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ORIGINAL ARTICLE

Malignant colorectal polyps: endoscopic polypectomy and watchful waiting is not inferior to subsequent bowel resection. A nationwide propensity score-based analysis

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Abstract

Background and aims The optimal treatment of patients with malignant colorectal polyps is unsettled. The surgical dilemma following polypectomy is selecting between watchful waiting (WW) and subsequent bowel resection (SBR), but the long-term survival outcomes have not been established yet. This nationwide study compared survival of patients after WW or SBR.

Methods Danish nationwide study with 100% follow-up of all patients with malignant colorectal polyps (the Danish Colorectal Cancer Group database) in a 10-year period from 2001 to 2011. All patients' charts and histological reports were individually reviewed. Survival rates were calculated with Cox proportional hazard model after propensity score matching.

Results A total of 692 patients were included (WW, 424 (61.3%), SBR, 268 (38.7%)) with a mean follow-up of 7.5 years (3–188 months). Following propensity score matching, there was no significant difference in overall or disease-free survival ($p = 0.344$ and $p = 0.184$) or rate of local recurrence (WW, 7.2%, SBR, 2%, $p = 0.052$) or distant metastases (WW, 3.3%, SBR, 4.6%, $p = 0.77$). In the SBR group, there was no residual tumor or lymph node metastases in the resected specimen in 82.5% of the patients.

Conclusion Subsequent bowel resection may not be superior to endoscopic polypectomy and watchful waiting with regard to overall and disease-free survival in patients with malignant colorectal polyps.

Keywords Malignant polyp · pT1 colorectal cancer · Polypectomy · Cancer in adenomas

Abbreviations

WW	Watchful waiting
SBR	Subsequent bowel resection
TRUS	Transanal endoscopic ultrasound
MRI	Magnetic resonance imaging
pT	Pathological T-stage of tumor
SD	Standard deviation
ASA-score	American Society of Anesthesiologists' score
BMI	Body mass index (kg/m^2)
CCI	Charlson comorbidity index
OS	Overall survival
DFS	Disease-free survival
OR	Odds ratio
CI	Confidence interval

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Introduction

Colorectal cancer is the second most common cancer in Europe and the third most common worldwide [1].The increasing use of endoscopy with more advanced technology for resection of large polyps, along with colorectal cancer screening programs, has resulted in the detection of colorectal cancer at earlier stages and a higher incidence of malignant polyps [2–4]. Malignant polyps (macroscopically benign polyps with incidental histological evidence of adenocarcinoma invading into submucosa) account for 15% of all screening-detected colorectal cancers [5].

A previous large-scaled retrospective population-based study showed similar survival in patients with malignant colonic polyps treated either with endoscopic polypectomy or primary bowel resection without prior endoscopic treatment [6]. However, malignancy is often first discovered after the histological examination of the polypectomy specimen, and improvement of endoscopic resection technology has resulted in increased use of endoscopy replacing primary bowel surgery for removal of colorectal polyps. Therefore, the dilemma is not whether patients should have endoscopic treatment or primary bowel resection but rather whether subsequent bowel resection (SBR) after polypectomy will improve survival and risk of recurrence despite postoperative morbidity and mortality compared with a watchful waiting (WW) strategy. Finally, the evidence for long-term benefits from SBR in terms of survival and recurrence is inadequately illuminated in the literature.

For the abovementioned reasons, the present study was primarily performed to analyze long-term overall and disease-free survival and secondarily to analyze morbidity in patients with malignant polyps followed by WW or SBR.

Methods and materials

Data collection

This was a nationwide retrospective controlled cohort study with prospectively collected data obtained from the Danish Colorectal Cancer Group (DCCG) database. The patients were selected by a primary extraction of data on all patients in Denmark who received polypectomy for a malignant polyp. This was achieved by sampling data from the prime source, the DCCG database. Subsequently, DCCG data was supplemented with data from National Pathology Data Bank (Patobank) and the Danish National Patient Registry to avoid missing patients (probably less than 1% of patients, see below). Malignant polyps were identified under the following subheadings: cancer in a polyp, cancer after polypectomy, cancer after endoscopic mucosa resection (EMR), and cancer after local resection. The DCCG database is a prospectively maintained clinical database with predefined clinical, surgical, radiological, and pathological variables, and contains 99% of all patients with colorectal cancer in Denmark [7]. Demographic variables were gender, height, weight, American Society of Anesthesiologists' (ASA) score, and Charlson comorbidity index (CCI).

Variables regarding surgical treatment included type of surgical procedure, operative approach (open or laparoscopic surgery), tumor location, type of intraoperative complications, and 30-day postoperative surgical and medical morbidity. To secure the ultimate diagnosis of malignant polyp, and to achieve information on endoscopic treatment, recurrences, and late surgical and oncological outcome, data from the DCCG database were cross-checked and supplemented with manual reviews of nationwide electronic hospital records, endoscopy, and pathology reports. Hospital and endoscopy reports were reviewed for information on polyp morphology (sessile or pedunculated), tumor location, and endoscopic resection technique (en bloc or piecemeal).

Pathology reports were manually reviewed for description of polyp size (mm), tumor differentiation (well, moderate, or poor), resection margin [negative (> 1 mm, R0), positive (≤ 1 mm, R1) or uncertain/could not be evaluated (Rx)], tumor level (Haggitt or Kikuchi classifications) [8, 9], lymphatic and/or vascular invasion (lymphovascular invasion), tumor budding, and in case of subsequent resection, TNM classification and UICC stage [10].

