Nonampullary Duodenal Adenomas Rarely Recur after Complete Endoscopic Resection: A Swiss Experience Including a Literature Review

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Keywords

Duodenal adenoma · Nonampullary duodenal adenoma · Duodenal polyposis · Endoscopic resection · Endoscopic treatment

Abstract

Introduction: Duodenal polyps and especially duodenal adenomas are a rare and mostly coincidental finding in patients undergoing upper gastrointestinal endoscopy. Due to their malignant potential, duodenal adenomas should be removed upon diagnosis. So far, the limited available data on the performance of endoscopic polypectomy show conflicting results with regard to adverse events and the adenoma recurrence rate. **Patients and Methods:** After summarizing the currently available data, we retrospectively analyzed all patients undergoing endoscopic resection of nonampullary duodenal adenomas (NAD) at our institution between 2006 and 2016. **Results:** A total of 78 patients underwent endoscopic polypectomy for NAD adenoma. End-of-treatment success with complete resection requiring a mean of 1.2 interventions was achieved in 91% ($n = 71$). Procedural hemorrhage occurred in 12.8% ($n = 10$), whereas delayed bleeding was noted in 9% ($n = 7$). Duodenal perforation was registered and successfully treated in 2 cases (2.6%). No adenoma recurrence was noted following primary complete adenoma resection after a mean follow-up time of 33 months. Acute post-polypectomy bleeding was statistically significantly as-

sociated with large polyp size ($p = 0.003$) and lack of endoscopic prophylaxis ($p = 0.0008$). Delayed post-polypectomy bleeding showed a trend in the occurrence of large polyps ($p = 0.064$), and was statistically significantly associated with familial cancer syndrome ($p = 0.019$) and advanced histopathology ($p = 0.013$). **Conclusion:** Our data suggest that endoscopic polypectomy of NAD is well feasible with high success rates. Procedural and delayed hemorrhage seems to be the primary issue rather than adenoma recurrence. We therefore advocate referral of patients with large NAD to experienced centers for endoscopic resection.

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Introduction

Duodenal adenomas are rare and mostly coincidental findings in patients presenting for routine upper gastrointestinal endoscopy. They can be divided into 3 subgroups: sporadically occurring duodenal adenomas or nonampullary adenomas of the duodenum (NAD), duodenal adenomas of the papilla of Vater, and duodenal adenomas associated with genetic polyposis syndromes such as familial adenomatous polyposis (FAP) or Peutz-Jeghers. Since duodenal adenomas bear a risk of malignant transformation comparable to colonic adenomas, removal is recommended upon diagnosis [1]. Due to the relatively low incidence of duodenal compared to colonic

Fig. 1. Patient intervention and follow-up flowchart.

adenoma, large mortality studies are lacking. Until recently, the management of duodenal adenomas consisted of local or radical surgical resection, which carries a high morbidity and mortality risk as well a high recurrence rate. Recently, thanks to refined endoscopic techniques such as endoscopic mucosal resection (EMR), minimally invasive endoscopic management of such lesions has become the therapeutic approach of choice. Comparable to EMR in the right-sided colon, duodenal polypectomy is performed after lifting the lesion with submucosal liquid injection in order to counteract perforation of the thin duodenal wall. Different alternative resection techniques such as hybrid endoscopic submucosal dissection [2], cap-assisted suck and cut [3], underwater EMR [4], and band and slough [5] have been reported in small populations so far. In addition, remnants of adenomatous tissue after primary endoscopic resection may be removed by ablative interventions such as argon plasma coagulation (APC), radio frequency ablation (RFA), or electrocautery [6].

Data currently available on the endoscopic management of duodenal adenomas and its adverse events remain limited. Especially, the rates of adverse events and adenoma recurrence after polypectomy are very heteroge-

neous among the few available publications. Recently, the American Society of Gastrointestinal Endoscopy has released their guidelines on the role of endoscopy in duodenal adenomas [7]. We here present a literature overview on the available literature and we analyzed the data of all patients ($n = 78$) who underwent EMR for duodenal adenoma at our institution between 2006 and 2016. The purpose of this study was to evaluate the efficacy and safety of EMR for NAD. We specifically evaluated the rate and risk factors of short-term (mainly bleeding and perforation) and long-term (bleeding) adverse events as well as the frequency of adenoma recurrence and the need for follow-up.

