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EDITORIAL

Methods and outcomes of screening for pancreatic adenocarcinoma in high-risk individuals

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a lethal neoplasia, for which secondary prevention (*i.e.*, screening) is advisable for high-risk individuals with "familiar pancreatic cancer" and with other specific genetic syndromes (Peutz-Jeghers, p16, BRCA2, PALB and mismatch repair gene mutation carriers). There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable PDAC, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. EUS performs better for solid and MRI for cystic lesions. However, only 2% of these detected lesions can be considered a successful target, and there are insufficient data demonstrating that resection of benign or low grade lesions improves survival. Many patients in the published studies therefore seemed to have received an overtreatment by undergoing surgery. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods either with computerized tools or molecular biomarkers, possibly in large multicentre studies. At the moment, screening should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

Key words: Endoscopic ultrasound; Pancreatic cancer; Screening; High-risk individuals; Magnetic resonance

Core tip: Screening for pancreatic cancer is advisable for high-risk individuals. There is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat. Successful target of screening are small resectable pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms with high-grade dysplasia and advanced pancreatic intraepithelial neoplasia. Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are employed for screening, and the overall yield for pre-malignant or malignant pancreatic lesions is of about 20% with EUS and 14% with MRI/magnetic resonance colangiopancreatography. However, only 2% of these detected lesions can be considered a successful target. It is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods.

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INDICATION FOR SCREENING FOR PANCREATIC ADENOCARCINOMA: WHICH PATIENTS SHOULD RECEIVE SCREENING AND WHICH LESIONS ARE WE LOOKING FOR?

Pancreatic ductal adenocarcinoma (PDAC) is the most common and lethal type of neoplasia occurring in the pancreas. Its incidence has progressively increased in Western countries, possibly due to changes in lifestyle[1]. The prognosis of PDAC is dismal, due to delayed diagnosis, biological aggressiveness and poor response to medical treatment[1,2]. PDAC is going to become the second cause of cancer-related death in the United States by 2030[2].

Prevention, therefore, seems one of the few reasonable approaches to tackle this deadly disease. Primary prevention, consisting of policies aimed at reducing the risk related with modifiable factors, such as cigarette smoking or overweight, is of paramount importance and might reduce substantially the incidence of PDAC[3].

On the other hand, secondary prevention (*i.e.*, screening) is not advisable for the general population, as the overall lifetime risk of developing PDAC is relatively low, being close to 1%. PDAC, indeed, does not meet some of the criteria set by the World Health Organization for considering a population screening worthwhile[4], such as being the target disease a common form of cancer, although it does have a high associated morbidity or mortality. Moreover, screening for cancer is justified if a there is an acceptable, safe and relatively inexpensive test procedure and if an effective treatment, capable of reducing morbidity and mortality, is available.

With regards to PDAC, there is limited evidence regarding the accuracy of screening tests, their acceptability, costs and availability, and agreement on whom to treat on the basis of screening results. Furthermore, as the accuracy of a given test also relies on the prevalence of the disease (pre-test probability), it is clear that screening is only advisable for specific population groups with a significantly increased risk of developing PDAC.

With regards to which individuals should undergo screening for early diagnosis of PDAC there is good general agreement among experts. The members of the International Cancer of the Pancreas Screening Consortium (CAPS)[5] have recently stated that screening is indicated for: (1) Individuals with "Familiar pancreatic cancer" (FPC), without a defined genetic syndrome, but with two or more blood relatives affected by PDAC, of whom at least one first degree relative (FDR); and (2) As far as regards known genetic syndromes, screening is indicated for all patients with Peutz–Jeghers syndrome regardless of family history of PDAC, while for p16 [familial atypical multiple mole melanoma syndrome (FAMMM syndrome)], BRCA2, PALB and hereditary non-polyposis colorectal cancer mutation carriers, screening is indicated only if one FDR or two family members are affected by PDAC.