Patient population and study design

The study comprised a non-screened population of consecutive Danish patients diagnosed with malignant polyps from January 2001 to December 2011 treated with either WW or SBR. Patients in the WW group were defined as patients where it was decided not to perform subsequent bowel resection after confirmed histological diagnosis of a malignant polyp. In the SBR group, it was decided to perform subsequent bowel resection after confirmed histological diagnosis. Denmark consists of five regions with a total population of approximately 5.7 million. The study profile is shown in Fig. 1. From the total number of eligible patients (3104), approximately 2000 were excluded based on review of pathology reports. Of those were reports not including information on a malignant polyp, per se, but rather a biopsy of a malignant

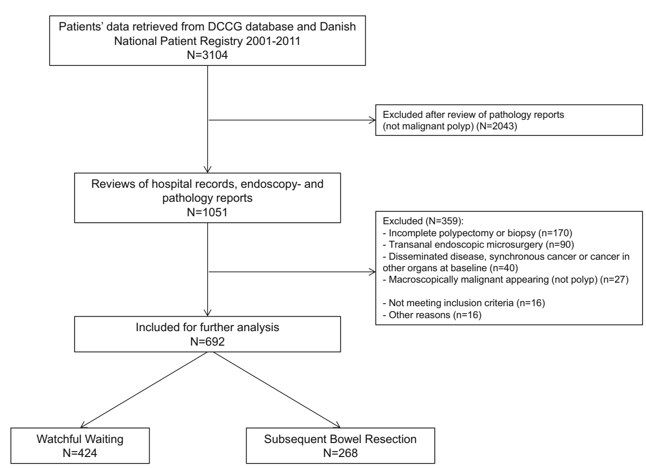

Fig. 1 Flow chart of study population

tumor and a polypectomy of a benign polyp. Subsequently, hospital records, endoscopy, and pathology reports were manually reviewed for the remaining 1051 patients. Inclusion criteria were patients > 17 years of age with a malignant colorectal polyp with submucosal invasion completely resected at the primary endoscopic procedure. Incomplete polypectomy was defined as a biopsy of a polyp or macroscopic suspicion of residual polyp at the end of the endoscopic procedure, as stated in endoscopy reports. If in doubt, consensus was obtained to include or exclude patients from the analysis. Exclusion criteria were biopsy, incomplete polypectomy or multiple endoscopic resections for the same malignant polyp, resection with transanal endoscopic microsurgery (TEM) (as these patients are often investigated with TRUS and/or MRI prior to the TEM procedure, and a full-thickness excision can, unlike a polypectomy, provide evaluation of penetration into the muscularis propria), patients with hereditary non-polyposis colorectal cancer (HNPCC), patients with familial adenomatous polyposis (FAP), advanced disease (T4 tumors, distant metastases, and suspicious lymph nodes on CT scan), multiple malignant polyps or synchronous cancer, previous surgery for colorectal cancer, current cancer in other organs, neoadjuvant chemo- or radiation therapy, active inflammatory bowel disease, and pregnancy. All patients were followed until 31 December 2016 or until death.

Outcome was registered after 90 days and after 3 and 5 years, and at the end of the follow-up period.

Endpoints for survival analysis were overall survival and disease-free survival.

The morbidity (complications) variables were predefined from the DCCG database and registered within 30 days postoperatively [7], and supplemented with a review of hospital records for the purpose of obtaining 90 day morbidity and mortality rates. Complications were separately registered and analyzed for polypectomy and SBR. All complications (more than one complication per patient) were registered and summarized as one complication per patient (the most severe) by using the Clavien-Dindo score [11]. Death was recorded as "cancer-related" or "other." Local recurrence was defined as histologically verified adenocarcinoma at endoscopic resection site, in case of polypectomy, or at the site of anastomosis, in case of SBR. Systemic recurrence (distant metastases) was defined as recurrence in other organs. Overall survival was measured as the date of polypectomy until the date of death, or date of last follow-up. Disease-free survival was measured as date of polypectomy until the date of recurrence, death, or last follow-up.

The study was approved by the National Committee on Health Research (No. 46597) and reported to Danish Data Protection Agency (No. 2013-41-2475). Data was obtained with the permission and support of the scientific committee of the Danish Colorectal Cancer Group.

Statistics

For survival and recurrence analysis, propensity score matching was used [12, 13]. Variables included for propensity score matching were age, gender, ASA, location of the polyp, resection margin, and polyp morphology. The choice of variables for propensity score matching was based on the clinical impact of the variable on both allocation to treatment group, and outcome (survival and recurrence). Missing data were categorized as unknown. Due to the large number of missing histological standard variables, these were not included in the propensity matching. Following construction of propensity score, patients in the WW group were matched with patients in the SBR group at a ratio of 1:1, with the nearest neighbor approach, and caliper of 0.2 times the standard deviation of the logit of the propensity score [14]. The balance in baseline covariates between treated (SBR) and untreated subjects (WW) in the propensity score-matched sample was tested with standardized mean differences and distribution of propensity scores. Following, covariate balance was massively improved in the matched sample (Fig. 2). Before matching, survival and recurrence rates were compared between the groups with a log-rank test and multivariate analysis was performed using Cox's proportional hazards regression model. After matching, survival comparisons were performed with a Cox proportional hazard model with reporting of hazard ratios (HR), with a 95% confidence interval (95% CI). Survival curves were plotted using the Kaplan-Meier method.

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as mean with standard deviation, unless stated otherwise. Differences between the treatment groups were calculated using a chi-square test or Fisher's exact test, as appropriate, for categorical variables, and Student's t test or Mann-Whitney U test, as appropriate, for continuous variables. A p value < 0.05 was considered statistically significant.

Statistical methods and analyses were consulted with, and reviewed by, the staff of the Section of Biostatistics at the University of Copenhagen. Data were collected and analyzed using the statistical package IBM® SPSS® Statistics version 24.0 for Windows.

