

Impact of a dedicated multidisciplinary meeting on the management of superficial cancers of the digestive tract



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Bibliography

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ABSTRACT

Background The recent development of endoscopic resection for superficial gastrointestinal cancers could justify the need for a dedicated oncological multidisciplinary meeting (MDM). The aim of our study was to evaluate the impact of the dedicated MDM on the management of superficial cancers of the digestive tract.

Methods A dedicated MDM was developed at our tertiary referral center. A retrospective review of the MDM conclusions for all patients referred from March 2015 to March 2017 was performed. Outcomes measurements were the outcomes of endoscopic resection, and the concordance rate between the MDM recommendations, European Society of Gastrointestinal Endoscopy (ESGE) guidelines, and final patient management.

Results In total, 153 patients with a median age of 69 years were included. Half of the patients had major comorbidities. The mean lesion size was 25 mm, and R0 and curative resection rate were 73.9% and 56.9%, respectively. Forty-three patients had an indication for surgery after endoscopic resection. The concordance rate between ESGE guidelines and MDM recommendation was 92.2%, and 12 patients did not receive the treatment recommended due to comorbidities.

Conclusion A MDM dedicated to superficial tumors helped tailor the ESGE guidelines to each patient in order to avoid unnecessary surgery.

Introduction

In 2015 in France, there were 385 000 new cases of cancer and 150 000 deaths from cancer [1]. Digestive cancers have the highest incidence and mortality of all types of cancer. “Early” or “superficial” cancer comprises any neoplastic lesion involving the epithelium (high grade dysplasia or carcinoma in situ, T1a m1), the lamina propria (T1a m2), the muscularis mucosae (T1a m3), or the submucosa (T1b sm 1,2,3) regardless of the

presence of lymph node metastasis [2, 3]. Among endoscopic treatments, endoscopic submucosal dissection (ESD) has been steadily developing over the last decade [4]. This treatment allows the two main limitations of endoscopic ablative therapies or endoscopic mucosal resection to be overcome by (i) minimizing the risk of local recurrence by providing en bloc resection of lesions regardless of their size, with healthy tissue margins; and (ii) allowing the risk of lymph node metastases to be

assessed thanks to an optimal histological analysis of a large, orientated, single resection specimen.

The European Society of Gastrointestinal Endoscopy (ESGE) recently published guidelines on the endoscopic resection of gastrointestinal superficial lesions, focusing on ESD [5]. Defining the optimal patient management after ESD requires taking into account the risk of lymph node metastases, the quality of the resection, and the risk of further treatments such as surgery or radiotherapy. Therefore, as for any other type of cancer, it requires a multidisciplinary meeting (MDM). Given the increasing complexity of endoscopic therapies and the specificity of the prognostic factors of superficial cancers of the digestive tract, we have started a dedicated MDM at our institution in 2015. The present work aims to assess the contribution of this specific MDM to patient management.

Materials and methods

Patients

We performed a retrospective study, in the department of gastroenterology and digestive oncology of a French tertiary referral center. All consecutive lesions resected by endoscopy and referred to the superficial cancer of the digestive tract MDM from March 2015 to March 2017 were included. Lesions discussed were all T1 lesions (including high grade dysplasia or early cancer) of the upper digestive tract, including the ampulla of Vater, and early adenocarcinomas of the colon and rectum.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the ethical review committee for publications of Cochin University Hospital (CLEP Decision N°: AAA-2018-08001) on 23 January 2018. All patients provided written informed consent to endoscopic procedures and additional treatments when indicated.

Endoscopic treatment

Data were collected from the patients' medical files, endoscopy and pathology reports. For each lesion, the location, size, Paris classification, endoscopic resection technique (polypectomy, endoscopic mucosal resection (EMR), ESD, full thickness resection, hybrid resection technique, and endoscopic papillectomy), and the type of resection (en bloc or piece meal) were recorded.