It is more difficult to agree on which lesions should be considered the target of screening examinations. Ideally small cancerous lesions (T1) amenable for surgery should be diagnosed in due time and receive appropriate treatment, and individuals with clear macroscopic preneoplastic lesions, such as intraductal papillary mucinous neoplasms (IPMNs), might also be considered for surgery depending on size and other cyst features. However, there is no evidence suggesting that cystic lesions should be treated differently than in sporadic cases[6-8]. The possibility to recognize and the need to treat microscopic preneoplastic lesions such as pancreatic intraepithelial neoplasia (PanIN), whose presence might be indirectly suspected at screening examinations by signs of chronic pancreatitis, is less clear. Advanced PanINs (grade 3) might be considered an appropriate target for screening, while PanIN1 and 2 are extremely common findings in healthy subjects, with their prevalence increasing with age. The yield of "successful" screening examinations should therefore be considered in terms of detection and indication for surgery of lesions such as small, resectable PDAC, PanIN3 and IPMN with high grade dysplasia[5].

Finally, no imaging modalities gained a univocal evidence-based consensus for screening high-risk indivi-

duals (HRI) for pancreatic cancer, and both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) have been proposed to be the first line modalities in terms of accuracy.

The present review article will discuss critically the rationale for the use, and the yield of EUS and MRI for detecting solid malignant and premalignant (solid or cystic) pancreatic lesions, and the outcome of surgery in this setting, in order to try to highlight the clinical impact of the screening policies.

EUS

EUS has emerged as an accurate imaging modality for the study of the pancreatic diseases providing high-resolution images of the pancreas without the risk of radiation exposure.

The CAPS Consortium suggests that initial screening of the HRIs should include EUS examination, with an agreement exceeding 83%[5].

EUS is, indeed, an extremely powerful diagnostic method, and is considered the most sensitive technique for the detection and diagnosis of PDAC. The sensitivity of EUS for solid lesions smaller than 2 cm is 93% compared to 53% and 67% of computed tomography (CT) scan and MRI respectively[9]. Moreover, the high negative predictive value (100%) of EUS for tumor detection suggests that the absence of a focal mass reliably excludes pancreatic cancer[10].

In the setting of cystic lesions, EUS obtains a good definition of their morphological characteristics, useful for the differential diagnosis and to identify features (mural nodules, wall thickness) associated with an increased risk of malignancy[11]. It has also been demonstrated that EUS performs better than MRI regarding the early detection of malignancy in patients with IPMN[12].

Finally, the possibility to perform guided fine needle aspiration (FNA) permits to obtain tissue samples for histopathological characterization of the lesion with low risk of complication[13]. However, although the sensitivity, specificity and accuracy of EUS-FNA in solid pancreatic masses was found to be high (84.3%, 97%, 84% respectively) the relatively low negative predictive value (64%) does not allow to exclude the diagnosis of PDAC if it is suspected[14]. The routine use of EUS – FNA in a screening program is therefore questionable.

On the other hand, microscopic precursor lesions of PDAC, such as PanINs cannot be reliably detected with current imaging methods. Some data, however, suggest that EUS might be able to detect parenchymal changes caused by these lesions. In HRIs PanINs are multifocal and might be associated with lobular atrophy of the surrounding parenchyma, but these features are not associated with the grade of dysplasia. The parenchymal changes caused by multifocal PanINs might be visualized at the EUS as chronic pancreatitis-like features (ectasia, irregularity of the duct and/or parenchyma heterogeneity and lobularity) that cannot be differentiated from non-neoplastic alterations[15].

For all these reasons, EUS has been used in several studies as the baseline screening test for PDAC in HRIs, alone or in combination with other abdominal imaging techniques. The diagnostic yield of this procedure in detecting any lesions - morphologically suspicious or histologically proven to be malignant or pre-malignant - ranged from 2.6% to 46% at baseline evaluation or during the follow-up. However, the actual rate of detected and resected lesions, for which screening might be considered successful, is much lower, as many patients undergoing surgery in these studies had PanIN 1 or 2, or IPMNs without dysplasia or even benign lesions such as serous cystoadenomas, and few others were diagnosed with unresectable PDAC (Table 1).

