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Endoscopic management of superficial nonampullary duodenal tumors: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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Appendix 1s
Supplementary material is available at
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MAIN RECOMMENDATIONS

1 ESGE recommends that all duodenal adenomas should be considered for endoscopic resection as progression to invasive carcinoma is highly likely.
Strong recommendation, low quality evidence.

2 ESGE recommends performance of a colonoscopy, if that has not yet been done, in cases of duodenal adenoma.
Strong recommendation, low quality evidence.

3 ESGE recommends the use of the cap-assisted method when the location of the minor and/or major papilla and their relationship to a duodenal adenoma is not clearly established during forward-viewing endoscopy.
Strong recommendation, moderate quality evidence.

4 ESGE recommends the routine use of a side-viewing endoscope when a laterally spreading adenoma with extension to the minor and/or major papilla is suspected.
Strong recommendation, low quality evidence.

5 ESGE suggests cold snare polypectomy for small (<6 mm in size) nonmalignant duodenal adenomas.
Weak recommendation, low quality evidence.

6 ESGE recommends endoscopic mucosal resection (EMR) as the first-line endoscopic resection technique for nonmalignant large nonampullary duodenal adenomas.
Strong recommendation, moderate quality evidence.

7 ESGE recommends that endoscopic submucosal dissection (ESD) for duodenal adenomas is an effective resection technique only in expert hands.
Strong recommendation, low quality evidence.

8 ESGE recommends using techniques that minimize adverse events such as immediate or delayed bleeding or perforation. These may include piecemeal resection, defect closure techniques, noncontact hemostasis, and other emerging techniques, and these should be considered on a case-by-case basis.
Strong recommendation, low quality evidence.

9 ESGE recommends endoscopic surveillance 3 months after the index treatment. In cases of no recurrence, a further follow-up endoscopy should be done 1 year later. Thereafter, surveillance intervals should be adapted to the lesion site, en bloc resection status, and initial histological result.
Strong recommendation, low quality evidence.

SOURCE AND SCOPE

This is the second part of a two-part guideline from the European Society of Gastrointestinal Endoscopy (ESGE) that covers the endoscopic management of superficial nonampullary tumors of the duodenum. The companion guideline gives guidance on ampullary tumors.

1 Introduction

Superficial nonampullary duodenal tumors (SNADTs) are less frequently observed compared with adenomas in the other areas of the gastrointestinal (GI) tract but recent studies have shown a gradual increase in incidence of these lesions [1]. This increase could be explained by some environmental factors but also by better accuracy of gastroscopy and new endoscopic detection technologies. Endoscopy has taken the main role in management of these lesions, particularly in a curative setting. Nevertheless, diagnostic and therapeutic strategies need to be clearly defined.

Lesions associated with predisposing genetic syndromes, including familial adenomatous polyposis (FAP), or of submucosal or neuroendocrine origin, will not be discussed here as they are considered in another Guideline from the European Society of Gastrointestinal Endoscopy (ESGE) [2]. While the indications for endoscopic treatment and follow-up may be different between the sporadic and polyposis-related forms, the statements regarding diagnosis, evaluation, technical modalities of SNADT treatment, and management of complications are similar.

2 Methods

ESGE commissioned this Guideline (Guideline Committee Chair, J.v.H) and appointed a guideline leader (G.V.) who invited the listed authors to participate in the project development. The key questions were prepared by the guideline leader on two topics (endoscopic management of ampullary tumors and of preneoplastic duodenal lesions) and then approved by the other project members. The coordinating team established task force subgroups, each with its own leader, that were assigned key questions (see **Appendix 1s**, online-only Supplementary Material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The literature search was performed for English-language articles in MEDLINE, Embase, and the Cochrane database, focusing on meta-analyses and fully published prospective studies, particularly randomized controlled trials (RCTs), performed in humans. Retrospective analyses and pilot studies were also included if they addressed topics not covered in the prospective studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendation and quality of evidence. Each task force proposed statements

