

Watchful waiting versus colorectal resection after polypectomy for malignant colorectal polyps

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ABSTRACT

INTRODUCTION: Unexpected malignancy in removed colorectal polyps is reported in up to 9% of cases. The introduction of screening for colorectal cancer will inevitably increase the number of removed colorectal polyps and therefore also the incidence of malignant polyps. The treatment strategy is either watchful waiting or subsequent colorectal resection. The aim of this study was to perform a preliminary evaluation of the oncological results of polypectomy for malignant polyps with or without subsequent resection, including the patients' long-term survival.

METHODS: This was a retrospective analysis of prospectively collected data on 50 patients with unexpected malignancy after a polypectomy treated between January 2003 and January 2008. A total of 27 patients (54%) were treated with watchful waiting, and 23 (46%) underwent subsequent surgery. The Mann-Whitney U-test and chi-square test were used to compare the results between the two groups.

RESULTS: There were more patients in the surgery group with positive resection margins after the polypectomy ($p = 0.002$). No difference was found regarding tumour differentiation grade, lymphovascular invasion, local recurrence or distant metastasis. Intraoperative complications occurred in three patients (13%, 95% confidence interval: 0-28%). In all, 16 of the 23 operated patients had no residual tumour. Overall long-term survival was higher among the operated patients ($p = 0.005$), but there was no difference in cancer-free survival ($p = 0.071$).

CONCLUSION: Overtreatment of patients with malignant colorectal polyps seems to occur. Which patients benefit from further surgery has yet to be determined.

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Colorectal cancer is one of the most common cancer types in the Western World and it mostly arises from non-malignant colorectal polyps [1]. Malignancy in polyps is reported in up to 9% of cases with an increasing risk in larger polyps [2]. Since the introduction of screening programmes for colorectal cancer around Europe, the number of removed colorectal polyps has increased. Therefore, the incidence of colorectal malignancy is believed to increase [3].

Along with patient frailty, a number of prognostic histopathological factors may influence the choice of treatment, including watchful waiting or resection [4].

Correct staging is not possible as all the layers of the bowel wall are not present at the resection margin and due to lack of lymph nodes in the polypectomy specimen.

The primary aim of this study was to evaluate the oncological results of polypectomy for malignant polyps with or without subsequent resection and to evaluate the patients' long-term survival.

METHODS

This was a retrospective single-centre study including 50 consecutive patients undergoing polypectomy with findings of malignancy between 2003 and 2008. None of the patients had more than one malignant polyp. Histopathological data were registered prospectively in a local database. Polypectomies were performed by an endoscopic snare excision (coagulation current 30-40 W; en bloc or piece-meal resection depending on the shape, size and accessibility of the polyp). Residual polypoid tissue due to inability to perform full-snare excision was treated with monopolar coagulation at the same endoscopic session. The inclusion criteria were endoscopically excised colorectal polyps containing histologically verified adenocarcinoma and having a benign macroscopic appearance. Before study start, we decided to exclude patients with previous or synchronous colorectal cancer, familial adenomatous polyposis and inflammatory bowel disease and patients receiving pre-operative chemo-radiation therapy. Database information, patient records, including patient- and polyp characteristics, intra- and post-operative complications, histopathological examination and 30-day mortality were analysed. Further follow-up was performed by records of reviews from all contacts with the surgical, oncological and medical departments at the regional hospitals. The histological reports were reviewed regarding resection margins, tumour differentiation, venous invasion, lymphatic invasion and tumour budding.

Patients with positive resection margins were offered subsequent colorectal resection. In addition, patients were discussed at the local colorectal conference prior to a final decision to offer a subsequent colorectal resection, and indication for resection was based on consensus. Patient frailty and the patient's treatment preference were taken into consideration.

Malignant rectal polyps were investigated with rec-

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 TABLE 1

Patient, tumour and histological characteristics.

