

Value of Additional Surgical Resection after Endoscopic Removal of a T1 Colorectal Carcinoma

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Abstract

Introduction: Colorectal cancer is diagnosed more frequently since the introduction of national screening programs. The value of additional surgery after endoscopic resection of early cancer is still under debate. We aimed to determine the role of additional surgical resection after endoscopic removal of early colorectal carcinoma.

Methods: Endoscopic resections between 1992 - 2013 from a single institution were retrospectively reviewed. T1 colorectal tumours were included. Patients who underwent additional surgical resection were compared to patients who did not. The indication for additional surgery according to international guidelines (resection margin < 2 mm, angiolymphatic invasion or poor differentiation of tumor cells) was assessed.

Results: A total of 109 patients were included. Surgical resection was performed in 58 patients, 45 of whom had an indication according to the guidelines. Surgery was less likely to follow endoscopic resection if repeated endoscopic resection or a second assessment of the pathology was performed ($p=0.018$ and $p=0.033$, respectively). Surgical specimens showed residual tumour cells at the endoscopic resection site in 31% and lymph node metastases in 12%. Residual tumour cells after endoscopic resection was significantly associated with a sessile polyp type ($p=0.006$) and judgment as incomplete endoscopic resection by the endoscopist ($p<0,001$). In patients with an indication for surgery according to the guidelines, 5 year disease free survival was comparable in the group with and without a surgical resection (98% and 92% respectively, $p=0,54$). 5 year overall survival was also not significantly different in these groups (83% and 76% respectively, $p=0,42$).

Conclusion: These findings indicate a substantial role for endoscopic resection as definitive treatment for T1 colorectal cancer. When unfavorable histological features are present and therefore an indication for additional surgery according to the guidelines exists, surgery might be omitted, especially in older patients with comorbidity.

Keywords: Early colorectal cancer, Colonic polyps, Endoscopic resection, Segmental colectomy, Oncological colorectal resection, Prognosis

Introduction

The early detection of colorectal cancer is rapidly increasing since the implementation of national colorectal cancer screening programs [1,2]. However, there is controversy about which strategy is best to treat patients with T1 colorectal cancers after endoscopic resection of a malignant polyp. It has been shown that endoscopic resection of superficial colonic tumors can prevent the morbidity of an additional surgical resection [3-6]. As residual tumor cells are often not found in the surgical specimen, the question arises whether the additional surgical resection was necessary. For patients without distant metastases, the presence of lymph node metastases is a prognosticator and determines the need for adjuvant therapy. Therefore, balancing the risks and benefits of endoscopic local excision alone versus additional surgical segmental resection according to oncological principles, depends primarily on the chance of lymph node involvement. Unfortunately, the ability to accurately predict nodal involvement preoperatively is limited. As a consequence, standard surgical resection including removal of adjacent lymph nodes is regarded as the gold standard [7,8].

According to international guidelines, oncological resection is indicated after endoscopic treatment of a T1 malignant colorectal polyp with one or more of the following characteristics: i) microscopic incomplete resection margins (<2mm), ii) angiolymphatic invasion or iii) poor differentiation of tumor cells [9]. These factors have been shown to predict nodal involvement or residual tumor cells at the resection

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site. For T1 colorectal carcinomas without these characteristics, nodal involvement is rare and endoscopic resection alone is considered sufficient.

The aim of this retrospective cohort study was to determine the value of additional surgical resection following endoscopic removal of a T1 colorectal cancer. We hypothesized that radical endoscopic resection of T1 colorectal adenocarcinomas, even with unfavourable histological characteristics which are commonly considered as an indication for surgery, results in similar long term oncological outcomes compared to patients that undergo an additional surgical resection.

Methods

Patients

All patients who underwent endoscopic resection between 1992 and 2013 in a single institution in the Netherlands were identified retrospectively through a nationwide hospital pathology database (PALGA). Patients with endoscopic removal of a histologically proven colorectal tumor with growth through the muscularis mucosae and invasion into the submucosa (T1 tumors) were included in this study. Patients with an in situ carcinoma, metastasized disease, a history of malignant colorectal polyps, familial polyposis syndrome or inflammatory bowel disease were excluded. Metastases were identified through either conventional radiological imaging, ultrasonography and/or computed tomography of the thorax and the abdomen. Clinical records were reviewed for patient-, tumor- and treatment-related data. Five patients underwent neoadjuvant radiotherapy and only patients with histologically proven lymph node metastasis received adjuvant chemotherapy. Endoscopy reports of all patients were studied for information on the morphology of the resected lesion and macroscopic resection margins as reported by the endoscopist. Pathology reports were studied and the following features were assessed: tumor size, microscopic resection margins, macroscopic growth pattern, histopathological differentiation, presence of angioinvasion and in the cases with additional surgical resection, the presence of residual tumor cells at the endoscopic resection site and the presence of lymph node metastases. A microscopic complete resection was defined as a cancer-free margin of at least 2mm. A second group was defined as a complete resection with margins <2mm. In some tumors, the pathologist was unable to determine the resection margins. Incomplete resection was defined as the presence of microscopic residual tumor cells at the resection margin. All patients were informed about the disease and both

surgical treatment and a non-surgical surveillance were discussed based on clinicopathological characteristics and the international guidelines mentioned above. In contrast to the proposed therapy, some patients underwent the alternative treatment. Therefore, patients were divided into groups based on the *referred* treatment according to the international guidelines and the actual *received* treatment after endoscopic resection (Figure 1).