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ABBREVIATIONS

APC	argon plasma coagulation
CA-EGD	cap-assisted esophagogastroduodenoscopy
CT	computed tomography
EMR	endoscopic mucosal resection
ERCP	endoscopic retrograde cholangiopancreatography
ESD	endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
EUS-BD	endoscopic ultrasound-guided biliary drainage
EUS-FNA/B	endoscopic ultrasound fine-needle aspiration/biopsy
FAP	familial adenomatous polyposis
FTRD	full-thickness resection device
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDUS	intraductal ultrasound
IHC	immunohistochemistry
MRCP	magnetic resonance cholangiopancreatography
NBI	narrow band imaging
OR	odds ratio
OTS	over-the-scope
RCT	randomized controlled trial
RFA	radiofrequency ablation
SEMS	self-expandable metal stent
SNADT	superficial nonampullary duodenal tumor
U-EMR	underwater endoscopic mucosal resection

on their assigned key questions which were discussed during a web meeting in July 2020. Literature searches were re-run in September 2020. This time-point should be the starting point in the search for new evidence for future updates to this Guideline.

In September 2020, a draft prepared by G.V. was sent to all group members for review. The draft was also reviewed by two external reviewers and then sent for further comments to the ESGE national societies and individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

This Guideline was issued in 2021 and will be considered for review in 2025, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim period will be noted on the ESGE website: http://www.esge.com/ esge-guidelines.html.

3 Diagnosis of superficial nonampullary duodenal tumors

3.1 Epidemiology, histology, presentation, and predictive factors

RECOMMENDATION

ESGE recommends that all duodenal adenomas should be considered for endoscopic resection as progression to invasive carcinoma is highly likely.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends performance of a colonoscopy, if that has not yet been done, in cases of duodenal adenoma.

Strong recommendation, low quality evidence.

The prevalence of SNADTs is relatively low, reported as between 1.0 % to 1.5 % in retrospective series [3, 4] and 4.6 % in a prospective one [5]. Among these and another retrospective series, the overall prevalence of adenoma ranged only from 0.03 to 0.4 % [3, 5, 6].

In contrast to ampullary tumors, duodenal adenomas are less often sporadic, being associated in 60 % of cases with FAP [7]. The other predisposing genetic syndrome is *MUTYH*-associated polyposis in which the prevalence of duodenal adenomas is estimated to be 17 %–25 % of patients [8]. Some independent predictive factors for sporadic duodenal adenomas have recently been determined, including current smoking (odds ratio [OR] 3.35, 95 %CI 1.79–6.30), Barrett's esophagus (OR 4.23, 95 %CI 2.17–8.25), fundic gland polyp (OR 2.29, 95 %CI 1.29–4.06), and malignant disease (OR 2.84, 95 %CI 1.57–5.15) [9]. When the patient presents with predictive factors, a careful gastroscopic examination of the whole duodenum must be carried out with fulfilment of the appropriate quality criteria [10].

In addition, a meta-analysis of several case–control studies (24 studies, 37 152 participants) has suggested an association between sporadic duodenal adenoma and colorectal adenoma [11]. The largest case–control study on the subject, published after the above meta-analysis, included 203 277 patients (537 with duodenal adenomas) who underwent upper and lower gastrointestinal endoscopy. Patients with duodenal adenoma showed a significantly higher prevalence of all types of colonic adenomas (OR 2.65, 95 %CI 2.16–3.25), advanced colonic adenomas (OR 4.30, 95 %CI 3.24–5.70), and colorectal cancer (OR 3.13, 95 %CI 1.38–7.12), without location preference between left and right colon [12].

Most of the lesions are diagnosed incidentally during a gastroscopy, with initial histopathological findings of low grade dysplasia [13]. After a follow-up of 6 months, 20.9 % (9/43) of low grade dysplasia adenomas showed progression to high grade dysplasia, including 4.7 % in situ carcinomas [13]. High grade dysplasia diagnosis at first biopsy and a lesion diameter

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of ≥ 20 mm are significantly predictive of progression to adenocarcinoma [13].

The progression from adenoma to adenocarcinoma is of two types [14]. In the first, intestinal-type lesions in proximal and distal duodenum follow the adenoma–carcinoma sequence, similarly to carcinogenesis in the colon. Secondly, progression of a de novo gastric type, including gastric foveolar-type or pyloric gland adenoma, is independent of the usual Wnt/β-catenin pathway and is associated with gastric duodenal metaplasia in the proximal segment (bulb). The gastric-type lesion is more frequently diagnosed as carcinoma, with a tendency to poorer prognosis [15]. The intestinal-type progression is associated with classic adenomas, most of which are located in the second part of the duodenum and are the most common form of presentation.