Patients, n	50
Gender, male/female, n (%)	30/20 (60/40)
Age, median (range), yrs	67 (22-93)
<i>Localisation of polyp, n (%)</i>	
Rectum	24 (48)
Sigmoideum	24 (48)
Descending colon	2 (4)
Tumour diameter, median (range), mm	20 (5-55)
<i>Polyp shape, n (%)</i>	
Pedunculated	23 (46)
Sessile	23 (46)
Not reported	4 (8)
<i>Type of resection, n (%)</i>	
En bloc	31 (62)
Piece-meal	18 (36)
Not reported	1 (2)
Suspicion of residual polyp after polypectomy, n (%)	9 (18)
<i>Resection margins, n (%)</i>	
Positive	16 (32)
Negative	12 (24)
Unassessable	20 (40)
Not reported	2 (4)
<i>Tumour differentiation, n (%)</i>	
Well differentiated	2 (4)
Moderately differentiated	28 (56)
Poorly differentiated	5 (10)
Not reported	15 (30)
<i>Venous invasion, n (%)</i>	
Yes	1 (2)
No	25 (50)
Not reported	24 (48)
Follow-up time, median (range), mo.	71 (4-114)

tal magnetic resonance imaging (MRI). Post-operative staging was performed according to the American Joint Committee on Cancer staging system. After colorectal resection, the post-operative cancer follow-up programme was performed by a minimally surgical strategy according to the guidelines of the Danish Colorectal Cancer Group and by thoracoabdominal computed tomography and colonoscopy according to a structured programme [4].

Statistics

Data are presented as medians and percentages, including 95% confidence intervals (CI) when appropriate. The Mann-Whitney U-test was used for continuous variables, and the chi-square and Fisher's exact test were used for categorical variables. Survival time was compared between groups using a Kaplan Meier analysis and log rank test. A p-value of < 0.05 was considered statistically significant.

Trial registration: not relevant.

RESULTS

Patient, tumour and histological characteristics are shown in **Table 1**.

A total of 27 patients were enrolled in the watchful waiting programme, and 23 patients underwent subsequent surgical resection of the polypectomy site (69 years (range: 22-93 years) versus 66 years (range: 51-78 years), $p = 0.141$).

Polypectomy details

In general, patients with pedunculated polyps had more free resection margins than patients with sessile polyps ($p = 0.003$). Polyps removed by piece-meal resection more often had positive and unassessable resection margins, but this difference was not significant ($p = 0.058$).

In the polypectomy group, 20 of the polyps were removed en bloc and seven by piece-meal resection. In the group that underwent subsequent surgery, eleven polyps were removed en bloc, eleven by piece-meal resection, and for one patient the resection mode was not reported ($p = 0.102$).

In the watchful waiting group, suspicion of residual polyp after the polypectomy was raised in three patients. These three patients did not undergo further surgery due to high age. They later died due to causes unrelated to cancer. Bleeding due to polypectomy occurred in one patient and was treated by applying clips to the bleeding artery.

Operative results of patients with subsequent resection

In the resection group, the median time from the polypectomy to surgery was 22 days (range: 4-120 days). The surgical resection procedures were low anterior resection ($n = 12$), sigmoideum resection ($n = 9$), left hemicolectomy ($n = 1$) and transanal endoscopic microsurgery ($n = 1$). Intraoperative complications occurred in three patients (13%, 95% CI: 0-6) and were lesions of the bladder ($n = 1$) and splenic bleeding ($n = 2$) with immediate haemostasis. Post-operative complications occurred in three patients (13%, 95% CI: 0-6) and were anastomotic leak requiring re-operation ($n = 1$), wound dehiscence ($n = 1$) and cardiac arrest due to aspiration to the lungs and pulmonary oedema ($n = 1$) resulting in death one week after the operation. Thus, the 30-day mortality was 4.3%.

Oncological results

Staging results were as follows: Stage I ($n = 4$), stage IIa ($n = 1$) and stage IIIa ($n = 5$). Two of the patients with lymphatic invasion (stage IIIa) had no residual tumour (40%). No residual tumour was seen in 16 of the 23 operated patients (70%, 95% CI: 11-21). Seven of these patients had unassessable resection margins, and eight patients had positive resection margins after their polypectomy.

No significant difference in tumour differentiation or lymphovascular invasion was seen between the two groups (**Table 2**). No difference in local recurrence (2 versus 0, $p = 0.495$) or distant metastasis (2 versus 0, $p = 0.495$) was observed.