Endoscopic and Surgical Resection

Snare polypectomy was performed en bloc whenever feasible, otherwise piecemeal resection was undertaken. In some cases saline solution was injected into the submucosa prior to the resection. Macroscopic assessment of the resection margins was performed by the endoscopist during the procedure. Endoscopic resection specimens were sent for pathological examination.

Surgical resection with regional lymph node dissection included ileocecal resection, left/right (hemi) colectomy, sigmoid resection, low anterior resection or abdominoperineal resection. Surgical specimens were presented unfixed to the pathologist for macroscopic assessment, after which microscopic examination was performed using hematoxylin and eosin staining.

Follow-up Program

Follow up during the first 2 years consisted of clinical assessment and measurement of serum carcinoembryonic antigen (CEA) every 3 months, abdominal ultrasonography every 6 months and annual chest X-rays. After this period, follow-up was performed every 6 months. Colonoscopy was indicated 1 year after surgery and every 2 years over the following 4 years.

Statistical Analysis

All statistical analyses were performed using SPSS software version 24 (SPSS, Chicago, IL). Comparisons between patient groups were made using the 2-sample t-test for continuous variables, and the chi-square test for categorical variables. Predictors for lymph node metastases or residual tumor cells after endoscopic resection were identified through Cox regression analysis. Kaplan-Meier survival analysis was used to assess overall and disease-free survival of patients with an indication for additional surgery. A p value of less than 0.05 was considered statistically significant.

Results

Patient and tumor characteristics are shown in Table 1.

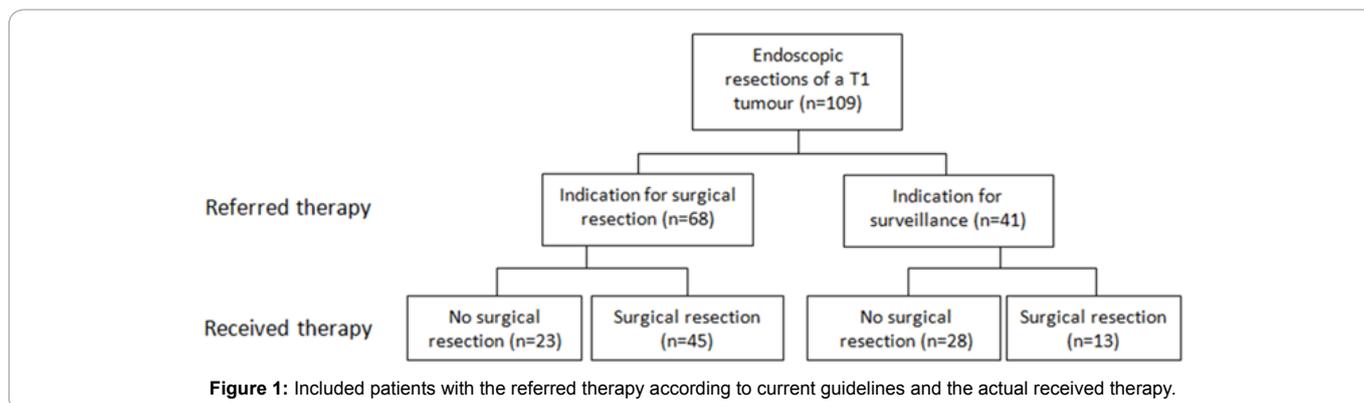


Table 1: Patient and tumour characteristics (n = 109).