A screening programme based on EUS was first proposed by Brentnall *et al*[16] in 1999. A small prospective cohort of 14 patients (kindreds that had two or more members in the last two generations with pancreatic cancer) were evaluated with both EUS and endoscopic retrograde cholangiopancreatography (ERCP) and compared to CT results. The EUS findings were available for 13 of 14 patients and resulted abnormal in 10 (ranging from minimal to marked signs of chronic pancreatitis) at the first examination. Seven patients were treated with total pancreatectomy, with findings of signs of widespread dysplasia, although the grade of such lesions was not clarified in the paper. The diagnostic yield of EUS in this study was very high (46%) but whether resecting such target lesions might be considered a success is unclear given the associated morbidity of total pancreatectomy. Kimmey *et al*[17] reported the experience of the same centre, with a similar protocol, a few years later on 46 patients with more than two first or second-degree relatives with PDAC. This second paper seems to include also the patients reported in their pivotal study. Cross-sectional imaging did not detect abnormalities in those patients, while EUS showed signs of chronic pancreatitis in 24 patients, most of them also reporting symptoms such as diarrhoea and diabetes. Twelve patients (including the seven subjects of their first paper) underwent surgery and the histological examination showed widespread dysplasia in all of them. The diagnostic yield of EUS was equal to 26%, yet it is not clear if the operated patients had PanIN3 or lower grades of dysplasia. Notably, these pivotal papers employed ERCP in all screened individuals, and this might have caused some false positive findings, with the addition of possible procedure-related risks.

The pilot study of Johns Hopkins Hospital[18] enrolled 38 patients with $\geqslant$ 2 FDR with PDAC or affected by PJS. EUS was performed as a baseline screening method and in case of abnormalities CT scan and ERCP were carried out. Twenty-nine patients had abnormalities at EUS (12 pancreatic lesions and 17 EUS changes of chronic pancreatitis). FNA was performed in 21 and 3 alterations were found at cytological examinations (1 atypical neoplastic and 2 atypical reactive pancreatic cells). Seven patients underwent surgery, but only one was diagnosed with a T2N1 PDAC and another with multiple PanINs

Table 1 Summary of diagnostic yields of endoscopic ultrasound based protocols for familiar pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield[1] of EUS	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/malignant lesions suspected at baseline or FU	Number with histologically confirmed target lesions for which treatment can be considered a success[2]
Brentnall *et al*[16]	13 (FPC)	46.2%	-	-	10 (77%)	6 (46.2%)	?
Kimmey *et al*[17]	46 (FPC)	26%	-	-	24 (52.2%)	12 (26%)	?
Canto *et al*[18]	38 (FPC, PJS)	10.5%	12 (31.5%)	-	17 (44.7%)	6 (15.7%)	2/7 patients who underwent resection (1 PDAC, 1 PanIN3)
Canto *et al*[19]	78 (FPC, PJS)	10.2%	8 (10.2%)	9 (11.8%)	61 (78.2%)	8 (10.2%)	3/7 patients who underwent resection (1 IPMN+ca *in situ*, 1 IPMN + PanIN3, 1 PanIN3)
Poley *et al*[20]	44 (FPC, PJS, FAMM, FBOC, HP, LFS)	22.7%	3 (6.8%)	7 (16%)	3 (6.8%)	10 (22.7%)	3/3 patients who underwent resection (3 PDAC)
Langer *et al*[21]	76 (FPC, FAMM)	2.6%	7 (9.2%)	3 (3.9%)	17 (22.3%)	7 (11.8%)	0/7 patients who underwent resection
Verna *et al*[23]	31 (FPC, FBOC)	22.5%	2 (6.4)	12 (38.7)	9 (29%)	7 (22.6%)	1/5 who underwent surgery (1 PDAC)
Canto *et al*[24]	216 (FPC, FBOC, PJS)	37%	3 (1.4%)	79 (36%)	54 (25%)	79 (37%)	3/5 who underwent surgery (2 MD-IPMN, 1 BD-IPMN + panIN3)
Total	542	22.2%	35 (6.5%)	110 (20.3%)	195 (36%)	135 (25%)	12/542 (2.2%) of total

[1]Endoscopic yield is defined as EUS detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN $\geqslant$ 2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; [2]Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration; FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz–Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis; LFS: Li fraumeni syndrome.