Two patients had local recurrence: An 81-year-old woman with a sessile polyp, positive resection margins and a rectal MRI showing invasion into the rectal wall declined surgical treatment and received chemotherapy. Local recurrence was discovered two years later and the patient died one year later from her cancer. The second patient was a 69-year-old male with unassessable resection margins after a piece-meal removal (pedunculated polyp). The patient declined to undergo follow-up. Recurrence occurred after five years and the patient underwent sigmoidectomy, showing a T3N2V1 tumour. The patient declined chemotherapy. He developed multiple metastases to the liver and died six months later. A 66-year-old woman with unassessable margins (piece-meal polypectomy of a pedunculated polyp) had a distant metastasis and was followed up with biopsies at the previous polypectomy site. No local recurrences developed.

Overall, long-time survival was significantly higher in the colorectal resection group ($p = 0.005$, **Figure 1**). Eleven patients in the polypectomy group and two in the resection group died during the follow-up period. However, nine of the 13 deaths were due to unrelated causes. All four cancer-related deaths occurred in the polypectomy group. Three patients declined follow-up. The difference in cancer-free survival was not significant between the two groups ($p = 0.071$, **Figure 1**).

The median follow-up time for the two groups was similar (68 months, range: 4-112 versus 73 months, range: 36-114, $p = 0.382$).

DISCUSSION

The present study indicated no important differences between the two treatment groups regarding local recurrences and distant metastasis. Sixteen of the patients who underwent colorectal resection had no residual tumour following the initial polypectomy, which may suggest overtreatment of patients with solitary malignant colorectal polyps.

During a colorectal endoscopic procedure, there is often no clinical suspicion of malignancy. Decision-making (watchful waiting versus subsequent resection) is often based on the risk of lymph node metastasis, local recurrence and distant metastasis (low tumour differentiation, lymphovascular invasion and positive resection margins) as well as on the patient's operability. Malignant colorectal polyps can be categorised into low-risk and high-risk lesions according to their likelihood of being associated with lymph node metastases [4, 5]. It

TABLE 2

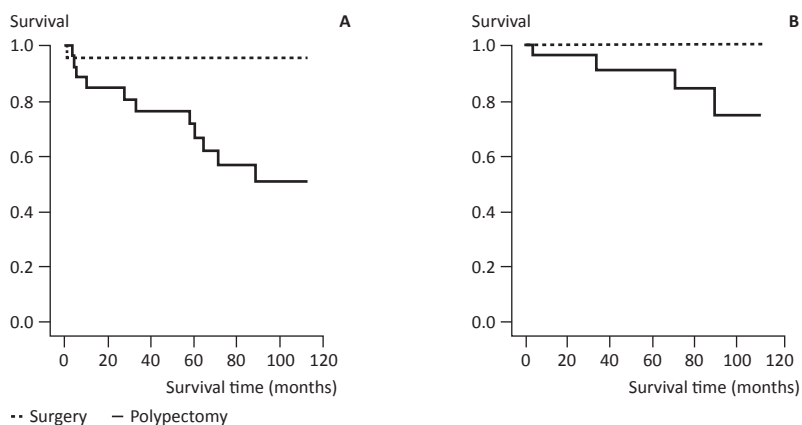
Measures of histopathological assessment after polypectomy.

	Polypectomy group	Polypectomy and resection group	p-value ^a
No. of patients, n	27	23	–
<i>Resection margins, n (%)</i>			0.002
Positive	4 (14.8)	12 (52.2)	
Negative	11 (40.7)	1 (4.3)	
Unassessable	11 (40.7)	9 (39.1)	
Not reported	1 (3.7)	1 (4.3)	
<i>Polyp shape, n (%)</i>			0.179
Pedunculated	15 (55.6)	8 (34.8)	
Sessile	9 (33.3)	14 (60.9)	
Not reported	3 (11.1)	1 (4.3)	
<i>Tumour differentiation, n (%)</i>			0.349
Well differentiated	2 (7.4)	0 (0)	
Moderately differentiated	13 (48.1)	15 (65.2)	
Poorly differentiated	2 (7.4)	3 (13)	
Not reported	10 (37)	5 (27.7)	
<i>Venous invasion, n</i>			1
Yes	1	0	
Not reported	13	11	
<i>Lymphatic invasion, n</i>			1
Yes	1	1	
Not reported	26	22	
<i>Tumour budding, n</i>			1
Yes	1	1	
Not reported	26	22	

a) Fisher's exact test.