Materials and Methods

Patients

The primary endpoint of our study was to examine the outcome of EMR of duodenal polyps with regards to short-term (duodenal perforation, bleeding) and long-term (bleeding) adverse events as well as the frequency of adenoma recurrence. For this reason, we reviewed our endoscopic charts from 2006 to 2016. Seventy-eight patients (Fig. 1) met the inclusion criteria (patients with nonampullary duodenal polyp(s) undergoing endoscopic adenoma resection at our institution). Both sporadically occurring duodenal adenomas as well as adenomas in the context of

Fig. 2. **a** Endoscopic assessment of the location and size of the NAD. **b** Submucosal saline injection in order to create a cushion. **c** Snare polypectomy of the entire NAD. **d** Prophylactic adaption of polypectomy site using hemoclips.

FAP were included. All patients gave their written consent to the procedure and use of their medical records for research purposes. The study was approved by the local Ethics Committee (KEK ZH 2014-0465).

Endoscopies and EMR

All esophagogastroduodenoscopies were performed by 3 experienced endoscopists under non-anesthetist application of propofol using flexible standard Olympus® endoscopes. If possible, all anticoagulant or antithrombotic medications were discontinued 7 days prior to the intervention. After careful assessment of location, size, spreading, and involvement of the major papilla (side-viewing endoscope), adenoma resection was conducted using either a biopsy forceps or snare polypectomy with prior submucosal isotonic saline injection (NaCl 0.9%) without or with blue dye. If technically feasible, en bloc EMR was always aimed for. Snare resection was the preferred polypectomy technique (Fig. 2). In case of residual adenoma tissue on the resection margins, APC or RFA was conducted. Intravenous butylscopolamine was administered at the discretion of the endoscopist. Duodenal hemorrhage provoked by polypectomy were subdivided into “minor” (hemoglobin drop <2 g/L) and “major” (hemoglobin drop

>2 g/L and/or need for red blood cell transfusion) bleeding. We differentiated between immediate (during the polypectomy) or delayed bleeding (a second esophagogastroduodenoscopies was necessary in the follow-up during the first 2 weeks after polypectomy). If required, endoscopic hemostasis was achieved using standard hemoclips, over-the-scope clips (OTSC®, Ovesco, Tübingen), loop ligation (endo loop, Olympus®) or argon plasma coagulation (APC, Erbe, Tübingen). In the absence of immediate hemorrhage, performed hemostatic interventions were considered prophylactic hemostasis.

Adenoma size was measured on the histopathological specimen. In case of piecemeal resection, the size of the largest pathological piece was recorded. After polypectomy, proton pump inhibitors were administered for at least 4 weeks. The majority of interventions were performed on an in-patient basis depending on the adenoma size, the difficulty of the procedure, and the comorbidities of the patient.

Follow-Up

The first follow-up endoscopy in case of complete resection was conducted 12 months after endoscopic polypectomy or at the discretion of the endoscopist.

Table 1. Patient and lesion characteristics

	<i>n</i>	Range	Percentage
Patients	78		
Age, years, mean	65.9	33–91	
Gender			
Male	47		60.3
Female	31		39.7
Non-FAP	70		89.7
FAP	8		10.3
HNPCC	0		0.0
Adenomas			
Size, mm, mean	17.2	2–55	
Solitary	62		79.5
Multifocal	16		20.5
Histopathology, <i>n</i>			
Tubular	54		69.2
Tubulo-villous	24		30.8
Dysplastic grading			
LGD	65		83.3
HGD	13		16.7

Statistical Analysis

The statistical analysis was focused on factors that predicted the occurrence of acute or delayed bleeding and the presence of advanced histopathology. Advanced histopathology was defined as the presence of tubulovillous changes and low or high-grade dysplasia. In 3 separate logistic regressions, acute bleeding, delayed bleeding, and advanced histopathology served as 3 separate outcome variables. Demographic characteristics (age, gender), polyp characteristics (size, number, histopathology), resection technique (snare, biopsy, RFA, piecemeal vs. en bloc resection, prophylactic measures of hemostasis), and clinical history (prior bleeding, anticoagulation treatment) all served as predictor variables. The results of the multivariate analyses were assessed in terms of significant odds ratios or *p* values associated with individual predictor variables.