Histological analysis

Resected specimens were pinned on polystyrene boards and fixed in 10% formalin for 24h. After fixation, specimens were cut into 2–3 mm slices and embedded in paraffin. Blocks were further sliced at 4 µm and stained with hematoxylin–eosin–safran. Histological slides were assessed by pathologists experienced in digestive pathology (FB and BT). The following data were assessed: en bloc resection, invasion of the lateral margins, grade of dysplasia; in the case of invasive carcinomas, the following data were recorded: grade of differentiation, presence of lymphatic or vascular invasion, deepest tumor extent, and tumoral infiltration of the vertical (deep) margin. In the case of submucosal invasion, the depth of the tumor front beyond the muscularis mucosae was measured, as well as the

width of this extension. For invasive carcinoma, the margins could be either tumor-free (R0) or infiltrated with tumor (R1). Submucosal invasion was assessed according to the Japanese classification of esophageal cancer [6]. R0 resection was defined as an en bloc resection, with horizontal and vertical margins free of cancer or high grade dysplasia. Curative endoscopic resection was defined as an R0 resection without deep mural infiltration or poor histoprostic factors, as defined for each tumor location by the ESGE guidelines: absence of poorly differentiated cancer, absence of lymphovascular involvement, absence of grade 2 or 3 budding for colorectal cancer (presence of de-differentiated single cells or small clusters of up to 5 cells at the invasive front of colorectal cancer) [7], and negative vertical margin. Deep mural infiltration was defined as > 1000 µm, > 500 µm, > 500 µm, and > 200 µm for colorectal cancers, gastric and Barrett's esophagus cancers, and squamous cell carcinoma (SCC) in the esophagus, respectively [5]. Infiltration of the muscularis mucosae for early esophageal SCC was considered to be a poor prognostic factor depending on the patient's general status and ability to tolerate a complementary treatment. There were no specific recommendations pertaining to the presence of signet-ring cells [5]. The presence of submucosal invasion in the ampulla of Vater was considered to be an indication for surgical treatment [8]. ESGE guidelines are summarized in ► **Table 1** [5].

Complementary treatments were: surgical resection, chemoradiotherapy (as an alternative to surgery for esophageal or rectal cancer), chemotherapy, additional endoscopic resection, or radiofrequency ablation (for the residual Barrett's esophagus after endoscopic resection of a visible neoplastic lesion).

Multidisciplinary meeting

The meeting was held on a monthly basis and the multidisciplinary group consisted of gastrointestinal endoscopists, oncologists, digestive surgeons, pathologists, radiotherapists, and radiologists. Cases were presented after endoscopic resection to discuss further management and define the surveillance modalities or the need for complementary treatment. Criteria used to indicate a complementary treatment are summarized in ► **Table 1**. Endoscopic images and videos were displayed and analyzed for all patients, as well as photographs of histological slides for selected patients. A second histological examination was performed by an expert pathologist for patients referred from other centers. Oncological outcomes after MDM decision were reported for patient management not in accordance with ESGE guidelines.

Statistical analysis

Data are presented as median with data range, and percentage.

Results

Patient characteristics

In total, 153 patients were included in this study. The primary tumor was located in the esophagus (n = 52; 34.0%), the stomach (n = 22; 14.4%), the ampulla of Vater (n = 6; 3.9%), or in the colon and rectum (n = 73; 47.7%). The median [range] age of

► **Table 1** Criteria for additional treatment (non-curative endoscopic resection) according to the European Society of Gastrointestinal Endoscopy Guidelines.

	Esophageal neoplasia		Gastric neoplasia ¹	Neoplasia of the ampulla of Vater	Colorectal neoplasia
	Squamous cell neoplasia	Barrett's neoplasia			
Qualitative criteria					
▪ Poor differentiation	+	+	+ ²	+	+
▪ Lymphovascular involvement	+	+	+	+	+
▪ Budding (grade 2 or 3)	+	+	+	+	+
Quantitative criteria					
▪ Positive vertical margin	+	+	+	+	+
▪ Deep submucosal invasion, μm	>200 ³	>500	>500	+	>1000

For all lesions, endoscopic follow-up and re-treatment are recommended if the horizontal margin is positive or there is piecemeal resection with no other high risk criteria.

¹ Surgery is also recommended in gastric neoplasia in the case where ulcerated lesions larger than 30 mm are diagnosed.

² Endoscopic resection can be curative for poorly differentiated lesions smaller than 2 cm without ulcerated features.

³ Infiltration of the muscularis mucosae (M3) should raise discussion on the benefit of an additional treatment depending on the patient's clinical status.