3.2 Endoscopic assessment, biopsy, and staging

RECOMMENDATION

ESGE recommends the use of the cap-assisted method when the location of the minor and/or major papilla and their relationship to a duodenal adenoma is not clearly established during forward-viewing endoscopy.
Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends the routine use of a side-viewing endoscope when a laterally spreading adenoma with extension to the minor and/or major papilla is suspected.
Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests the use of magnifying chromoendoscopy for endoscopic diagnosis and staging of duodenal lesions.
Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests that if endoscopic features are suggestive of superficial duodenal adenoma, the use of biopsy for histological assessment should be limited prior to endoscopic resection, since its additional diagnostic yield might be limited and resection might be compromised.
Weak recommendation, low quality evidence.

The macroscopic presentation for sporadic duodenal adenoma is mainly milk-white or reddish mucosa (▶ **Fig. 1**) [16, 17], and the morphology of the lesion is usually 0-IIa in the Paris classification [17–19]. The associations between the macroscopic type or the tumor size and malignancy have been analyzed with conflicting results [1, 13, 20, 21]. Nevertheless, Paris 0-IIc or III lesions with ulcerated forms and loss of superficial pit pattern remain potentially significantly more likely to have an unfavorable outcome and to be invasive and therefore more likely to lead to a definitive histological finding.

Evaluation of the extent of the SNADT may require some technical adaptations. The use of a transparent cap on the tip of a forward-viewing endoscope (cap-assisted esophagogastroduodenoscopy [CA-EGD]), for the duodenal folds and the area of the ampulla, enhances visualization and targeting of lesions especially at the genu superius [22]. It also has been shown to effectively visualize the ampulla, with failure rates of only 3 %–9 % [23–26]. Although CA-EGD appears significantly better than standard gastroscopy to explore the papilla, comparative studies of CA-EGD versus side-viewing duodenoscopy had conflicting results [25–27]. CA-EGD can therefore be used when the location of the papilla and its relationship to the duodenal adenoma have not been definitively established. However, the use of a side-viewing endoscope remains essential when extension of the lesion to the papilla is suspected.

Indigo carmine chromoendoscopy has consistently been shown to increase detection rates especially in high risk populations [28–31]. The use of narrow-band imaging (NBI) also improved the detection capability for duodenal adenomas in a



▶ **Fig. 1** Sporadic duodenal adenoma: different macroscopic presentations. **a** Type 0-Is with milk-white mucosa; **b** Type 0-IIa with reddish mucosa; **c** Type 0-IIa with milk-white mucosa.

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prospective study in patients with FAP [21]. The magnifying NBI criteria for microsurface structures and microvessel patterns were reported to be useful to distinguish neoplastic from non-neoplastic lesions [32,33]. Considering the pit and vascular patterns in the largest retrospective study of 107 patients (114 lesions), and using a propensity score-matching analysis, NBI showed sensitivity of 92% (95%CI 86–98), specificity 79% (95%CI 67–91), positive predictive value 87% (95%CI 80–95), negative predictive value 87% (95%CI 77–97), and accuracy 87% (95%CI 81–94), with good interobserver agreement (κ coefficient 0.60–0.76) [33]. NBI was also useful for distinguishing between low and high grade dysplasia and adenocarcinoma [34–36]). Crystal violet staining appears more accurate for differentiating adenoma with low grade dysplasia from high grade dysplasia and adenocarcinoma when compared to white light endoscopy [37]. Nevertheless, it failed to show any significant superiority in a comparative retrospective study with NBI chromoendoscopy; the latter may be preferable because it is a simple, less time-consuming procedure [38].

Recent studies have reported limited diagnostic performance for endoscopic duodenal biopsy sampling [1,32,33,39,40]. A multicenter case series of 364 patients with histologically proven adenoma found significantly higher diagnostic performance for preoperative endoscopic assessment (with high resolution endoscopy) compared to biopsies, for sensitivity (77% vs. 58%, $P<0.01$) and accuracy (75% vs. 68%, $P=0.03$) [1]. In a retrospective analysis of 95 resected duodenal adenomas, the sensitivity of biopsies was only 37.5% (95%CI 18.8–59.4) for prediction of final histologic diagnosis of carcinoma [40]. Furthermore, preoperative biopsies can induce submucosal fibrosis that makes endoscopic resection more difficult and increases the risk of adverse events. Thus, Kinoshita et al. [40] noted a conversion from endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) because of the non-lifting sign in 24.6% of cases, to which prior biopsies may have contributed.