Results

Patients

We here present a retrospective cohort of patients undergoing EMR of histologically confirmed adenomas of the duodenum performed at our institution, the largest tertiary referral center in Switzerland. A total of 78 patients (47 male [60%] and 31 female [40%]) with NAD underwent endoscopic removal (Table 1). The mean age of the population was 65.7 years. Eight out of the 78 adenomas (10%) were associated with FAP, whereas 70 of the adenomas were sporadic (90%).

Adenoma Features

The mean adenoma size was 16.8 mm (range 2–55 mm). Sixty-two (79.5%) adenomas were solitary, whereas 16 (20.5%) were multifocal. Histopathological evaluation re-

vealed 54 (69.2%) tubular and 24 (30.8%) tubulovillous adenomas. Sixty-five (83.3%) were graded as low grade and the remaining 13 (16.7%) as high grade dysplasia.

Endoscopic Resection Features

The majority (*n* = 72, 92.3%) of the adenomas were hot snare resected after submucosal saline injection. The remaining 6 (7.7%) polypectomies of small adenomas were performed using a standard biopsy forceps (Table 2). In 35.9% (28) en bloc resection was possible, whereas the remaining 64.1% (50) of the lesions were resected in a piecemeal technique. A mean of 1.2 (range 1–6) procedures were necessary to achieve a primary adenoma-free resection site in 91% (71) of patients. Six patients (7.7%) remain under regular observation including repetitive endoscopic resection of remaining adenomatous tissue. In one patient (1.3%), after an initial attempt to endoscopically resect a multitude of polyps, a secondary surgical resection had to be performed due to incomplete endoscopic removal. In 49 (62.8%) of the cases, prophylactic hemostasis using hemoclips (*n* = 26, 53.1%), APC (*n* = 8, 16.3%), OTSC® (*n* = 6, 12.2%), loop ligation (*n* = 1, 2%) or a combination of these (*n* = 8, 16.3%) was performed at the time of primary endoscopic resection.

Adverse Events

All of the 10 (12.8%, 7 minor, 3 major) intra-procedural bleedings were stopped by endoscopic measures. In 7 cases (9%), delayed bleeding (major 6, minor 1) was noticed after the primary intervention. Endoscopic hemostasis was then achieved in all cases. The mean time from the endoscopic adenoma resection to occurrence of delayed bleeding was 52 h (range 5–240 h). Of the patients with delayed bleeding, one patient underwent resection while still on a low-dose treatment with acetyl salicylic acid. A second patient had stopped the antiplatelet medication more than 7 days before the polypectomy. The remaining 5 patients did not take any anticoagulants. In 4 out of these 7 patients with delayed bleeding, prophylactic endoscopic hemostasis or hemostasis of a procedural bleeding had already been performed (APC and or clip application).

Two out of 78 (2.6%) patients had a duodenal perforation that was successfully closed using an OTSC®.

Risk Factors for Adverse Events

Acute post-polypectomy bleeding was statistically and significantly associated with large polyp size (*p* = 0.003) and lack of endoscopic prophylaxis (*p* = 0.0008). Delayed

post-polypectomy bleeding showed a trend in large polyps ($p = 0.064$) and was statistically and significantly associated with familial cancer syndrome ($p = 0.019$) and advanced histopathology ($p = 0.013$). Lastly, advanced histopathology was statistically significantly associated with large polyp size. In general, age and gender did not affect bleeding or polyp type.

Follow-up

Endoscopic long-term (mean 33 months, range 1–121) follow-up was available in 68 patients. During follow-up, there was no recurrence of duodenal adenoma in any of the patients who achieved complete endoscopic resection.