Results

A total of 3104 patients were retrieved from the Danish Colorectal Cancer Group database. Following a review of pathological reports and hospital and endoscopy reports, 692 patients (100% follow-up) fulfilled the inclusion criteria and were eligible for analysis (Fig. 1).

A total of 424 (61.3%) patients underwent WW and 268 (38.7%) patients SBR. The unmatched WW and SBR groups differed significantly (Tables 1 and 2).

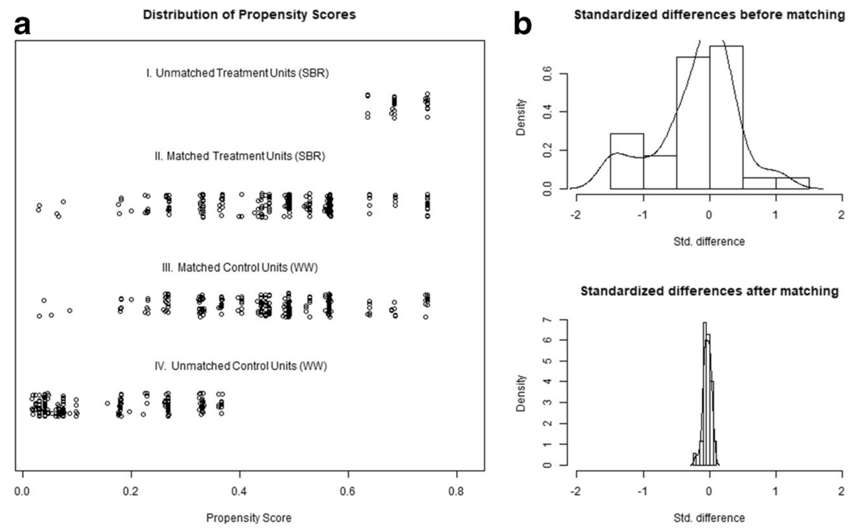

Fig. 2 Graphic distribution of **a** patient propensity scores and **b** standardized differences. **a** The balance in baseline covariates between treated (SBR) and untreated subjects (WW) in the propensity score was improved in the matched sample (plot II mirrors plot III). Due to difference in patient group size before matching (424 vs. 268) the number of graphic circles in the unmatched units differs (I and IV). Each circle represents one patient and dark circles are overlapping patients. **b** Graphical display of standardized differences (SD) was wider before than after matching

Table 1 Patient demographics

	Before propensity score matching					After propensity score matching				
	Watchful waiting		Subsequent bowel resection		*P*	Watchful waiting		Subsequent bowel resection		*P*
	N = 424		*N* = 268			*N* = 152		*N* = 152		
Variables	No.	%	No.	%		No.	%	No.	%	
Patient characteristics										
Sex					0.023					1
Female	182	42.9	139	51.9		75	49.3	76	50	
Male	242	57.1	129	48.1		77	50.7	76	50	
Mean age (±SD), years	71.3	10.9	65	10.3	< 0.001	68.1	11.76	66.6	10.02	0.299
Age					< 0.001					0.286
≤ 70 years	188	44.3	183	68.3		90	59.2	100	65.8	
> 70 years	236	55.7	85	31.7		62	40.8	52	34.2	
Mean BMI (±SD), kg/m^2	26.5	5	26.3	4.5	0.786	27.6	5.8	26.7	4.4	0.7
BMI					< 0.001					< 0.001
< 30 kg/m^2	158	37.3	170	63.4		59	38.8	94	61.8	
≥ 30 kg/m^2	37	8.7	34	34		23	15.1	17	11.2	
Missing	229	54	64	23.9		70	46.1	41	27	
ASA-score					< 0.001					0.927
1	87	20.6	96	35.8		45	29.6	48	31.6	
2	164	38.8	126	47		68	44.7	69	45.4	
3	64	15.1	37	13.8		30	19.7	27	17.8	
4	5	1.2	3	1.1		1	0.7	2	1.3	
Missing	103	24.3	6	2.2		8	5.3	6	3.9	
CCI					0.017					0.401
0	282	66.5	204	76.1		105	69.1	115	75.7	
1–2	111	26.2	46	17.2		35	23	26	17.1	
≥ 3	31	7.3	18	6.7		12	7.9	11	7.2	
Mean follow-up (±SD), years	7.1	3.7	8	3.7	0.004	7.4	3.6	7.6	3.6	0.434

The table indicates that the selected variables for propensity score matching (age, gender, ASA, location of the polyp, resection margin, and polyp morphology) were not significantly different after propensity score matching ($p > 0.05$)

SD standard deviation, *ASA-score* American Society of Anesthesiologists' score, *BMI* body mass index (kg/m^2), *CCI* Charlson comorbidity index