► **Table 2** Patient characteristics.

	Patients (n = 153)
Age, median [range], years	68.6 [33.6–92.1]
Sex ratio male/female, n (%)	95/58 (62.1%/37.9%)
Comorbidity, n (%)	74 (48.4%)
▪ Advanced age (>80 years)	25 (33.8%)
▪ Cardiovascular disease	17 (23.0%)
▪ Previously treated cancer	17 (23.0%)
▪ Liver cirrhosis or portal hypertension	10 (13.5%)
▪ Respiratory insufficiency	4 (5.4%)
▪ Renal insufficiency	1 (1.4%)
Time between endoscopic resection and multidisciplinary decision, median [range], days	33 [8–187]

the patients was 68.6 [33.6–92.1] years. There were 95 men and 58 women. One half of the patients (48.4%) had comorbidities that may increase the mortality and morbidity of a surgical approach. The median time between the diagnostic and multidisciplinary decision was 33 days. The main patient characteristics are presented in ► **Table 2**. Of the 153 patients included, 138 were treated in our tertiary referral center and 15 patients were referred from other centers.

Endoscopic and histological characteristics of the lesions

The median [range] size of the lesions at endoscopy was 25 mm [4–150 mm]. There were 4 tumors with signet-ring cells, in the stomach or at the esophagogastric junction. Besides 7 failures or macroscopically incomplete resections (1 esophageal squamous cell carcinoma, 1 gastric adenocarcinoma, and 5 colorectal adenocarcinomas), the adverse events were 6 perforations (treated conservatively), and 1 severe bleeding episode requiring transfusion. Failure was defined as an incomplete resection with macroscopically visible residual tumor or a technical problem (no submucosal lifting for EMR, no dissection in ESD).

The R0 resection rate was 81.0% (124/153) for cancer, and 73.9% (113/153) for cancer and high grade dysplasia. The overall curative resection rate was 56.9% (87/153). Breaking down the cases according to histology and tumor location, the rates of curative resection were 45.0% (9/20), 68.8% (22/32), 72.7% (16/22), 50.0% (3/6), and 50.7% (37/73) for esophageal squamous cell carcinoma, Barrett's carcinoma, gastric adenocarcinoma, neoplasia of the ampulla of Vater, and colorectal adenocarcinoma, respectively. Intramucosal (T1a) cancer was diagnosed in 54.2% (83/153) of patients. A superficial and deep submucosal involvement was present in 18 (11.8%) and 47 (30.7%) patients, respectively. The vertical margins were not analyzable (Rx) for 5 patients. Budding was present in 10 (6.5%) patients and lympho-vascular involvement in 23 (15%) patients. Endoscopic and histological characteristics based on tumor localization are reported in ► **Table 3** and ► **Table 4**, respectively.

► **Table 3** Endoscopic characteristics of the lesions and resection techniques.

	Esophageal neoplasia (n = 52)		Gastric neoplasia (n = 22)	Neoplasia of the ampulla of Vater (n = 6)	Colorectal neoplasia (n = 73)
	Squamous cell neoplasia (n = 20)	Barrett's neoplasia (n = 32)			
Size, median [range], mm	35 [5–100]	15 [5–50]	25 [4–70]	12.5 [10–25]	35 [10–150]
Paris classification, n (%)					
▪ Ip	–	2 (6.3)	–	–	15 (20.6)
▪ Is	2 (10)	2 (6.3)	3 (13.6)	2 (33.3)	39 (53.4)
▪ Ila	8 (40)	14 (43.7)	6 (27.4)	2 (33.3)	11 (15)
▪ Iib	3 (15)	4 (12.5)	–	–	–
▪ Iic	–	3 (9.4)	2 (9)	–	1 (1.4)
▪ III	–	–	–	–	–
▪ Ila + Iib	2 (10)	1 (3.1)	1 (4.5)	–	1 (1.4)
▪ Ila + Iic	4 (20)	5 (15.6)	10 (45.5)	2 (33.3)	6 (8.2)
▪ Iib + Iic	1 (5)	1 (3.1)	–	–	–
Endoscopic resection technique, n (%)					
▪ Polypectomy	–	–	–	–	7 (9.6)
▪ EMR	2 (10)	5 (15.6)	3 (13.6)	–	34 (46.6)
▪ Hybrid dissection	–	–	–	–	5 (6.9)
▪ ESD	18 (90)	27 (84.4)	19 (86.4)	–	25 (34.2)
▪ FTRD	–	–	–	–	2 (2.7)
▪ Endoscopic papillectomy	–	–	–	6 (100)	–
Type of resection, n (%)					
▪ En bloc resection	19 (95)	28 (87.5)	18 (81.8)	4 (66.7)	51 (69.9)
▪ Piecemeal ¹	–	4 (12.5)	3 (13.6)	2 (33.3)	17 (23.3)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FTRD, full thickness resection device.
¹ Macroscopically incomplete resection: 1 esophageal squamous cell carcinoma, 1 gastric adenocarcinoma, and 5 colorectal adenocarcinomas.