Three (3.8%) patients were lost to follow-up after initial polypectomy. Follow-up was not yet due at the time of data analysis in 7 patients (9%). Seven patients (9%) did not achieve a primary complete adenoma removal and were therefore under regular surveillance for a longer time with repetitive endoscopic resections going on (Fig. 1).

Review of the Literature

A PubMed search was performed using the following Mesh-Terms: duodenal adenoma; nonampullary duodenal adenoma; duodenal polyposis; endoscopic resection; endoscopic treatment. After review of the abstracts, 17 publications were found to be clinically relevant and were then further analyzed (Table 3). A total of 519 patients were included in the 17 cohorts. The mean population size was 38 patients (range 12–106) with a mean follow-up of 26 months (range 0–100).

One of the first publications was presented by Apel et al. [6] in 2005. Using a classic EMR technique after submucosal saline injections, a total of 21 polypectomies were performed. The authors did not report any short-term adverse events, whereas delayed bleeding occurred in 9.5% of the cases. Adenoma recurrence rate upon follow-up was 25%. Three years later, Lepilliez et al. [8] presented another retrospective analysis of endoscopically resected nonampullary duodenal adenomas. Among their 35 patients, the procedural bleeding rate was 14%, while delayed bleeding occurred in 11.6%. After a mean follow-up of 15 months, no adenoma recurrence was noted. Several other authors found an immediate bleeding rate in the same range (6–18%) [3, 9–12]. In 2 studies, high rates of procedural hemorrhage (57.8 and 43%, respectively) were observed [13, 14], whereas 3 authors did not observe any procedural bleeding complications [2, 5, 15]. Duodenal perforation occurred in 8 cases among all

Table 2. Endoscopic treatment and follow-up

Endoscopic treatment	<i>n</i>	Range	Percentage
Snare	72		92.3
Biopsy	6		7.7
En bloc	28		35.9
Piecemeal	50		64.1
Amount of EMR, mean	1.2	1–6	
Amount of EMR, median	1		
End of treatment success			
Yes	71		91.0
Ongoing	6		7.7
Surgery	1		1.3
Prophylactic endoscopic hemostasis			
No	29		37.2
Yes	49		62.8
APC	9		18.4
Hemoclip	26		53.1
OTSC	6		12.2
Loop	1		2.0
Combination	8		16.3
Adverse events			
Procedural bleeding			
No	68		87.2
Minor	7		9.0
Major	3		3.8
Endoscopic hemostasis			
APC	1		10.0
Hemoclip	5		50.0
OTSC	4		40.0
Delayed bleeding			
No	71		91.0
Minor	1		1.3
Major	6		7.7
Mean time to bleeding, h	52		
Endoscopic hemostasis			
APC	1		14.3
Hemoclip	3		42.9
OTSC	2		28.6
Combination	1		14.3
Perforation			
No	76		97.4
Yes	2		2.6
Treatment			
OTSC	2		100.0
Follow-up			
Incomplete initial resection	7		9.0
No follow-up yet	4		5.1
Lost to follow-up	3		3.8
Cases with a follow-up	64		82.1
Mean follow-up, months	33	2–112	
Adenoma recurrence			
No	64		100.0
Yes	0		0.0