Table 2 Morphological and histological characteristics following polypectomy

	Before propensity score matching					After propensity score matching				
	Watchful waiting		Subsequent bowel resection		P	Watchful waiting		Subsequent bowel resection		P
	N = 424		N = 268			N = 152		N = 152		
Variables	No.	%	No.	%		No.	%	No.	%	
Polyp location					0.047					0.204
Colon	291	68.6	203	75.7		103	67.8	114	75	
Rectum	133	31.4	65	24.3		49	32.2	38	25	
Mean polyp size (±SD), mm	19.34	10	19.75	10.5	0.589	18.54	9.5	20.15	9.43	0.06
Polyp size					0.16					0.07
≤ 10 mm	78	18.4	36	13.7		31	20.5	16	10.9	
11–20 mm	211	49.9	148	56.5		75	49.7	85	57.9	
> 20 mm	134	31.7	78	29.8		45	29.8	46	31.3	
Polyp morphology					< 0.001					0.602
Pedunculated	304	71.7	155	57.8		97	63.8	96	63.2	
Sessile	80	18.9	89	33.2		42	27.6	47	30.9	
Missing	40	9.4	24	9		13	8.6	9	5.9	
Polypectomy technique					0.142					0.99
En bloc	332	78.3	196	73.1		112	73.7	113	74.3	
Piecemeal	92	21.7	72	26.9		40	26.3	39	25.7	
Histological type					0.002					0.043
Adenocarcinoma, common type	414	97.6	248	92.5		148	97.4	139	91.4	
Mucinous adenocarcinoma	10	2.4	20	7.5		4	2.6	13	8.6	
Differentiation					0.013					0.098
Well	36	8.5	12	4.5		14	9.2	5	3.3	
Moderate	121	28.5	69	25.7		44	28.9	41	27	
Poor	6	1.4	12	4.5		3	2	7	4.6	
Missing	261	61.6	175	65.3		91	59.9	99	65.1	
Resection margin					< 0.001					0.474
Negative (> 1 mm)	273	64.4	50	18.7		46	30.3	49	32.2	
Positive (≤ 1 mm)	60	14.2	119	44.4		45	29.6	52	34.2	
Uncertain/missing	91	21.5	99	36.9		61	40.1	51	33.6	
Lymphovascular invasion					0.057					0.89
Yes	22	5.2	18	6.7		3	2	4	2.6	
No	140	33	66	24.6		6	3.9	5	3.3	
Missing	262	61.8	184	68.7		143	94.1	143	94.1	
Tumor budding					0.331					0.28
Yes	45	10.6	25	9.3		4	2.6	8	5.3	
No	6	1.4	8	3		18	11.8	12	7.9	
Missing	373	88	235	87.7		130	85.5	132	86.8	
Haggitt level					0.607					0.606
1	8	2.3	3	1.7		5	4.5	3	2.9	
2	4	1.2	1	0.5		0	0	1	1	
3	2	0.6	3	1.7		1	0.9	2	1.9	
4	2	0.6	0	0		0	0	0	0	
Missing	328	95.3	172	96.1		110	94.5	99	94.3	
Kikuchi level					0.057					0.319
Sm1	6	7.5	1	1.1		2	4.8	1	2.1	
Sm2	2	2.5	4	4.5		1	2.4	3	6.4	
Sm3	2	2.5	0	0		2	4.8	0	0	
Missing	70	80	84	94.4		37	88.1	43	91.5	

The table indicates that the selected variables for propensity score matching (age, gender, ASA, location of the polyp, resection margin, and polyp morphology) were not significantly different after propensity score matching ($p > 0.05$)

N number of patients

The propensity score matching was only used for analysis of survival and recurrence, and the morbidity and mortality rates therefore represent the unmatched population. The number of centers per region varied over time and between regions but the ratio between SBR and WW was steady, and this variable was therefore not used in the propensity model (Fig. 3A, B). There was no significant difference in number of performed imaging modalities (CT and/or MRI) and MDT conferences between the two groups.

Short-term outcomes

Morbidity following the polypectomy procedure and the surgical bowel resection is summarized in Table 3.