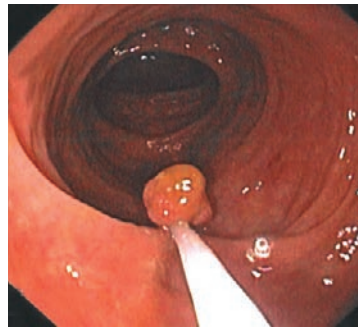
FIGURE 1

Kaplan-Meier plot illustration of overall survival (log rank, $p < 0.005$) (A) and cancer-free survival (log rank, $p = 0.071$) (B) among 50 patients with malignant colorectal polyps with a watchful waiting strategy or subsequent colorectal resection after polypectomy.



was previously demonstrated that positive resection margins and low tumour differentiation (high-risk lesion) are associated with an increased risk of local recurrence, lymph node metastasis and cancer-related death [6-8]. A positive resection margin may therefore often result in

A colon polyp with benign macroscopic appearance. Histopathological examination showed adenocarcinoma with unassessable resection margin.



surgical colorectal resection with subsequent surgical complications [9, 10]. If the cancer penetrates to the lower third of the submucosa Haggitt level 4 (submucosa (SM) stage 3), the risk of synchronous lymph node metastasis is up to 23% [11]. However, margins and invasion are often difficult to interpret due to piece-meal resection or thermal damage caused by cautery [12, 13]. This could result in a decision to perform further surgery and therefore lead to a risk of overtreatment. Large and/or sessile polyps should be removed by endoscopic mucosa resection (EMR), and transrectal ultrasound and/or MRI should be used for these polyps to estimate the level of invasion and to detect potential lymph node metastasis, respectively [14]. Danish national guidelines state that patients with positive resection margins, low tumour differentiation and vascular invasion should undergo further surgery [4]. An option for patients with unassessable margins could be to perform mucosectomy at the previous polypectomy site and to re-evaluate the margins, which in case of clear margins could prevent further surgery. This was done by Seitz et al who found that 28 of 33 patients with initially unclear resection margins had negative margins at the second histological evaluation [15]. The present study shows that seven of the nine patients (78%) with unassessable resection margins who proceeded to surgery had no residual tumour. More interesting, eight of the 12 patients (67%) with positive margins were without remnant tumour. Hackelsberger et al found no residual tumour in 70% of patients with doubtfully complete margins and in 86% of patients with incomplete resection margins [16]; and Seitz et al found no residual tumour in 71% although the surgery was performed on patients with high-risk lesions [15]. In all, we found no residual tumour in 69.6% of the operated patients, which is similar to the shares reported in the literature [6, 15-18].

Based on our findings that are supported by other studies, overtreatment of patients with malignant polyps may occur. This is associated with a risk of causing unnecessary surgical complications. The difficulty lies in determining which patients should be operated and

which patients should only be monitored with colonoscopy and other diagnostic tools.

We observed no significant difference in local recurrence or distant metastasis between the two groups in our study. However, overall survival was low in patients treated with polypectomy alone, which was also observed by Cooper et al [19]. In our study, however, we observed no difference in cancer-free survival. The lower overall survival rate could be explained by selection bias, resulting in a non-surgical treatment in the elderly or generally ill patients. Selection bias may also explain why not all patients with sessile polyps and unassessable/positive resection margins progressed to further surgery. It is therefore crucial to develop better methods for staging and evaluating the margins in these patients. Among the important limitations of the present study are the low number of patients, the absence of data on certain pathological factors along with the retrospective observational nature of the study. Cancer-free survival did not differ between the two groups. However, a higher rate of lymphovascular invasion and tumour differentiation grade in the histological reports would possibly have resulted in a different treatment option; and a larger number of included patients would have produced a more accurate estimate of survival. Centralised pathological evaluation of polyps, multidisciplinary team (MDT) conference discussions and second revision of polyps with unclear margins may lead to more precise evaluations. Future large-scale comparative studies with multivariate analysis should analyse in detail risk factors for outcome after different approaches to the treatment of malignant colorectal polyps and whether or not surgery is of benefit in these patients.

CONCLUSION

This preliminary, small and retrospective study suggests a higher overall survival but not cancer-specific survival after resection following polypectomy for malignant colorectal polyp. The indication for watchful waiting versus subsequent colorectal resection should be further investigated in large-scaled study taking relevant pathological risk factors into consideration.

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