Table 3. Literature review

Title	Year	First author	Journal	Method	Population size	Follow up time, m	Resection technique	Short term complications	Long term complications	Adenoma recurrence
1 Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success, adverse events, and long-term outcomes	2016	Klein	Gastrointest Endosc	Retrospective	106	22	EMR	Intraprocedural bleeding in 43%	Delayed bleeding in 15% perforation in 3 pat.	SE1: 14.4% SE2: 4.2%
2 Safety and efficacy of EMR for sporadic, nonampullary duodenal adenomas: a single U.S. center experience (with video)	2016	Singh	Gastrointest Endosc	Retrospective	51	15	EMR	Bleeding in 11.8%	na	25.6–5.2%
3 Prospective study of acute complication rates and associated risk factors in endoscopic therapy for duodenal adenomas	2015	Aschmoneit-Messer	Surg Endosc	Prospective	50	Only acute	EMR	Major bleeding in 6.5% minor bleeding in 18%	na	Na
4 Efficacy and safety of the band and slough technique for endoscopic therapy of nonampullary duodenal adenomas: a case series	2015	Kortala	Gastrointest Endosc	Retrospective	10	24	Band and slough	None	None	0%
5 Endoscopic resection of large sporadic non-ampullary duodenal polyps: efficacy and long-term recurrence	2014	Navaneethan	Surg Endosc	Retrospective	54	10.8	EMR	na	Major complications in 5.6% (1 × perforation, 2 × bleeding)	7.40%
6 Endoscopic resection of sporadic duodenal adenomas: comparison of endoscopic mucosal resection (EMR) with hybrid endoscopic submucosal dissection (ESD) techniques and the risks of late delayed bleeding	2014	Basford	Surg Endosc	Prospective	34	38	EMR/ESD hybrid	none	Delayed bleeding in 7.5%	EMR = 25%, hybrid = 33%
7 “Underwater” EMR of sporadic laterally spreading nonampullary duodenal adenomas	2013	Binmoeller	Gastrointest Endosc	Prospective	12	4	Underwater EMR	na	Delayed bleeding in 3 pat. stricture in 1 pat., water intoxication in 1 pat.	Na
8 Efficacy and safety of endoscopic treatment for nonampullary sporadic duodenal adenomas	2013	Min	Dig Dis Sci	Retrospective	23	11.4	EMR and APC	2 × intraprocedural bleeding, 1 × perforation	na	10% (APC), 0% (EMR)
9 Giant laterally spreading tumors of the duodenum: endoscopic resection outcomes, limitations, and caveats.	2012	Fanning	Gastrointest Endosc	Retrospective	46	11.5	EMR	Intraprocedural bleeding in 57.8% (giant), 19.3% (small)	na	23% for giant, 15 % for small
10 Cap-assisted EMR of large, sporadic, nonampullary duodenal polyps.	2012	Conio	Gastrointest Endosc	Retrospective	26	72	EMR-C	Intraprocedural bleeding in 11.5%	None	None
11 Endoscopic predictors of successful endoluminal eradication in sporadic duodenal adenomas and its acute complications	2010	Kedia	Gastrointest Endosc	Retrospective	36	No	EMR	Acute bleeding in 13.9%	na	Na

Table 3. (continued)

Title	Year	First author	Journal	Method	Population size	Follow up time, m	Resection technique	Short term complications	Long term complications	Adenoma recurrence
12 Outcome based on management for duodenal adenomas: sporadic versus familial disease	2010	Johnson	J Gastrointest Surg	Retrospective	44	77/100	EMR	9% (2 × perforation, 2 × pancreatitis)	na	Endoscopic: 52% local resection; 32% definitive resection; 0%
13 Nonampullary duodenal polyps: characteristics and endoscopic management	2010	Abbass	Gastrointest Endosc	Retrospective	59	26	EMR	None	Delayed bleeding in 3 cases (5%)	37%
14 Efficacy and long-term outcome of endoscopic treatment of sporadic nonampullary duodenal adenoma	2010	Kim	Gut Liver	Retrospective	17	29	EMR	None	Delayed bleeding in 1 pat.	None
15 EMR of large sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome	2009	Alexander	Gastrointest Endosc	Retrospective	21	13	EMR	1 pat. With early bleeding	None	na
16 Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding	2008	Lepilliez	Endoscopy	Retrospective	36	15	EMR	Intraprocedural bleeding in 14%, 1 × fatal perforation	Delayed bleeding in 11.6%	None
17 Follow-up after endoscopic snare resection of duodenal adenomas	2005	Apel	Endoscopy	Retrospective	21	71	EMR	None	Delayed bleeding in 9.5%	25%

studies leading to an overall perforation of 1.5% [8, 13, 16–18]. Delayed bleeding was noted in 7.5–15% in those studies that evaluated delayed adverse events. The incidence of adenoma recurrence showed substantial variation between 0 and 52% for a mean follow-up time of 23 months (range 0–100).