	Surgical resection (n=58)	No surgical resection (n=51)	p-value
Age (years)	Mean 68.7 (SD ¹ 8.9)	Mean 65.7 (SD ¹ 11.5)	NS
Gender			
Male	35 (60%)	25 (49%)	NS
Female	23 (40%)	26 (51%)	
Endoscopic resection			
Snare	19 (33%)	13 (25%)	NS
Piecemeal	12 (21%)	4 (8%)	
Other	0 (0%)	2 (4%)	
Unknown	27 (46%)	32 (63%)	
Tumour location			
Proximal colon ²	3 (5%)	5 (10%)	NS
Sigmoid	34 (59%)	28 (55%)	
Rectosigmoid	8 (14%)	2 (4%)	
Rectum	13 (22%)	16 (31%)	
Tumour size			
<2cm	32 (55%)	29 (57%)	NS
≥2cm	25 (43%)	20 (39%)	
Unknown	1 (2%)	2 (4%)	
Macroscopic growth pattern			
Sessile	8 (14%)	5 (10%)	NS
Pedunculated	13 (22%)	17 (33%)	
Unknown	37 (64%)	29 (57%)	
Histopathological differentiation			
Well	15 (26%)	15 (29%)	NS
Moderate	3 (5%)	2 (4%)	
Poor	19 (33%)	19 (37%)	
Unknown	21 (36%)	15 (29%)	
Endoscopic resection margin			
Complete (>2mm)	10 (17%)	28 (55%)	<0.001
Complete (≤2mm)	5 (9%)	12 (24%)	
Unable to determine margins	15 (26%)	8 (16%)	
Incomplete	23 (40%)	2 (4%)	
Unknown	5 (8%)	1 (2%)	
Repeated endoscopic resection			
Yes	5 (9%)	13 (25%)	0.018
No	53 (91%)	38 (75%)	
Pathology revision			
Yes	1 (2%)	6 (12%)	0.033
No	57 (98%)	45 (88%)	
Indication according to guidelines			
Yes	45 (78%)	23 (45%)	<0.001
No	13 (22%)	28 (55%)	
Surgery			
Colectomy	5 (9%)	-	-
Sigmoid resection	28 (48%)	-	
Rectosigmoid resection	10 (17%)	-	
Low anterior resection	11 (19%)	-	
Abdominoperineal resection	4 (7%)	-	
Residual tumour cells in surgical specimen			
Yes	22 (38%)	-	-
- At endoscopic resection site	18 (31%)	-	
- In lymph nodes	7 (12%)	-	
No	36 (62%)	-	

Median follow-up was 80 months, 60 male (55%) and 49 females (45%) with a mean age of 67 years (range 26 – 86) at diagnosis were included. Malignant polyps were more frequently seen in the sigmoid colon (57%) and consisted mainly of small tumors <2cm (56%). 18 patients underwent repeated endoscopic evaluation/resection. A second pathological examination of the pathology specimen was performed in seven patients. Surgery was less likely to follow endoscopic resection if repeated endoscopic resection or a second assessment of the pathology was performed (p=0.018 and p=0.033, respectively).

Residual Tumor Cells and Lymph Node Metastases

In the surgical specimens (n=58), residual tumor cells at the endoscopic resection site were found in 18 patients (31%). Of these patients, endoscopic resection was considered incomplete in 10 patients and doubtful in 3 cases. Lymph node metastases were present in 7 patients (12%). In patients with an indication for surgical resection according to the guidelines within the surgery group (n=45), 13 surgical specimens showed residual cells at the endoscopic resection site (29%) and 5 had nodal involvement (11%). In only 1 out of 16 surgical patients, where the endoscopist had considered the polypectomy as complete, there were residual tumor cells in the surgical specimen. After endoscopic resection, 42/64 (66%) patients with incomplete, dubious or unknown resection margins as assessed by the endoscopist underwent additional surgery. Of these patients, 17 (40%) had residual tumor cells at the location of the polypectomy.

In surgical specimens, a sessile growth pattern (p=0.006) together with incomplete resection as reported by the endoscopist (p<0.001) were significant predictors for residual tumors cells at the endoscopic resection site. No significant predictive factors were found for nodal involvement. Tumor size, tumor location, method of endoscopic resection, resection margin reported by the pathologist, repeated endoscopic resection, neoadjuvant radiotherapy and the presence of a surgical indication were not significantly related to residual tumor cells or lymph node metastases.

Survival and Recurrence

Overall, 40 patients (37%) died, all except 1 due to other causes than colorectal cancer. One of the 58 surgical patients and two of the 51 patients that were treated only endoscopically developed cancer recurrence. One non-surgical patient died of metastatic disease. To investigate the role of surgery on the long term oncological outcomes, survival analysis was performed only in patients with an indication for surgical resection according to the current guidelines (resection margin <2mm, lymphovascular invasion or poor differentiation). Of the 68 patients with an indication, 45 patients underwent an additional surgical resection. Five year overall survival and disease free survival were equal for patients with and without surgery (Table 2). Median survival for patients who underwent surgical resection was 81 months, compared to 76 months for those without additional surgery (p=0.706). Multivariable analysis showed age as a predictive factor for overall survival (p<0.001) and neoadjuvant radiotherapy for disease free survival (p=0.034). Additional surgical resection was not significantly related to survival in this analysis.

Discussion

A number of histopathological and endoscopic characteristics have previously been investigated to determine which resected

Table 2: Survival of patients with an indication for surgical resection according to current guidelines.