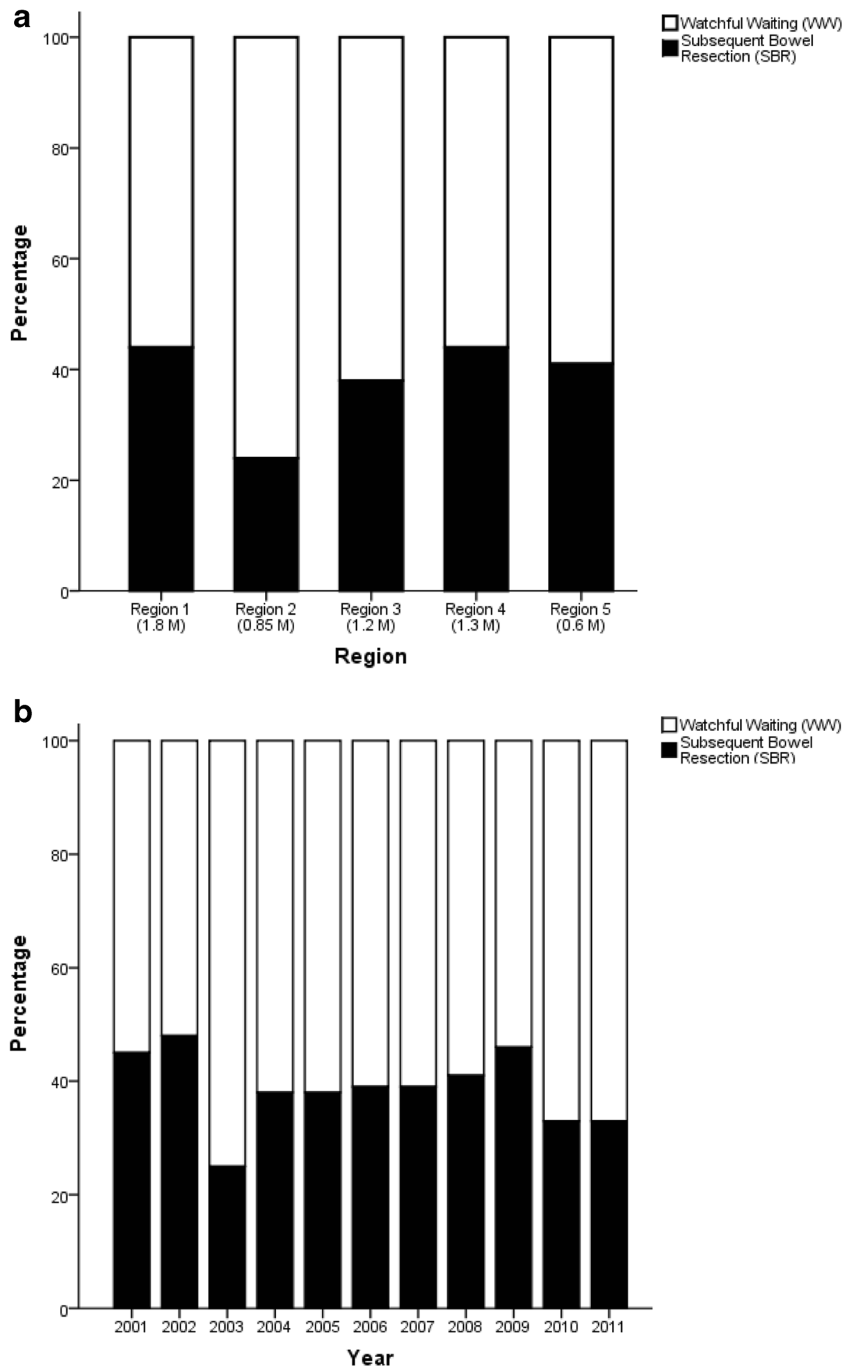

Fig. 3 Ratio between WW and SBR per **a** region and **b** year (population per region, *M* million)

Arterial bleeding managed at the primary endoscopic procedure comprised most of the complications following polypectomy. Surgical intervention due to endoscopic complication was required in two and three patients in the WW and SBR group, respectively. The surgical procedures performed in the SBR group are shown in Table 3. The laparoscopic approach was used in 148/268 patients (55.2%), and the conversion rate was 12.8%.

The 90-day mortality rate after SBR was 3.7% (10/268). Anastomotic leakage occurred in 19 patients, which constituted 7.6% of all patients with anastomosis (colon, 6.4%; rectum, 10.9%). During the follow-up period, late complications were registered in 36 patients (13.4%), of which 27 required surgical interventions, with incisional hernia being the most common complication.

Histological data following polypectomy for both groups are shown in Table 2. Data regarding tumor differentiation, lymphovascular invasion, tumor budding, and tumor level were missing in 61–96% of pathological reports.

Table 3 Surgical procedures and morbidity following polypectomy and subsequent bowel resection

	Before propensity score matching					After propensity score matching				
	Watchful waiting		Subsequent bowel resection		*P*	Watchful waiting		Subsequent bowel resection		*P*
	N = 424		*N* = 268			*N* = 152		*N* = 152		
Variables	No.	%	No.	%		No.	%	No.	%	
Polypectomy complications	13	3.1	8	3	1	3	2	6	3.9	0.501
Bleeding	12		6			3		4		
Polypectomy-snare entrapment	1		–			–		–		
Perforation	–		2			–		2		
Type of surgical procedure										
Abdominoperineal resection	–		10	3.7		–		5	3.3	
Low anterior resection	–		64	23.9		–		38	25	
Sigmoid colectomy	–		151	56.3		–		88	57.9	
Hartmann procedure	–		7	2.6		–		5	3.3	
Left hemicolectomy	–		24	9		–		11	7.2	
Transverse colectomy	–		2	0.7		–		2	1.3	
Right hemicolectomy	–		8	3		–		2	1.3	
Subtotal colectomy	–		2	0.7		–		1	0.7	
Complications following SBR										
Intraoperative complications			8	3				6	3.9	
Lesion of small bowel	–		2			–		2		
Lesion of colon	–		1			–		0		
Lesion of bladder	–		1			–		1		
Lesion of spleen	–		4			–		2		
Lesion of sacral vein	–		1			–		1		
Surgical postoperative complications			45	16.8				30	19.7	
Bleeding	–		10			–		8		
Wound dehiscence	–		6			–		5		
Small bowel obstruction	–		4			–		3		
Intraabdominal abscess	–		1			–		1		
Wound infection requiring opening of wound	–		11			–		7		
Anastomotic leakage	–		19			–		12		
Other	–		5			–		4		
Medical postoperative complications			20	7.5				15	9.9	
Stroke	–		1			–		1		
Acute myocardiac infarction	–		2			–		1		
Aspiration	–		1			–		1		
Pneumonia	–		8			–		5		
Pulmonary embolism	–		1			–		1		
Kidney failure	–		4			–		4		
Sepsis	–		5			–		4		
Lung insufficiency	–		1			–		1		
Clavien-Dindo score			55	20.5				14	9.2	
1	–		2	0.7		–		–	–	
2	–		12	4.5		–		8	5.3	
3	–		22	8.2		–		13	8.6	
3a	–		1			–		0		
3b	–		21			–		13		
4	–		9	3.4		–		7	4.6	
5 (mortality)	–		10	3.7		–		7	4.6	

OS overall survival, *DFS* disease-free survival, *SD* standard deviation, *N* number of patients

Following SBR, histopathological examination of the resected specimen showed no residual cancer disease in 221/268 patients (82.5%). Only 22 patients (8.2%) had remaining tumor in the bowel wall. The UICC staging of the 22 patients was stage I in 17 patients, stage II in 2 patients, and stage III in 3 patients. The pT-classification was T1 in 11 patients, T2 in 8 patients, and T3 in 3 patients. Resection margins after polypectomy were positive in 13/22 patients with residual tumor and uncertain or missing in the remaining nine patients. Only 22/218 of patients (10%) with R1 or Rx after polypectomy presented with residual tumor.