ranging 1-3. The other 5 resected patients had either a borderline IPMN, PanIN2 or benign lesions (serous cystoadenoma). The diagnostic yield of EUS was 10.5%, if one considers borderline IPMN and PanIN2 appropriate targets for screening. The subsequent prospective study conducted by Canto *et al*[19] screened 78 consecutive HRIs with EUS. In case of abnormal findings at EUS, further evaluations with EUS- FNA/ERCP were performed. In four patients pancreatic malignancy was suspected at baseline screening. The surgical findings were of IPMN with carcinoma in situ in one case, and of IPMN with numerous foci of PanIN3 in another, while the other two patients had IPMN with diffuse and multiple PAnIN1-2, or diffuse PanIN1-2. During the follow-up, within 1 year, further 4 patients were diagnosed having suspected pancreatic neoplasia, and while 1 had an advanced unresectable adenocarcinoma, the others underwent surgery with findings of PanIN3 in one case, and either IPMN with/without PanIN1-2 in the other cases. Therefore, although EUS diagnosed 7 of 8 pathologically confirmed pancreatic neoplasms (yield of 10.2%), one might discuss that a large part of the resected patients did not have significant lesions, and that, despite the screening process, one lesion was diagnosed at mestastatic stage.

Poley *et al*[20] reported their data of a first-time EUS screening on a prospective study of 44 patients (with a relatively large proportion of carriers of a clearly defined genetic syndrome associated with an increased risk to develop PDAC). In case of EUS abnormalities, CT or MRI were performed, as well as a multidisciplinary discussion of all the findings. A total of 7 cystic lesions were diagnosed. Their morphological features at EUS examination were typical of IPMN without signs of malignancy (diameter between 4 and 15 mm without solid component or intramural nodules). In this study this was not considered an indication for surgery. Three asymptomatic solid lesions were detected by EUS and, after resection, the histological examination indeed showed adenocarcinoma. The stage of the tumour was T3N1M0 in two patients and T1N0M0 in the other, but even in this case distant metastases were found 16 mo after surgery. The diagnostic yield of EUS in detecting neoplasms in HRIs in this study was 22.7%.

No malignant lesion was diagnosed in the German surveillance program[21]. This prospective screening study was carried out in 76 HRIs. The imaging procedures performed at baseline were MRI combined with magnetic resonance colangiopancreatography (MRCP) and EUS. A total of 7 suspected lesions were further evaluated with FNA, but none showed cytological alterations. Surgical exploration of the pancreas was performed in 7 individuals, but the histological diagnoses were 3 serous cystoadenomas, 1 PanIN1, 1 PanIN2 and 1 IPMN. The diagnostics yield of EUS in this study was 2.6%, considering as a "successful" target precancerous lesions also the histologically presence of PanIN2 in the pancreatic parenchyma. This low yield compared to the other previous studies could be correlated to a

selection bias of the patients (the study included a large number of patients at moderate risk). The subsequent German study[22] evaluated 5-year of prospective screening in the HRIs from this same series, showing a higher yield in detection of pre-malignant lesions using EUS and MRI/MRCP as follow-up methods. Further 9 patients underwent surgical resection, with diagnosis of 1 advanced PDAC and 1 PanIN3, with the other lesions being either serous cysts (n = 3) or lower grade PanIN or IPMN.

Verna *et al*[23] screened a total of 51 HRIs, 31 of them with EUS. The most common abnormal findings, as expected, were parenchymal changes seen in chronic pancreatitis: two patients had a mass lesion confirmed to be PDAC after FNA, one was resectable (2 cm moderately differentiated adenocarcinoma arising from main duct IPMN), and one metastatic to the liver. Five BD (branch-duct) IPMN were diagnosed and in 4 of them surgery was carried out (all of these had BD IPMN with moderate dysplasia and multifocal PanIN2 lesions on pathology). In this cohort study the diagnostic yield was 22.5%, although only one of these lesions might be considered a successfully detected target.