Discussion

Duodenal polyps are a relatively rare finding upon endoscopy in usually asymptomatic patients [19–22]. They consist of duodenal adenomas, gastric metaplasia, or submucosal lesions such as lipoma or GISTs. Even though little is known about the tumor biology of duodenal adenomas, they are believed to follow an adenoma-carcinoma sequence comparable to colonic adenomas [6]. Due to their malignant potential, duodenal adenomas occurring sporadically or in familial polyposis syndromes should be removed. Compared to tubular adenomas, tubulovillous lesions bear an increased risk to undergo malignant transformation [6]. In our cohort, approximately one third of the adenomas were tubulovillous. Historically, duodenal adenomas have been approached surgically, associated with substantial morbidity and mortality and with elevated recurrence rates most likely due to incomplete resection. Today, the approach of choice in limited disease should be endoscopic resection. Currently, there is only limited and mostly retrospective data available concerning the endoscopic removal of NAD. Despite the lack of large, prospective studies analyzing the efficacy and safety of endoscopic treatment of duodenal adenomas, the advantages such as accurate identification and visualization of complete resection, organ preservation, reduction of perioperative risks, recovery, and length of hospital stay are evident.

A significant portion of the patients undergoing polypectomy of NAD at our tertiary-care center were referrals from other gastroenterology centers. So far, we here present the largest cohort of NAD polypectomies in Switzerland.

In our cohort, we found a fairly high rate of immediate bleeding (14%) compared to colonic polypectomy [23, 24] with classic bleeding rates below 5%. This fact is most likely due to the abundant vascularization of the duodenal mucosa. The occurrence of acute post-polypectomy hemorrhage was statistically and significantly associated with large polyp size and the lack of endoscopic. Prophylactic hemostasis was performed in over

60% of our patients. Delayed bleeding occurred in almost 10% of the cases with a statistical trend in advanced adenoma histology and familial polyposis syndrome. Interestingly, no significant association was found between continued antithrombotic (low dose aspirin, $n = 4$) medication and hemorrhage. In our experience, diffuse oozing was the predominant type of bleeding most likely due to the highly vascularized duodenal wall. Using standard through-the-scope clips seem less suitable for dealing with such bleeding. APC offers additional ablation of residual adenomatous tissues at the resection edges, yet bears the risk of transmural injury of the thin duodenal wall. The recently introduced OTSC® now offers an endoscopic tool for the compression of larger areas. Further studies need to assess which of the available tools for endoscopic hemostasis is the optimal one in case of duodenal polypectomy.

The frequency of perforation in our cohort was comparably low with 2.6% (2/76). Both duodenal perforations among our patients were successfully closed immediately after resection using an OTSC® and surgery was avoided. These findings underline an approximately 10-fold increased perforation risk in the duodenum compared to the reported perforation rate of 0.07–0.13% in the ascending colon and the caecum [24].

In our cohort, we were able to confirm that the most relevant adverse event of endoscopic duodenal adenoma resection despite prophylactic measures is immediate and

delayed bleeding from the polypectomy site. Given this relatively high frequency of adverse events compared to colonic polypectomy, we suggest that endoscopic resection of NAD should be performed in centers with expertise in the field.

Compared to a fairly high adenoma recurrence rate in other cohorts, our data show that once a duodenal adenoma is removed in toto, the risk of recurrence is very low to absent in the long-term follow-up (mean 3 years). We therefore believe that this discrepancy in recurrence rates is more likely due to the initial incomplete resection rather than adenoma recurrence. Yet, no consensus regarding surveillance intervals has been found among experts so far. To exhaustively address this question, larger cohorts are needed.

In conclusion, given the high rates of successful complete resection, our data support the opinion that sporadic and syndrome-associated NAD should be approached endoscopically. The most prevalent adverse event seems to be hemorrhage even in cases of prophylactic hemostasis. Furthermore, our data show that adenoma recurrence is less frequent than previously suggested in case of primary R0 resection.

Disclosure Statement

The authors hereby declare no conflicts of interest.

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