4 Endoscopic treatment of small (<6 mm) duodenal adenomas

RECOMMENDATION

ESGE suggests cold snare polypectomy for small (<6 mm in size) nonmalignant duodenal adenomas.

Weak recommendation, low quality evidence.

Traditionally, duodenal adenomas were removed by hot snare polypectomy**.** However, hot snare polypectomy has associated risks of delayed bleeding, post-polypectomy syndrome, and perforation that are higher compared with those of the stomach and colon, because of the thin and vascular walls of the duodenum [41,42].

Cold snare polypectomy is the preferred technique for removal of small duodenal adenomas <6 mm in size. The evidence for this was initially extrapolation from studies on small colonic polyps [41,43]. Recently, increasing evidence is supporting the use of cold snare polypectomy for small polyps in the duodenum, even in polyposis syndromes such as FAP [44–46]. In a prospective study of 30 patients, 39 lesions (mean [SD] size 3.9 [1.2] mm, range 2–6 mm) were removed via cold forceps polypectomy (9 lesions in 8 patients) or cold snare polypectomy (30 lesions in 22 patients) [47]. The en bloc resection rate was 77.8% for cold forceps polypectomy and 96.7% for cold snare polypectomy. No delayed bleeding or perforation occurred, and the recurrence rate was 0% at 3 months [47].

5 Endoscopic treatment of large duodenal adenomas

5.1 Duodenal EMR in management of large adenomas

RECOMMENDATION

ESGE recommends EMR as the first-line endoscopic resection technique for nonmalignant large nonampullary duodenal adenomas.

Strong recommendation, moderate quality evidence.

The largest prospective study on EMR of duodenal adenomas included 110 patients with 118 lesions (mean size 15 mm, range 4–70) and showed a complete resection rate of 94.1% of lesions [48]. Adverse events were noted in 22.9% (mainly delayed bleeding in 18.6% of lesions) and major adverse events occurred in 15.3% of all lesions with a procedure-related mortality of 1.7% (n=2 patients) [48]. Nearly all other studies of duodenal EMR are retrospective and, when compared to EMR for similar-sized lesions elsewhere in the gastrointestinal tract, show higher rates of complications such as intraprocedural bleeding, post-procedural bleeding, and perforation [19,42,49–51]. In a systematic review and meta-analysis that included 440 patients with 485 duodenal nonampullary adenomas from 14 retrospective studies published up to May 2015, the mean polyp size ranged from 13 to 35 mm and complete endoscopic resection by polypectomy or EMR was achieved in 93% of lesions [52]. The overall bleeding rate including intra- and post-procedural bleeding was 16% and the pooled delayed bleeding rate was 5%. The rate of perforation was 1% and the rate of surgical intervention because of noncurative EMR or adverse events was 2%. There was no procedure-related mortality [52].

In more recent retrospective studies, high rates of complete endoscopic resection (90.5%–96.1%) have been obtained with EMR, whereas the adverse event rates ranged from 2% to 24.4% [17,19,53–61]. Increasing lesion size was associated with reduced rates of en bloc resection as well as increased rate of adverse events [50,53,55–57,62]. However, the majority of duodenal EMR adverse events can be safely managed endoscopically [54, 55,60].

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▶ **Table 1** Outcomes of endoscopic mucosal resection (EMR) for superficial nonampullary duodenal lesions in recent literature.