The multicentre prospective cohort CAPS 3 study[24] enrolled three groups of asymptomatic HRIs (FPC, BRCA and PJS). It is the first blinded study that compared standardized protocol CT, gadolinium and secretin-enhanced MRCP and EUS. Of 226 patients, EUS diagnosed parenchymal and ductal abnormalities (chronic pancreatitis features) in 25%. Surgery was performed in 5 HRIs, and three of 5 them had IPMN with main duct involvement, high-grade dysplasia and/or associated PanIN3. The diagnostic yield in detecting precursor lesions was considered equal to 37%, but the number of significant lesions was relatively low, with few cases with indication for surgery as compared with previous studies.

MRI

MRI is a widely available technique, and when compared to EUS, has the advantages of being non-invasive, less operator-dependent, easier to be compared and reviewed over time by different specialists taking care of the patients. MRI also offers the opportunity to image the entire abdomen and pelvis. This latter aspect is noteworthy, as it might help diagnosing extra-pancreatic neoplasms, which are fairly common in some specific groups of HRI[25]. Moreover, MRCP provides excellent visualization of the pancreatic and biliary tree and is particularly useful for characterizing cystic lesions such as IPMNs that are the most common precursor lesions diagnosed in HRI[6,20,26].

Seven papers investigated the use of MRI for the screening of individuals at high risk for developing a pancreatic cancer. The employed methods are extremely heterogeneous in terms of employed MR scanner, acquisition phases, use of contrast agents and use of secretin. The diagnostic yield for the detection of pancreatic lesions also varies among the different studies (Table 2), ranging from 3.3% to 57.4%[21,23-25,27-29].

Secretin-enhanced sequences have been used in three of these seven papers[21,24,29], but its use has not been univocally validated to improve the diagnostic yield of MRCP in this setting. Nevertheless, a recently published paper on patients with a strong family history of pancreatic cancer undergoing a multicenter Cancer of the Pancreas Screening-3 trial (CAPS 3), proved evidences that the use of secretin can improve the visualization of ductal communication of cystic pancreatic lesions[30].

Some authors decided to use non-contrast MRI protocol for screening, basing on the hypothesis that changes in pancreatic duct and/or focal drop in pancreatic signal would be detectable even without contrast and that these alterations would have triggered further investigations[28]. Other authors indeed used a contrast-enhanced MRI protocol. The former argued against this latter position because, even if using a contrast enhanced protocol, all pancreatic cancers individuated in screening programmes were advanced and/or metastatic and due to patient's death[27,28].

The diagnostic yield of MRI varies sensibly among the different studies with a wide range, between 3% and 50%, probably due to the heterogeneity both of investigated populations and screening protocols[23,25]. The rate of solid lesions found at MRI seems to be low, ranging between 0.4% and 9%[24,27]. Similar results have been reported for the detection of chronic pancreatitis-like changes, duct ectasia and PanIn lesions, while pancreatic cystic lesions are diagnosed in a higher percentages of patients (2.6%-35.3%)[21,24,29]. In two series, a percentage of about 3% of patients with non-reproducible alterations has been reported[21,28].

Recently a series of 40 high risk individuals undergoing a MRI based screening protocol has been published. Patients underwent a baseline secretin-enhanced MRCP and then a yearly MRI imaging in case of negative result or a EUS with FNA/additional CT scan imaging protocol in case of suspicious result. An overall 40% MRI yield was reported (35% IPMNs, 5% PDAC) at a median 1 year follow up. An additional, synchronous PDAC was found during the IPMN follow up. Five patients underwent a surgical resection, all of them with a successful surgical treatment (3 PDAC, 2 IPMNs with indeterminate grade dysplasia)[30].

COMPARISON OF EUS AND MRI

There are few studies comparing the diagnostic yield of MRI and EUS in screening HRIs, and it is therefore still unclear which is the best method in detecting early stage PDAC and premalignant lesions in these subjects. The CAPS 3[24] study evaluated, in a blinded fashion, the ability of these two screening methods in detecting pancreatic lesions in HRIs. This study showed a high concordance between the two diagnostic examinations for the detection of any pancreatic lesion (91%). In

Table 2 Summary of diagnostic yield of magnetic resonance imaging based protocols for familiar pancreatic cancer screening in high risk individuals

