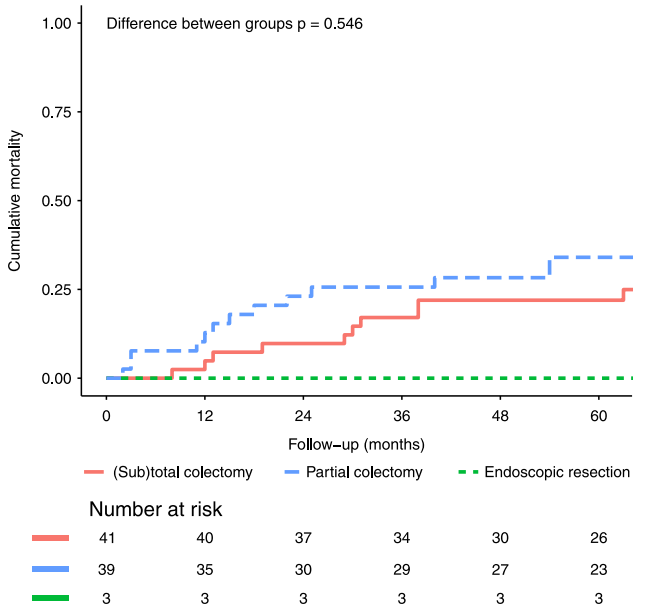

Figure 3. Cumulative all-cause mortality by treatment modality.

Table 5

Multinomial regression results for characteristics associated with treatment modality of index advanced neoplasia (endoscopic vs. partial colectomy vs. (sub)total or proctocolectomy).

Characteristics	Univariable OR [95% CI]	*P*	Multivariable OR [95% CI]	*P*
IBD type (Crohn's disease)				
PC	2.21 [10.7–4.53]	0.03		
ER	1.18 [0.51–2.73]	0.71		
Limited disease extent				
PC	6.33 [2.72–14.75]	< 0.01	4.52 [1.77–11.57]	0.04
ER	3.54 [1.38–9.08]	< 0.01	3.49 [1.09–11.24]	< 0.01
Absence of pseudopolyps				
PC	1.09 [0.54–2.17]	0.82		
ER	1.12 [0.51–2.45]	0.78		
No family history of CRC				
PC	0.72 [0.24–2.11]	0.55		
ER	0.64 [0.20–2.06]	0.45		
No fistulas or stricture				
PC	0.58 [0.29–1.17]	0.13		
ER	1.23 [0.53–2.86]	0.64		
No perianal disease				
PC	0.47 [0.18–1.25]	0.13		
ER	0.13 [0.33–5.34]	0.68		
Absence of PSC				
PC	15.33 [1.97–119.0]	< 0.01	8.94 [1.09–73.5]	0.04
ER	3.25 [0.89–11.88]	0.08	2.73 [0.63–11.87]	0.18
No prior dysplasia				
PC	2.61 [1.11–6.14]	0.03		
ER	0.86 [0.38–1.93]	0.71		
Index AN (HGD)				
PC	0.37 [0.17–0.81]	0.01	0.62 [0.25–1.52]	0.30
ER	15.91 [4.51–56.19]	< 0.01	27.26 [6.79–109.43]	< 0.01
Unifocal AN[a]				
PC	2.62 [1.03–6.70]	0.04		
ER	1.53 [0.61–3.85]	0.37		
Polypoid lesion[b]				
PC	2.13 [0.93–4.87]	0.08		
ER	7.98 [3.25–19.57]	< 0.01		
Age at time of index AN, (per year increase)				
PC	1.08 [1.05–1.12]	< 0.01	1.06 [1.02–1.09]	< 0.01
ER	1.07 [1.03–1.11]	< 0.01	1.08 [1.03–1.13]	< 0.01
Academic centre				
PC	0.22 [0.09–0.56]	< 0.01		
ER	0.51 [0.17–1.52]	0.23		

(Sub)total or proctocolectomy was used as reference group.

AN, advanced neoplasia; CRC, colorectal cancer; ER, endoscopic resection; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; OR, odds ratio; PC, partial colectomy; PSC, primary sclerosing cholangitis.

[a]Six patients with missing values were not included in analysis

[b]Thirty-four missing values were not included in analysis

high-risk population and less frequent use of EMR and ESD. The limited data on EMR and ESD in advanced neoplasia warrants further research on metachronous neoplasia rates. Our findings underline that endoscopic advanced neoplasia treatment should only be considered if the lesion is endoscopically resectable and close surveillance is feasible without impairment of mucosal visualization due to, for example, chronic disease activity or pseudopolyps. We recommend a multidisciplinary approach with gastroenterology and a gastro-intestinal surgeon with expertise in IBD to carefully select the treatment modality based on individual patient characteristics. In line with guidelines, we suggest performing strict endoscopic surveillance 3–6 months for the first year after endoscopic treatment[13,29]. Longer subsequent intervals could be considered in case of negative colonoscopies.

This study has several strengths. First, our PALGA search made it possible to construct a unique large cohort of patients with advanced neoplasia in IBD, including a large proportion of patients with HGD. Most previous studies focused on CRC, leaving HGD a fairly under-researched topic. Second, we employed competing risk analyses to prevent overestimation of metachronous advanced neoplasia rates due to proctocolectomy or death during follow-up. Third, we collected extensive information on disease course, including long-term follow-up and mortality data. There are also limitations, most notably the retrospective design. Despite the multicenter design this study has a relatively limited sample size compared to non-IBD studies due to the low incidence of advanced neoplasia in IBD. Treatment decisions in clinical practice are based on a variety of factors. Although we adjusted for multiple confounders in our analyses, residual confounding due to patient or physician preferences could impact our results. Due to the limited number of metachronous advanced neoplasia, we were not able to assess independent associations. Separate multivariable competing risk analyses for CD and UC/IBD-U could not be performed due to the limited group size. Nevertheless, patient characteristics between IBD types were similar, and there was no significant effect modification of IBD type on the metachronous (advanced) neoplasia risk. Considering the long time period of our study, advances in surveillance techniques over the years could impact our results. In order to account for this, we performed a time-frame analysis, showing results in line with the main analysis.

To conclude, partial colectomy yielded a comparable metachronous (advanced) neoplasia risk compared to (sub)total colectomy in a selected cohort of CD and UC patients. This underlines the consideration of this treatment modality for patients with limited disease extent without other risk factors. Endoscopic resection of advanced neoplasia is associated with a high risk of metachronous neoplasia and advanced neoplasia, emphasizing the importance of stringent endoscopic surveillance after treatment.

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Author contribution

M.E.W.D.: conceptualization, data curation, formal analysis, writing—original draft, review and editing. M.t.G.: conceptualization, data curation, formal analysis, writing—original draft, review and editing. C.P P.: data curation, writing—review and editing. G.D.: data curation, writing—review and editing. A. C.d.V.: data curation, writing—review and editing. T.E.R.: data curation, writing—review and editing. C.S.H.: data curation, writing—review and editing. N.K.H.d.B.: data curation, writing—review and editing. W.A.B.: conceptualization, writing—review and editing. I.D.N.: conceptualization, data curation, writing—review and editing.

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