Decision of the multidisciplinary meeting

Forty-three patients (28.1%) had an indication for a surgical treatment after endoscopic resection. The recommendations of the MDM are summarized in ► **Fig. 1**. After endoscopic resection of a squamous cell superficial neoplasia, endoscopic surveillance was considered for 6 patients. Additional endoscopic treatment was recommended for 4 patients due to positive or non-evaluable horizontal margins. For patients with poor histoprognostic factors (either qualitative or quantitative), positive or uncertain vertical resection margins, complementary treatment by surgical resection was proposed for 2 patients, and chemoradiotherapy for 8 patients in the case of comorbid conditions and contraindications to surgery. Following endoscopic resection of a Barrett's superficial carcinoma, endoscopic treatment by radiofrequency ablation of endoscopic mucosal resection was considered for 13 patients, in order to treat the resi-

dual Barrett's esophagus. Esophagectomy was advised for 3 patients.

For gastric lesions, endoscopic surveillance was considered for 13 patients (► **Fig. 2c, d**). Re-treatment by endoscopic resection was advised for 3 patients, for positive or non-evaluable horizontal margins. Surgery was recommended for 6 patients.

After endoscopic papillectomy, endoscopic surveillance was considered for 2 patients. Re-treatment by endoscopic radiofrequency ablation was needed for one patient, due to residual adenoma in the main bile duct. Surgery was advised for 3 patients presenting ampullary carcinomas with submucosal invasion. Following colorectal endoscopic resection, endoscopic surveillance was considered for 21 patients (► **Fig. 2a, b**). A complementary endoscopic resection was advised for 23 patients, for positive or non-evaluable horizontal margins, and EMR failure. Surgery was recommended for 29 patients.

► **Table 4** Histological characteristics of the lesions.

	Esophageal neoplasia (n = 52)		Gastric neoplasia (n = 22)	Neoplasia of the ampulla of Vater (n = 6)	Colorectal neoplasia (n = 73)
	Squamous cell neoplasia (n = 20)	Barrett's neo- plasia (n = 32)			
Size of the specimen, median [range], mm	48 [14–86]	15 [5–50]	41.5 [18–100]	19 [15–22]	30 [8–110]
R0 resection, n (%)					
▪ Carcinoma	16 (80)	25 (78.1)	20 (90.9)	3 (50)	60 (82.2)
▪ Carcinoma and HGD	13 (65)	22 (68.6)	19 (86.4)	3 (50)	56 (76.7)
Positive vertical margin, n (%)	3 (15)	5 (15.6)	1 (4.5)	3 (50)	7 (9.6)
Positive horizontal margin, n (%)	2 (10)	3 (9.4)	1 (4.5)	2 (33.3)	1 (1.4)
Qualitative criteria, n (%)					
▪ Poor differentiation	2 (10)	4 (12.5)	3 (13.6)	–	–
▪ Lymphovascular involvement	4 (20)	4 (12.5)	5 (22.7)	1 (16.7)	9 (12.3)
▪ Budding	–	–	1 (4.5)	1 (16.7)	8 (11)
Quantitative criteria, n (%)					
▪ Mucosal invasion					
– M1	7 (35)	7 (21.9)	3 (13.6)	3 (50)	3 (4.1)
– M2	2 (10)	7 (21.9)	10 (45.5)	–	26 (35.6)
– M3	2 (10)	7 (21.9)	1 (4.5)	–	2 (2.7)
– M4	–	3 (9.4)	–	–	–
▪ Submucosal invasion, n (%)					
– Superficial	–	3 (9.4)	2 (9)	–	13 (17.8)
– Deep ¹	8 (40)	5 (15.6)	5 (22.7)	3 (50)	26 (35.6)

M, mucosal; HGD, high grade dysplasia.