Ref.	Patients and syndrome	Diagnostic Yield[1] of MRI	No. of solid lesions (mass or nodule)	No. of cystic lesions	No. with chronic pancreatitis features	No. with pre/ malignant lesions suspected at baseline or FU	Number with histologically target lesions for which treatment has to be considered a success[2]
Langer *et al*[21]	76 (FAMMM, MPCS, FBOC)	23.3%	6 (7.8%)	2 (2.6%)	1 (1.3%)	12 (15%)	1/7 who underwent surgery (1 PDAC)
Vasen *et al*[27]	77 (FAMMM)	20.7%	7 (9%)	Not specified	9 (11.6%)	7 (9%)	4/5 who underwent surgery (4 R0 PDAC)
Ludwig *et al*[28]	109 (FPC)	16.5%	1 (0.9%)	Not specified	2 (1.8%)	18 (17.4%)	4/6 who underwent surgery (2 MD-IPMN, 1 PDAC, 1 PanIn3)
Canto *et al*[24]	216 (PJG, FPC, FBOC)	33.7%	1 (0.4%)	71 (32.8%)	-	45 (20.8%)	3/5 who underwent surgery (1 MD-IPMN + HGD, 1MD IPMN, 1 BD IPMN + PNET + HGD)
Al-Sukhni *et al*[25]	226 (PJG, FPC, FBOC, FAMMM, HP)	50.4%	2 (0.8%)	80 (35.3%)	25 (11%)	5 (2%)	1/4 who underwent surgery (1 PDAC)
Verna *et al*[23]	33 (FPC, FAMMM, FBOC, HNPCC)	3.3%	3 (9%)	7 (21.2%)	1 (3%)	5 (15%)	Not specified how may pathological reports had been previously described in MRI
Del Chiaro *et al*[30]	40 (FPC, BRAC 2, BRAC 1, FAMMM)	40%	3 (7.5%)	14 (35%)	-	4 (10%)	5/5 (3 PDAC: 1 of them T1N0M0, 1 developed on a synchronous BD-IPMN in FU; 2 intermediate grade dysplasia IPMN of which one mixed type and one branch duct)
Total	777	26.8%	23 (2.9%)	174 (22.39%)	38 (4.8%)	96 (12.35%)	18/777 (2.3%) of total

[1]MRI yield is defined as detection of any lesions morphologically suspicious for BD-IPMN or histologically proven (pre) malignant lesion (PanIN $\geqslant$ 2, IPMN and pancreatic adenocarcinoma) at baseline evaluation and, when performed, during the follow up; [2]Treatment is considered a success if any of the following lesions is found at surgery: resectable PDAC, MD-IPMN or IPMN with dysplasia, PanIN3. FPC: Familial pancreatic cancer; BD: Branch duct; MD: Main duct; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PJS: Peutz–Jeghers syndrome; PanIN: Pancreatic intraepithelial neoplasia; FAMMM: Familial atypical multiple mole melanoma; FBOC: Familial breast ovarian cancer; HP: Hereditary pancreatitis.

particular, a strong positive correlation was found for the size of the lesions, and a moderate agreement for the number of pancreatic cystic lesion/solid mass was described. MRI better assessed communication of the cyst with the main pancreatic duct, being superior to EUS (53% *vs* 27%). EUS missed five patients with a cystic lesion seen by MRI (2 of which BD-IPMN) but diagnosed 12 patients with cystic lesions not reported by MRI (3 of which BD IPMN).

A prospective blinded comparison study was conducted by the Rotterdam group and has recently been submitted for publication. A total of 139 high-risk patients were enrolled and screened with both MRI and EUS. There was high agreement regarding location and size of all lesions. Instead, only a moderate agreement (55%) was reached for the detection of the 11 clinically relevant described lesions. MRI was very sensitive for the diagnosis of cystic lesions, while EUS detected two solid lesions that were not found by MRI (one of these was shown to be PDAC). The results of this study suggest that both techniques are useful, and that they might be complementary rather than interchangeable in screening HRIs, with MRI being able to detect cystic lesions better than EUS, but EUS being more accurate for the diagnosis of small solid lesions, which are the primary target of screening.