First author, year	Participants, n (Lesions, n), Study design	En bloc resection, n/N (%)	Complete resection[1], n/N (%)	Overall morbidity, n/N (%)	Residual adenoma[2], n/N (%)	Recurrence, n/N (%)
Probst, 2020 [48]	110 (118), Prospective	46/118 (39.0 %)	111/118 (94.1 %)	27/118 (22.9 %)	19/93 (20.4 %)	NA
Kuroki, 2020 [17]	163 (171), Retrospective[3]	152/157 (93 %)	141/157 (90 %)	9/157 (5.7 %)	NA	2/157 (1 %)
Na, 2020 [61]	92 (95), Retrospective[4]	49/59 (83.1 %)	48/59 (81.4 %)	7/59 (11.9 %)	NA	0/59 (0)
Zou, 2019 [58]	54 (54), Retrospective[5]	8/21 (38.1 %)	NA	2/21 (9.6 %)	NA	4/21 (19 %)
Tomizawa, 2018 [55]	142 (166), Retrospective	88/166 (53 %)	130/142 (92 %)	18/166 (11 %)	NA	32/142 (23 %)
Valerii, 2018 [54]	68 (75), Retrospective	42/75 (56 %)	75/75 (100 %)	16/75 (21.3 %)	9/68 (14.5 %)	6/68 (10.9 %)
Klein, 2017 [63]	102 (102), Retrospective	NA	95/102 (93.1 %)	19/102 (18.6 %)	14/79 (17.7 %)	6/55 (10 %)
Valli, 2017 [56]	78 (78), Retrospective	28/78 (35.9 %)	71/78 (91 %)	9/78 (11.6 %)	7/78 (9 %)	0/78 (0)
Jamil, 2017 [53]	42 (49), Retrospective	10/49 (20.4 %)	38/42 (90.5 %)	10/59 (16.9 %)	4/42 (9.5 %)	0/32 (0)
Navaneethan, 2016 [52]	440 (485), Systematic review	– 45 %	– 93 % (95 %CI 89–97 %)	– Delayed bleeding: 5 % (95 %CI 2 %–7 %) Perforation: 1 % (95 %CI 1 %–3 %)	NA	– 15 % (95 %CI7 %–23 %)

NA, Not available; 95 %CI, 95 % confidence interval.
[1] Complete resection was defined as a complete removal of the lesion after the first endoscopic treatment session.
[2] Residual adenoma was defined when tumoral tissue was confirmed by histology at the first endoscopic follow-up.
[3] 157 lesions only treated by EMR.
[4] 59 lesions only treated by EMR.
[5] 21 patients only treated by EMR.

▶ **Table 1** summarizes the outcomes from recent EMR studies and the findings of the abovementioned systematic review [52].

5.2 Emerging and alternative EMR techniques

Underwater EMR (U-EMR) may improve duodenal EMR outcomes [59, 64, 65]. The filling of the lumen with water in U-EMR would theoretically limit the risk of ensnaring the muscularis propria layer. In a recent retrospective Japanese study, 104 patients underwent U-EMR for duodenal nonampullary adenomas of size ≤ 20 mm [59]. The complete resection rate without conversion to ESD was higher with U-EMR (87 %) compared with conventional EMR (70 %) (P < 0.01). There was no difference in adverse event rates between the two techniques [59].

Recently, the efficacy and safety of piecemeal cold snare EMR for large duodenal adenomas were evaluated in small retrospective series [66, 67]. In a study of 15 patients with lesions ranging from 10 to 60 mm in size, the technical success rate was 100 % with no cases of perforation and with only one case of delayed bleeding in a patient who was on warfarin [67].

5.3 Duodenal ESD in management of large adenomas

RECOMMENDATION
ESGE recommends that ESD for duodenal adenomas is an effective resection technique only in expert hands.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends that duodenal ESD should be reserved for select indications at expert ESD centers.
Strong recommendation, low quality evidence.

ESD for adenomas in the duodenum is more challenging than in other locations such as the esophagus stomach, or rectum. In expert Asian centers, larger lesions (> 20 mm) are often considered for ESD at the outset [68], whereas in Western

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centers this technique is usually reserved for cases of suspected superficial submucosal invasion, or for nonmalignant lesions that are nonlifting due to de novo submucosal fibrosis or secondary to previous biopsy or incomplete resection. However, duodenal ESD is associated with a high incidence of adverse events, even in experienced centers [69–72]. Perforation incidences of 13 %–50 % have been reported [39, 73–79].

Since a previous ESGE Guideline that recommended against routine use of ESD in the duodenum because of its high risk of perforation [80], further series have been published, mainly from expert Asian centers. En bloc resection rates of higher than 90 % have been reported, even in lesions larger than 20 mm [74, 75]. Nevertheless, more limited duodenal ESD data from Europe are available [20, 81, 82], and the largest series reported a disappointing en bloc resection rate of 29.7 %, with a 14.7 % recurrence rate [20]. Furthermore, comparative data analysis between EMR and ESD showed better R0 rates for large lesions with ESD but no differences in long-term outcomes and survival [20, 61, 74, 76, 82]. However, intraprocedural perforation (up to 30 %) and delayed perforation was significantly associated with ESD [20, 61, 75, 77, 83]. Therefore, in most cases, the focus of duodenal endoscopic resection should primarily be on safety, rather than on achieving en bloc or R0 resection. The superior safety profile of EMR compared to ESD lends greater weight to EMR's being the first-line technique for duodenal adenomas in most cases, despite the higher recurrence rate with EMR, that may require further endoscopic therapy.