¹ Macroscopically incomplete resection: 1 esophageal squamous cell carcinoma, 1 gastric adenocarcinoma, and 5 colorectal adenocarcinomas.

MDM recommendations

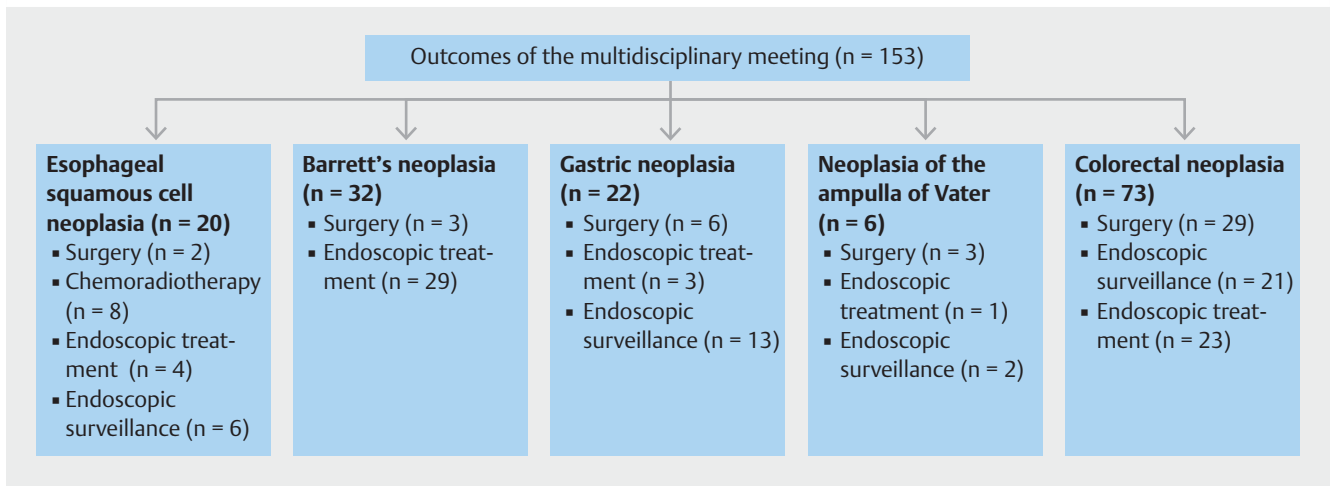
The concordance rate between the MDM recommendation and the ESGE guidelines [5] was 92.2% (141/153). The reason for non-concordance was mostly the presence of comorbidities that contraindicated surgical resection or even chemoradiotherapy. This concordance was 95% (19/20), 81.3% (26/32), 100% (22/22), 100% (6/6), and 93.2% (68/73) for esophageal squamous cell carcinoma, Barrett's carcinoma, gastric adenocarcinoma, neoplasia of the ampulla of Vater, and colorectal adenocarcinoma, respectively.

The concordance rate between the MDM recommendations and the final patient management was 90.8% (139/153). The reasons for non-concordance were: loss to follow-up (n = 7), patient refusal (n = 4), contraindication to surgery (n = 1), and contraindication to radiotherapy (n = 2). The concordance rate between the ESGE guidelines and the final patient management was 83.7% (128/153).