Lymph node metastases without residual tumor were seen in 25 patients (9.3%). The total nodal metastases rate was 10.5% (28/268). Out of the 28 patients with lymph node metastases, 19 underwent adjuvant chemotherapy. The remaining nine patients did not receive adjuvant chemotherapy due to comorbidities ($n = 3$), patient's wishes ($n = 2$), and tumor localization in the rectum ($n = 4$). Pathological examination showed no remaining tumor or lymph node metastases in 8/10 patients with postoperative death.

Long-term outcomes

Long-term outcomes are presented in Table 4.

In the unmatched population, the median time to recurrence in the WW group was 26 months (range 3–132). A total of 12/23 patients (52.2%) with local recurrence and/or metastases in the WW group were managed with endoscopic or surgical resection (and were alive and disease-free at the end of the follow-up period). The rate of local recurrence for the total follow-up period did not differ between patients with a R1 pathological margin (2.3%) compared with patients with R0 margins (1.5%; $p = 0.566$). The difference remained non-significant after adjustment for age, sex, polyp morphology, polyp localization, and group allocation (WW or SBR) (OR, 0.31; 95% CI 0.05–1.92; $p = 0.21$).

Both overall and disease-free survival was lower in patients with WW in the unmatched population, but there was no difference in the cumulative incidence of cancer-related death (Fig. 4). Correspondingly, the cumulative incidence of cancer-related death did not differ between the two groups following propensity score matching. When patients with R1 or Rx resection were excluded, survival analysis showed no significant difference in disease-free survival or overall survival between WW and SBR ($p = 0.396$ and $p = 0.535$, respectively). In the WW group, the total overall survival and the end of follow-up period was lower in patients with a pathological R1 margin compared with patients with a R0 margin (45% vs. 60.8%; $p = 0.015$). However, after adjustment for age, sex, ASA, polyp morphology, and localization, the difference was not significant (OR = 1.57; 95% CI, 0.88–2.82; $p = 0.13$).

After propensity score matching, the cohort consisted of 304 patients (WW, 152; SBR, 152). Overall and disease-free survival rates are shown in Table 4. SBR did not improve total overall survival (Odds ratio (OR), 1.196; 95% CI, 0.825–1.735, $p = 0.344$) or total disease-free survival (OR, 1.278; 95% CI, 0.89–1.833, $p = 0.184$) compared with WW (Fig. 4). Furthermore, no difference was observed in the local recurrence rate in the WW group compared with the SBR group (7.2% vs. 2%, $p = 0.052$).

Discussion

The main finding of the present study was that there was no long-term difference in overall or disease-free survival, or recurrence in patients with malignant polyps after WW compared with SBR. A majority of the patients (82.5%) had no residual disease after SBR, and there was no remaining tumor in 8/10 patients with postoperative mortality. Furthermore, half of the patients in the WW group and recurrence were successfully treated by endoscopic resection or bowel surgery.

Colorectal cancer is one of the most common cancers worldwide with 4/5 patients offered a surgical intervention at the time of diagnosis. Mortality rates following colorectal cancer surgery range between 2.5–6% and increase for the elderly patient [15–18]. Nationwide morbidity rates are 16% with approximately half of the patients requiring re-operation [15]. Furthermore, postoperative altered bowel function, chronic pain, and reduced quality of life affect many patients [19–21]. The risks related to colorectal surgery are considerable. Considering the similar survival and recurrence rates regardless of treatment option, and the low rate of residual disease following SBR, the issue of possible surgical over-treatment of patients with malignant polyps needs to be

Table 4 Long-term outcome before and after propensity score matching

	Before propensity score matching					After propensity score matching						
	Watchful waiting		Subsequent bowel resection		*P*	Watchful waiting		Subsequent bowel resection		OR	95% CI	*P*
	N = 424		*N* = 268			*N* = 152		N = 152				
Variables	No.	%	No.	%		No.	%	No.	%			
Local recurrence ± distant metastases	23	5.4	5	1.9	0.028	11	7.2	3	2			0.052
Distant metastases only	16	3.8	12	4.7	0.559	5	3.3	7	4.6			0.77
3 year OS	361	85.1	237	88.4	0.247	133	87.5	133	87.5	0.985	0.522–1.86	0.963
5 year OS	310	73.1	223	83.2	0.003	116	76.3	121	79.6	1.16	0.718–1.875	0.545
Total OS	237	55.9	193	72	< 0.001	92	60.5	100	65.8	1.196	0.825–1.735	0.344
3 year DFS	346	81.6	231	86.2	0.131	125	82.2	128	84.2	1.121	0.647–1.944	0.683
5 year DFS	298	70.3	219	81.7	0.001	109	71.7	118	77.6	1.285	0.82–2.015	0.274
Total DFS	227	53.5	189	70.5	< 0.001	87	57.2	98	64.5	1.278	0.89–1.833	0.184

SD standard deviation, *ASA-score* American Society of Anesthesiologists' score, *OS* overall survival, *DFS* disease-free survival, *OR* odds ratio, *CI* confidence interval, *N* number of patients