▶ **Table 2** shows comparative results for EMR and ESD of superficial nonampullary duodenal adenomas.

▶ **Table 2** Retrospective comparative results of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for treatment of superficial nonampullary duodenal adenomas. (Statistically significant values are in bold.)

First author, year		EMR, n/N (%)	ESD, n/N (%)	*P* value
Na, 2020 [61]	Complete resection	48/59 (81.4 %)	8/11 (80 %)	>0.99
	Morbidity	7/59 (11.9 %)	5/11 (45.5 %)	**0.03**
	Recurrence	0	0	1
Esaki, 2020 [83]	Complete resection	20/28 (71.4 %)	25/28 (83.3 %)	0.18
	Morbidity	1/28 (3.6 %)	5/28 (17.9 %)	0.19
	Recurrence	1/28 (3.6 %)	0/28 (0)	1
Yahagi, 2018 [75]	Complete resection	123/146 (82.2 %)	148/174 (85.1 %)	0.65
	Morbidity			
	▪ Delayed bleeding	2/146 (1.4 %)	9/174 (5.2 %)	0.072
	▪ Perforation	1/146 (0.68 %)	27/174 (15.5 %)	**<0.001**
	Recurrence	NA	NA	–
Pérez-Cuadrado-Robles, 2018 [20]	Complete resection	43/129 (35.5 %)	7/37 (19.4 %)	0.069
	Morbidity			
	▪ Delayed bleeding	12/129 (9.3 %)	3/37 (8.1 %)	0.823
	▪ Perforation	3/129 (2.3 %)	6/37 (16.2 %)	**0.001**
	Recurrence	17/129 (16.7 %)	5/37 (14.7 %)	0.788
Hoteya, 2017 [77]	Complete resection	33/55 (60 %)	65/74 (87.8 %)	NA
	Morbidity	5/55 (9 %)	22/74 (29.7 %)	NA
	Recurrence	2/55 (3.6 %)	0/74 (0)	NA

NA, not available.

5.4 Alternative modalities to EMR or ESD for duodenal adenomas

RECOMMENDATION

ESGE suggests that, in expert hands, endoscopic full-thickness resection could be an alternative to surgery or ESD for select cases of nonlifting duodenal adenomas up to 25 mm in size without signs of deep submucosal invasion.

Weak recommendation, very low quality evidence.

Endoscopic full-thickness resection applying an over-the-scope (OTS) clip-based technique (i. e., with a full-thickness resection device [FTRD]) has been used for the resection of difficult and nonlifting duodenal lesions [84–87]. Currently, limited data from retrospective studies and small case series have shown technical success rates of 85 %–100 %, high rates of complete resection of the target lesion (75 %–80 %), and very low rates of major complications. However, these studies included heterogeneous duodenal lesions, and the FTRD has some technical limitations in the upper gastrointestinal tract (the large diameter of the bulky device makes passage through the upper esophageal sphincter and the pylorus challenging). The device size limits en bloc resection to lesions ≤ 25 mm in size [85]. Furthermore, a minimum distance of 20 mm is required between the lesion and the major papilla, to avoid the risk of clipping and closing the bile duct or pancreatic duct, with potentially severe consequences [85].

Recent small case series have demonstrated a good safety and efficacy profile for combined laparoscopic and endoscopic surgery in patients with advanced duodenal adenomas or early adenocarcinomas [88–92]. Ichikawa et al. [92] reported no local or distant recurrence at a median follow-up of 14 months

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in 10 patients with mucosal adenocarcinoma treated with combination laparoscopic and endoscopic surgery. In a retrospective observational study by Ojima et al. [91], this technique showed no adverse events (0 %) compared to ESD (28 %). However, larger prospective studies are needed to confirm these results.

5.5 Role of tumor-destruction techniques

RECOMMENDATION

ESGE suggests that an additive role for ablative or other tumor-destruction techniques is minimal because of lack of efficacy.