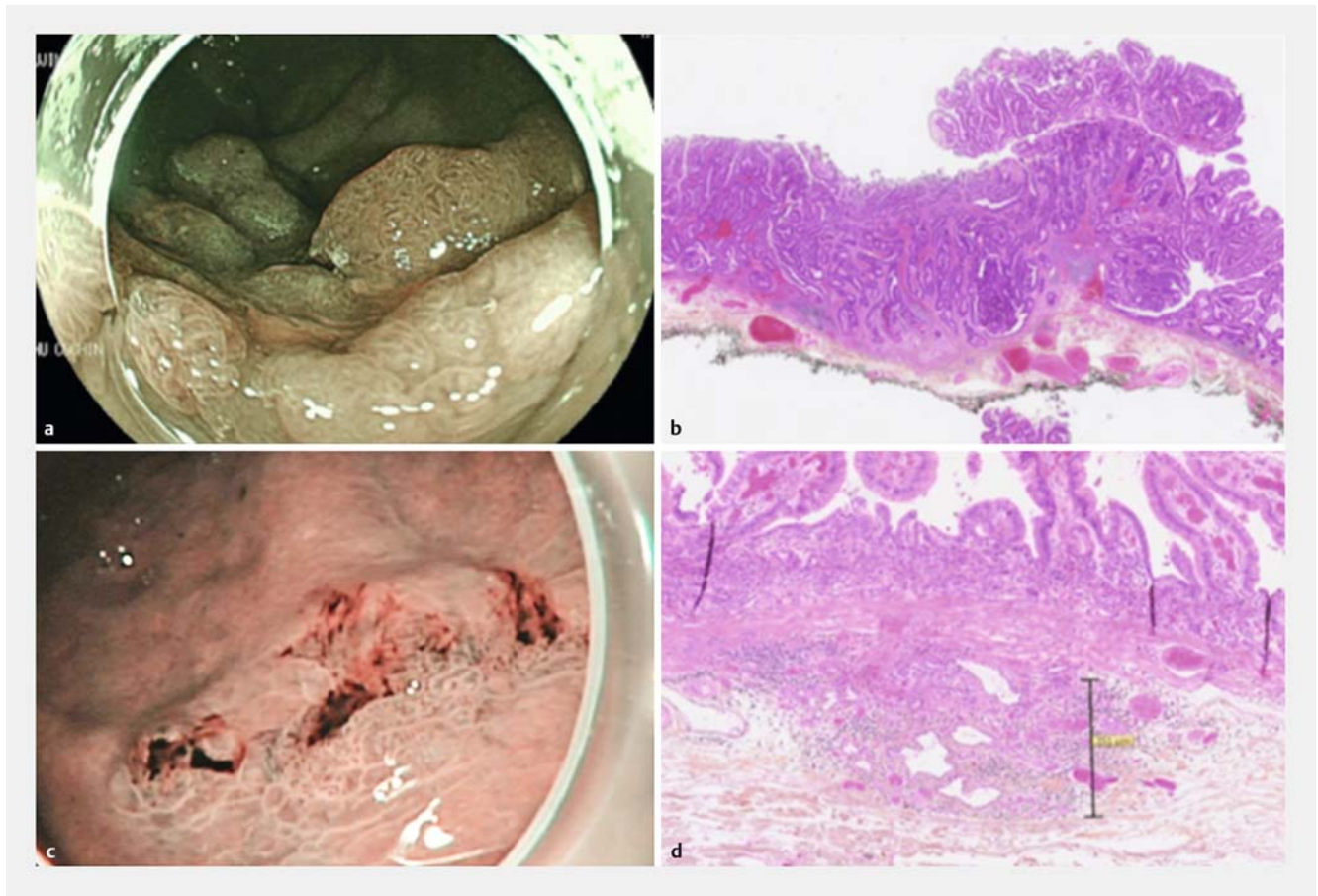
Twelve patients (7.8%) were informed that the MDM conclusions were not in accordance with the ESGE guidelines. All pa-

tients accepted the proposal from the dedicated MDM and received a close follow-up by endoscopy and cross-sectional imaging rather than additional treatment by surgery or chemoradiation. Of them, 58.3% had a complete R0 resection. The mean follow-up after endoscopic resection was 18.5 months (6–30 months). There was no cancer related death, one tumor-unrelated death (congestive heart failure at 21 months, unrelated to endoscopic treatment) and one loco-regional recurrence. This patient had an esophageal squamous cell carcinoma with an indication for surgery (deep submucosal involvement). The loco-regional relapse was diagnosed after 2 months, and the patient was treated with neo-adjuvant chemotherapy (5-fluorouracil/cisplatin) and esophagectomy. Pathology revealed pT3N2 squamous cell carcinoma and subsequent follow-up was unremarkable. Finally, the recurrence rate, the non-cancer related survival, and the disease-specific survival were 8.3%, 91.7%, and 100%, respectively.