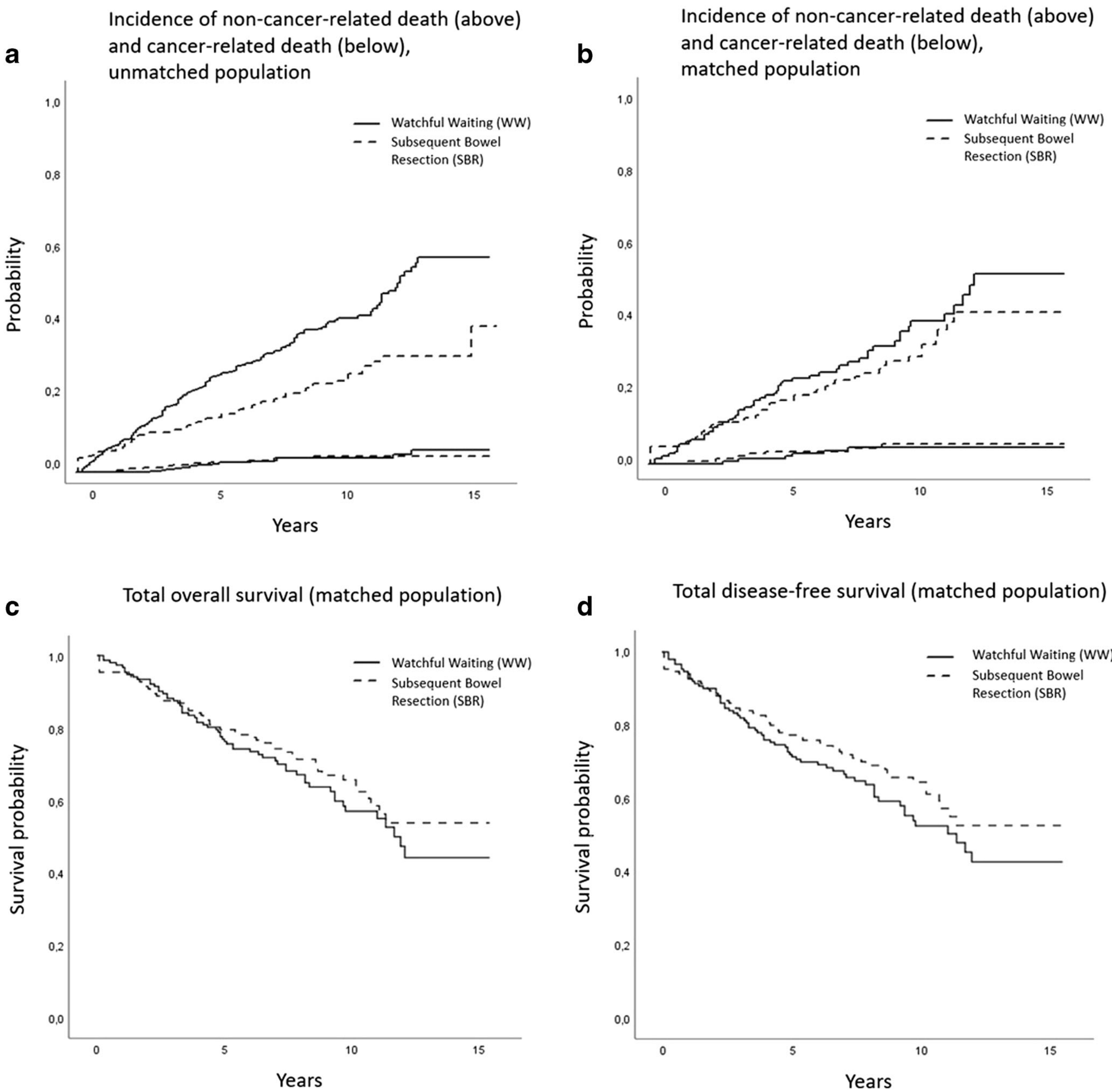

Fig. 4 Kaplan-Meier curves with log rank test for **a** cumulative incidence of cancer-related and non-cancer-related death before propensity score matching ($p = 0.735$ and $p < 0.001$ respectively), **b** cumulative incidence of cancer-related and non-cancer-related death after propensity score matching ($p = 0.843$ and $p = 0.344$ respectively), **c** Total overall survival after propensity score-based analysis ($p = 0.344$), and **d** Total disease-free survival after propensity score-based analysis ($p = 0.184$)

addressed. As shown in the present study, watchful waiting with endoscopic surveillance may present a viable option to surgical resection in selected patients. The majority of the patients in the present study (82.5%) had no residual disease following SBR, which is comparable to other studies on the subject [5, 22–29]. Mortality and morbidity (including anastomotic leakage rate) did not differ from those reported in the literature (3.7 and 20% respectively) [15–17, 30, 31]. However, lymph node metastases were present in 10.5% of patients with SBR, which may have led to a metastatic disease if patients were to adhere to a watchful waiting program, and not undergo oncological bowel resection. Nonetheless, it should be emphasized that 8/10 patients who died following SBR in the present study did not have a residual tumor. Furthermore, only 10% of patients with R1 or Rx after polypectomy presented with residual tumor. Although not fully illuminated in the literature, such patients could be objects to endoscopic full-thickness resection (EFTR) or combined endoscopic-laparoscopic resection (CELS) in case of no presence of other histological risk factors. The decision making for selection of subsequent bowel resection should weigh similar long-term survival and recurrence rates against the risk of postoperative morbidity and mortality following bowel resection.