Weak recommendation, low quality evidence.

Historically, several complementary tissue destruction techniques had been used for nonampullary duodenal lesions. These included monopolar/bipolar coagulation, lasers such as the Nd-YAG [93–95], photodynamic therapy [96], and cryotherapy [97, 98]. However, most of these have been abandoned because of lack of efficacy or unacceptable adverse events [95, 96].

Argon plasma coagulation (APC) is still used [60, 99–101], although it is not effective as a primary therapy, showing adenoma recurrence rates of 39 %–75 % [7, 102–104]. APC has been used as an adjunctive technique to eliminate residual adenoma when technical difficulties resulted in incomplete endoscopic resection [99, 100, 104–111]. However, in one such study, the reported recurrence rate was high at 25.7 % [105]. In another study by Apel et al. [99], the use of APC for residual duodenal adenoma did not lead to eradication in most of the lesions. However, a study by Alexander et al. [100] showed complete eradication of residual adenoma using APC in all 5 patients reported in the study. Given these findings, a careful endoscopic surveillance is required.

5.6 Prevention of delayed adverse events after duodenal endoscopic resection

RECOMMENDATION

ESGE recommends using techniques that minimize adverse events such as immediate or delayed bleeding or perforation. These may include piecemeal resection, defect closure techniques, noncontact hemostasis, and other emerging techniques, and these should be considered on a case-by-case basis.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that the high adverse event rate with duodenal resection may be reduced by mucosal defect closure techniques such as endoscopic clipping or OTS clipping, and by noncontact hemostatic measures.

Strong recommendation, low quality evidence.

The evidence for routine prophylactic clip closure following duodenal EMR is limited. Prophylactic through-the-scope clipping was associated with a significant reduction in delayed bleeding (0 % vs. 22 %, $P = 0.044$) when compared to no prophylaxis, in a retrospective study involving 43 duodenal EMR sessions [50]. In a prospective study using U-EMR for 31 duodenal adenomas of size ≤ 20 mm, clip closure of the defect was performed for all lesions with no procedure-related adverse events being reported [64]. However, the risk of perforation due to clip application and large resection sites that cannot be fully closed are limiting factors, and therefore clips should be applied carefully and their use considered on a case-by-case basis.

Noncontact hemostatic products have been successfully used to minimize bleeding following duodenal EMR; however the evidence is still limited [112, 113].

In the multivariate analysis of a recent case series of duodenal ESDs, lesion location in the duodenal flexure, lesion size > 40 mm, and occupied duodenal circumference of > 50 % were associated with increased adverse events [114]. In a recent large retrospective Japanese study involving 168 patients, the rate of delayed adverse events after duodenal ESD was significantly reduced when the mucosal defect was completely closed, compared with only partial closure or no closure (1.7 % vs. 25 % vs. 15.6 %, respectively, $P < 0.01$) [115]. These data were confirmed by two more studies where delayed bleeding was effectively prevented by prophylactic endoscopic closure of the defect [18, 116]. Recently, closure of the defect by OTS clipping has also been shown to be effective in reducing delayed adverse events after ESD [117]. Furthermore, the additional use of conventional through-the-scope clips, to cover the inverted submucosa after defect closure with OTS clipping, was found to significantly reduce the risk of delayed bleeding [118].

6 Follow-up, risk and management of recurrence after endoscopic duodenal resection

RECOMMENDATION

ESGE recommends that recurrences after endoscopic treatment for superficial nonampullary duodenal lesions can be managed endoscopically, if this is deemed technically feasible and in the absence of suspected malignancy.

Strong recommendation, low quality evidence.

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RECOMMENDATION
ESGE suggests that the choice of endoscopic technique to manage recurrent adenoma should be left to the discretion of the endoscopist, according to the morphology of the lesion and patient characteristics.
Weak recommendation, very low quality evidence.

RECOMMENDATION
ESGE recommends endoscopic surveillance 3 months after the index treatment. In cases of no recurrence, a further follow-up endoscopy should be done 1 year later. Thereafter, surveillance intervals should be adapted to the lesion site, en bloc resection status, and initial histological result.
Strong recommendation, low quality evidence.