Twenty-four patients (15.7%) in this cohort had a surgical resection following non-curative endoscopic resection. Among those, 10/24 (41.7%) had residual neoplasia: local residual can-



► **Fig. 1** Recommendations of the multidisciplinary meeting for superficial cancer of the digestive tract.



► **Fig. 2** Superficial gastric and colorectal cancers. **a** Endoscopic image under virtual chromoendoscopy by blue laser imaging of a rectal adenocarcinoma arising on a granular type lateral spreading tumor. **b** Histological view after resection by endoscopic submucosal dissection showing a T1b well-differentiated adenocarcinoma with superficial submucosal invasion (100 µm), hematoxylin and eosin staining. **c** Endoscopic image under virtual chromoendoscopy using narrow-band imaging of a gastric Paris 0-IIa + c lesion. **d** Histological view on a digitized slide after hematoxylin and eosin staining, showing a well-differentiated T1b adenocarcinoma with superficial submucosal invasion (351 µm). Given the histologically complete resections and the absence of poor histoprognotic factors, both endoscopic resections were considered curative and no additional treatment was needed.

cer in 7 patients (29.2%) (3 gastric lesions, 2 ampullary carcinomas, and 2 colorectal lesions) and lymph node metastases in 4 patients (16.7%) (1 signet ring cell gastric adenocarcinoma and 3 colorectal lesions). All had deep submucosal invasion, and 6 had positive vertical resection margins.

Discussion

We herein stress that the development of an MDM dedicated to superficial tumors of the gastrointestinal tract was feasible in a tertiary center. The recommendations of the MDM were in line with the ESGE guidelines in 92.2% of cases.

The ESGE guidelines advise a multidisciplinary discussion in the management of superficial cancers of the digestive tract after endoscopic resection, according to technical and histological outcomes [5]. This discussion is of paramount importance to assess the risk of lymph node metastasis or local recurrence. This risk will determine whether or not the endoscopic resection was curative. It is usually considered acceptable – and the resection curative – when below 10%. However, the risk of lymph node metastasis should be weighed against the risk of further treatments recommended in the case of non-curative endoscopic resection, mostly surgical resection or chemoradiotherapy. Therefore, the MDM discussion must take into account not only the risk of lymph node metastasis or local recurrence of the tumor, but also the patient's will, his or her comorbid conditions, and general health status. We hypothesized that this discussion would require focusing on endoscopy, pathology, and surgery, while discussions in digestive oncology multidisciplinary meetings mainly involve radiology and chemotherapy.

To our knowledge, this is the first study to report the role of an MDM dedicated to superficial cancers of the digestive tract. Palmer et al. reported the impact of a dedicated MDM for colposcopy to avoid overtreatment in the case of discrepant cytological or histopathological samples [9]. We found that the MDM recommendations were in accordance with the recently published ESGE guidelines [5] in 92.2% of all cases, and were actually followed in 90.8% of all cases. About a third of the patients had further treatment by surgery or chemoradiotherapy following endoscopic resection, and 7.8% (12/153) did not receive the treatment advised by the guidelines due to their comorbid conditions. Among these 12 patients, we diagnosed one loco-regional recurrence during a median follow-up of 18.5 months. This underlines the role of the MDM discussion in high volume endoscopy centers, to adapt the ESGE guidelines to each patient case and avoid overtreatment. To achieve this goal, endoscopists need to collaborate with digestive oncologists, pathologists, and surgeons for optimal patient management.

An unexpected finding of this work is the high rate of deep submucosal invasion, accounting for one-third of all resections, despite the high R0 resection rate. This result underlines the challenge of diagnostic endoscopy, even for experienced endoscopists, and strongly prompts the need for an MDM discussion of cases before endoscopic resection, to avoid unnecessary treatments.

To conclude, a multidisciplinary meeting dedicated to the superficial cancers of the digestive tract should aim at improving patient management before and after endoscopic resection, by indicating endoscopic resection, further treatments or by defining adequate surveillance modalities. Monthly discussions are needed in order to allow timely complementary treatment if needed, and conclusions should be included in the patient's medical record and addressed to the referent gastroenterologist.

Competing interests

None

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