Although an increasing interest in treatment of patients with malignant colorectal polyps, the present study is the largest cohort study on long-term survival in patients with malignant polyp after a WW or SBR strategy. There are only a few studies addressing survival in patients with malignant polyps [5, 6, 26, 32–34] and the majority report comparable survival rates between polypectomy and bowel resection. However, interpretation of survival outcomes in these studies may be difficult due to selection bias, difference in treatment comparisons (WW compared with SBR or primary bowel surgery), and short follow-up time. Cooper et al. showed comparable survival rates in patients with colonic malignant polyps managed either by polypectomy alone or primary bowel resection [6]. Although Cooper et al. also found comparable recurrence rates between the polypectomy and surgery group, the high rate of early re-resection and recurrence in the study population, along with the unclear measurement of recurrence through presence of claims for cancer chemotherapy, raises the question whether the primary endoscopic resection of the malignant polyp was macroscopically complete and puts the results in question. In the present study, both overall and disease-free survival was lower in the WW group before propensity-matched analysis, but no difference was found in incidence of cancer-specific death. This may be in part explained by the older and more comorbid (higher ASA score) population in the WW group. Furthermore, the WW group also presented with higher recurrence rates that were not related to resection margin positivity. Following propensity score-analysis, the difference between WW and SBR regarding recurrence rates and overall and disease-free survival was non-significant. Although there was no difference in the overall survival in the propensity-matched analysis, there was a non-significant trend towards a higher recurrence rate in the WW group. No difference was found regarding distant metastases. Findings may be in part explained by a statistical type II error, which might have been introduced by reducing the sample size after propensity score matching. Moreover, there was a lack of information on many histopathological risk factors in the present study. A potentially skewed distribution of histopathological risk factors between the two study groups may therefore, in part, explain the surprising intragroup discrepancy between recurrence rates and overall survival. As shown in the present study, many patients with recurrence after watchful waiting could be treated with a new endoscopic procedure or bowel resection and were alive and disease-free at the end of the follow-up period. This could, in part, also explain the similar overall survival between the groups.

There are currently no evidence-based clear guidelines in how to treat patients with malignant polyps [35, 36]. The decision of WW or SBR is often based on the risk of lymph node metastases. The high rate of missing histological data, which was also not available for the treating physician, prevented us from determining which patients with malignant polyps are under higher risk for lymph node metastases and should be offered SBR. Because the missing histopathological data was also not available for the treating physicians at the time of their decision, this may represent real-life practice and clinical reality of this dilemma. However, a high rate of missing histological data is unfortunately often seen in the literature and risk of lymph node metastases and remaining disease based on such data should be interpreted cautiously [5, 26, 29, 33]. Lymphatic invasion, along with tumor budding, submucosal invasion depth ≥ 1 mm, and poor histological differentiation have in several studies shown to predict the presence of lymph node metastases [37, 38]. However, as shown in a systematic review, no single risk factor is allowed for an optimal selection of a low-risk patient, as the individual risk factors were not sensitive or specific enough [38]. This issue was illustrated in a study by Richards et al., who suggested that subsequent bowel resection should be performed in the presence of a lymphovascular invasion in the polypectomy specimen [5]. The study was retrospective comprising 485 patients but unfortunately lacked information on histological data on the tumor level and lymphovascular invasion in more than 80–90% of the patients. Only 17% of the patients with lymphovascular invasion presented with lymph node metastases in the resected bowel specimen. The issue with low specificity and sensitivity of individual risk factors for prediction of lymph node metastases should be considered when discussing strategy options with the patient, especially in elderly patients with comorbidities. Furthermore, recent studies have shown that area of submucosal invasion and width of invasion, along with the absence of T cell infiltration, and tumor budding have also been shown to predict nodal metastases in T1 colorectal cancer [39–41]. Future studies should therefore focus on assessment of risk of residual disease and nodal metastases based on a combination of the presence of adverse high-risk histological factors, so a more appropriate selection for WW or SBR can be made.

The present study has several limitations. First, the study is not randomized, which together with the retrospective design and missing histological risk factors introduces a potential risk for selection bias. On the other hand, for a more accurate estimate of survival outcome, we performed propensity score matching, in an effort to increase comparability, minimize treatment selection bias, and to reduce the effect of confounding between the two treatment groups. The choice of variables for propensity score matching was based on the impact of the variable on both allocation to treatment group and outcome. For statistical reasons, the use of 6 co-variables in the propensity model prevented a skewed propensity matching ratio to reduce confidence intervals.

Secondly, a high rate of missing histological data prevented the estimation of risk factors for lymph node metastases and poor outcome. The missing histopathological data was due to the lack of description of the risk factors in the pathological reports, and these data were also not available for the treating physician. As the histological variables were not known at the time of decision in most cases, these were not included in the propensity score model. Thirdly, the fact that we did not account for family history of colorectal cancer, other than HNPCC and FAP, may have contributed to selection bias. Fourthly, as mentioned above, a statistical type II error may have been introduced by reducing the sample size after propensity score matching.

The follow-up after treatment also differed between patients with WW and SBR. There is a national follow-up program for patients undergoing bowel resection for colorectal cancer in Denmark, but not for patients with malignant polyps and WW. During chart review, it became clear that the strategy for the follow-up program for patients with WW differed greatly between treating surgeons and/or institutions. Due to great heterogeneity, this could not be accounted for in the analysis. The non-uniformity of the WW follow-up strategy may have affected time to diagnosis of recurrences, and thereby treatment options and ultimately survival in the WW group.

There is no evidence for the optimal follow-up program including time-lead periods between image modality and endoscopic surveillance in patients with malignant polyps and a WW setup. Short intervals between investigations may have an impact on the health care system, the radiation dose to the patient, but also on patient's quality of life. This might on the other hand identify recurrences earlier, thus making it suitable for repeated endoscopic or surgical treatment. Future studies should focus on the optimal surveillance management of patients undergoing polypectomy with WW.

The strength of the present study is its external validity by obtaining nationwide data with a 100% follow-up. The data was manually cross-checked with all hospital records to ensure accuracy, and no patients were lost to the mean follow-up of almost 8 years. Also, the present study is the largest cohort study on long-term survival in patients with malignant polyp after a WW or SBR strategy.

In conclusion, subsequent bowel resection may not be superior to endoscopic polypectomy and watchful waiting with regard to overall and disease-free survival in patients with malignant polyps. The findings underline the necessity for further studies with analysis of histopathology and molecular biology in order to identify reliable risk factors and the importance of a possible additive effect of the risk factors, preferably in a randomized control trial setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors (retrospective study). The study was approved by the National Committee on Health Research and reported to Danish Data Protection Agency.

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