Over a median follow-up period ranging from 6 to 72 months, the local recurrence rate after EMR was 15 % (95 %CI 7 %–23 %) in the largest review of the literature [52]. Advanced histopathology, defined as the presence of villous changes (OR 4.86, 95 %CI 1.62–14.63) or high grade dysplasia, was shown to increase the risk of local recurrence [52, 56, 62]. Similarly, increasing lesion size was associated with a higher recurrence rate [19, 52, 55, 63, 106]. With regard to the techniques originally used to remove the lesion, no significant difference in recurrence rate was observed between EMR versus ESD or EMR versus hybrid ESD [18, 81]. After a median follow-up of 6.5 months (2–125), Pérez-Cuadrado-Robles et al. [20] showed 5/37 recurrences (14.7 %) after ESD and 17/129 (16.7 %) after EMR (P = 0.788). Furthermore, there were no demonstrable differences in recurrence rates between en bloc or piecemeal EMR in the largest review of duodenal EMR studies [52].

The available studies have shown that recurrent lesions are usually small in size and can be successfully treated endoscopically in most cases by an expert endoscopist [19, 119]. In the review from Navaneethan et al., six studies reported the outcomes of managing recurrent adenoma, and further endoscopic therapy was successful in 62 % (95 %CI 37 %–87 %) [52]. In the absence of relevant comparative data, no specific endoscopic technique could be preferentially recommended to manage adenoma recurrence.

Regarding the surveillance interval after index endoscopy, expert opinions are in favor of a first endoscopy at 3–6 months. The evidence for this approach is limited, but it has been recently supported by a prospective study showing that at 3 months, residual or recurrent adenoma was noted in 20.4 % of patients who then had endoscopic re-treatment [48]. Valerii et al. [54] retrospectively reported 15 recurrences in 62 lesions, with 9 of them (60 %) being found at the first follow-up endoscopy performed 3 months after the initial endoscopic treatment. A second surveillance endoscopy 1 year later seems to be advisable, if no residual or recurrent adenoma has been detected during the first surveillance endoscopy [41, 48, 52, 120]. Subsequent surveillance intervals should then be individualized, taking into account lesion factors (size, high grade dysplasia, or villous component) and patient factors (age, comorbidities) [52]. Late recurrences are uncommon, but possible.

7 Role of surgery for nonmalignant sporadic duodenal adenomas

The literature on duodenal surgery for SNADT is limited and mainly consists of studies on patients with FAP, as detailed in the ESGE Guideline for FAP [2]. For sporadic nonmalignant duodenal lesions, less invasive options such as transduodenal excision and segmental duodenal resection are preferred compared with pancreaticoduodenectomy or pancreas-sparing duodenectomy, as the less invasive approaches demonstrate lower morbidity rates [121–124]. A retrospective study of 86 patients showed morbidity rates of 17 % after transduodenal excision compared with 40 % and 45 % after pancreaticoduodenectomy and pancreas sparing duodenectomy, respectively [121]. In three other retrospective studies, the morbidity rate for pancreaticoduodenectomy was significantly higher compared to the less invasive transduodenal excision or segmental duodenal resection [7, 122, 125]. However, a 5-year recurrence rate of 32 % after transduodenal excision for villous adenomas is reported [121]. Therefore, postoperative endoscopic surveillance is mandatory after surgery, and endoscopic resection of recurrences following surgery is still possible [125].

In a cohort of 121 patients with nonampullary duodenal lesions, 91 were treated by EMR, as opposed to surgical therapy with pancreas-sparing duodenectomy [125]. The recurrence rate during follow-up was significantly higher in the EMR than in the surgical group (32 % vs. 0 %, P < 0.001). However, there was a trend towards higher adverse event rates in the surgical group than in the EMR group (26 % vs. 15 %), although it should be noted that larger and more advanced lesions had been treated in the surgical group [125]. Other studies have also shown lower mortality and morbidity, shorter procedural time and shorter hospital stay in endoscopically treated patients [7, 118, 122, 124]. Therefore, while adenoma recurrence is low following pancreas-sparing duodenectomies, the high morbidity and mortality associated with these procedures make them options of last resort for most cases of sporadic duodenal adenoma [7, 125].

Finally, in cases of confirmed duodenal malignancy, an oncological resection including lymph node dissection, such as achieved by pancreaticoduodenectomy is required, whereas pancreas-sparing duodenectomy and transduodenal excision are not oncological resections and are reserved for premalignant lesions only.

Disclaimer

The legal disclaimer for ESGE guidelines [126] applies to this Guideline.

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