	Surgical resection (n=45)	No surgical resection (n=23)	p-value
5-year DFS ¹	98%	92%	0.540
5-year OS ²	83%	76%	0.422

¹DFS: Disease Free Survival; ²OS: Overall Survival

polyps have the highest risk of residual tumor cells, lymph node involvement and/or local recurrence. Predictive factors include tumor cells at the resection margin, morphology of the polyp, histopathological differentiation and presence of angiolymphatic invasion [9-17]. In this study the percentages of patients with local tumor residue (31%) or lymph node metastasis (12%) are comparable to the percentages reported in the literature [8,18,19]. Furthermore, recurrence rates of endoscopically treated patients as well as survival data of both patients groups were comparable to previously reported results [20,21]. We also found evidence that the morphology of a polyp, i.e. a sessile form, is associated with residual tumor cells. In addition, the judgment by the endoscopist of the completeness of resection was found to be a predictor of residual tumor. This study is the first to report the role of the endoscopist in determining the resection margin of the endoscopic polypectomy. In current practice, pathology reports are the golden standard to determine resection margins after endoscopic resection. Our findings suggest a role for the judgement by the endoscopist as well, especially in those cases with equivocal or inconclusive pathology reports. Such a judgement can contribute in the decision to refrain from surgery and should be well discussed in a multidisciplinary team. As an alternative, repeated polypectomy or revision of the pathology can be performed in difficult cases. Our results indicate that these strategies are useful in the decision to refrain from an oncological resection and to prevent the inherent risks of radical surgery.

A study from England on 386 polyp cancers investigated the role of resection margins [13]. They suggest that a resection margin of >0mm in subsequently surgically resected specimens was associated with the absence of residual cancer. Naqvi, et al. presented 20 patients with resection margins <1mm of which none had adverse outcomes; whether surgically treated or not [22]. These findings, together with the predictive value of the judgement by the endoscopist in this study, indicate that radicality alone, even with a very small margin, is enough for an adequate oncological treatment. A tumor free resection margin of more than 2 mm does not seem to be a prerequisite to omit surgery.

Current guidelines suggest additional surgical resection after endoscopic removal of early stage colorectal carcinomas if risk criteria are met [9]. In this study we present evidence that even in the presence of one or more of these risk factors, long term oncological outcomes of patients with and without additional surgery after endoscopic resection of T1 colorectal tumors are comparable. In a large retrospective study from Korea with 430 patients with a T1 colorectal cancer, there was also no difference in overall survival in the group with unfavourable histologic features between patients with a local resection and patients with a surgical resection, if there was no lymphatic or venous invasion. Vascular invasion appeared to be the most important risk factor that was associated with recurrence and survival [23]. These data indicate that the current guidelines for the treatment of T1 colorectal cancer are possibly too strict and that there is a place for local/endoscopic resection with intensive surveillance, even in the presence of unfavourable histologic features but without vascular invasion. Large prospective cohort studies are essential to provide more evidence for this treatment strategy.

The results of the present study must be seen in light of its limitations. Data were evaluated retrospectively and pathology

reports were not standardized at the time of treatment. Therefore, pathology reports were not always complete, often not describing the presence of angiolymphatic invasion. Ideally, histopathological re-examination would solve some of these shortcomings. Since this was not feasible for practical and logistical reasons, all data were extracted from the original pathology reports and therefore show limitations associated with a retrospective study. For the same reason we have only analyzed predictors as used in the current guidelines. Although multiple studies provide reasonable evidence for novel predictors that could be of help when determining malignant potential of colonic polyps, such as vertical tumor margin and tumor budding [24-27], recent recommendations still advise the aforementioned items as core pathological assessment [28]. Furthermore, only patients with an indication for surgical resection were included in the survival analysis in order to minimize bias. In this group the reason for omitting surgical resection in 23 patients was unclear. A sub-analysis of the baseline characteristics between the two therapy groups revealed no significant differences. Selection bias of patients with comorbidities might influence the group of patients who did not undergo additional resection in the presence of this indication. An attempt to correct for these biases through Propensity Score Matching resulted in no difference in outcome with regard to survival.

In conclusion, despite the indication for additional surgery after endoscopic resection of T1 colorectal adenocarcinomas according to international guidelines, long term outcome seems to be comparable for patients with and without additional surgical resection after endoscopic removal of the polyp with the T1 tumor. This indicates an important role for endoscopic resection alone as definitive curative treatment, even in the presence of risk factors for lymph node metastasis or residual tumor cells, such as a resection margin less than 2mm or poor differentiation. Local resection with intensive surveillance is particularly useful for high risk surgical patients, such as older individuals with comorbidities.

Conflicts of Interest and Source of Funding

None to declare

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