Thus, even taken for granted the major sensitivity of EUS in detecting small solid pancreatic lesions, one might argue that there are no solid data suggesting that such ability has a beneficial effect on the disease outcome in this setting. On the other hand, MRI with MRCP protocols have reasonably a good accuracy for the detection of IPMNs, which represent a precancerous lesion, that potentially progress towards pancreatic cancer. Future studies should compare the ability of these methods in a randomized designed study, and their impact on the long-term outcome of screened subjects.

USE OF SERUM CARBOHYDRATE ANTIGEN 19-9 AS A SCREENING TEST

Serum carbohydrate antigen (CA) 19.9 is the most widely used biomarker for pancreatic cancer, and its use is recommended to monitor the response to treatment[31] in patients who had elevated level before treatment (between 5% and 10% of the general population are unable to express CA-19-9).

However, the dosage of Ca 19.9 in screening asymptomatic population is not recommended. A number of 70940 asymptomatic patients were screened by Kim *et al*[32] using Ca 19.9 (cut off > 37 U/mL)[32]. Although it showed an high sensitivity (the CA 19-9 level was increased in all four patients diagnosed with pancreatic cancer), in screening pancreatic cancer in the general population it showed a very poor predictive positive value (0.9%). Similar results were obtained by Chang *et al*[33] that found high sensitivity and specificity of this biomarker in predicting pancreatic cancer (100% and 92% respectively) but a 0.5% of positive predictive value.

Slightly better results were obtained in screening symptomatic patients (with high prevalence of pancreatic cancer equal to 49%) where it was found an high positive predictive value (71%) using a cut off Ca 19.9

> 40 U/mL[34].

The diagnostic role of Ca 19.9 in screening HRIs patients was poorly investigated. The serum dosage of Ca 19.9 was carried out in 8 of 14 patient screened by Brentnall *et al*[16] and found to be normal in all these patients. Between the patients enrolled by Verna *et al*[23] only one had elevated Ca 19.9. This patient was found to have a pancreatic cyst without dysplasia, and Ca 19.9 remained elevated after surgery. In the german study by Langer *et al*[21] all but one patient showed a normal Ca 19.9. The imaging examinations did not show any abnormality of the pancreas at the first evaluation and during the subsequent 28 mo of follow up, and after further investigations the cause of elevation of this biomarker remained unclear. Therefore, although data are limited, the dosage of Ca 19.9 doesn't seem helpful during the screening of HRIs.

SURGICAL INDICATIONS AND OUCTOME

Although screening policies for the prevention or early detection of pancreatic cancer have been initiated about 15 years ago, there are still not enough data to generate evidence-based guidelines regarding the role of pancreatic surgery in this setting. In many of the initial studies screening HRIs, indication for surgery was possibly too wide, and many patients undergoing surgery were diagnosed with benign or borderline findings[16-19]. As discussed above, what makes the current picture more complicated is the definition of the targets for surgery, as reasonable goals of the screening programme are early invasive or resectable pancreatic cancer, high grade dysplasia IPMNs, and PanIN3 lesions, while the significance of other lesions is less clear. The different approaches to screening and treatment of HRIs is reflected in the results from different surveillance programmes. In this view, not surprisingly, the more recent studies, and personal viewpoints now point toward a less aggressive surgical approach, both in terms of timing for surgery and in extent of pancreatic resection[35].

PanIN lesions are considered detectable by EUS, by some Centers[19]. Those lesions may appear as parenchymal changes resulting from a lobulocentric atrophy (LCA) that is present in chronic pancreatitis. However, recent studies showed that this association between PanIN and LCA is not clear and for this reason the use of LCA as a target for early detection of pancreatic cancer should be considered with extreme caution. First, PanIN might not be the cause of LCA; second, LCA can be found in other conditions (as aged pancreas); third, the value of low grade dysplasia at FNA can't exclude another area of high grade dysplasia in a distinct area, sometimes distant from the biopsy site, but not associated with LCA, and not visible at EUS[36]. Furthemore, while the agreement among different operators for the interpretation of EUS findings when a frank solid or cystic lesion is diagnosed is generally good, this is not the case for the diagnosis of chronic pancreatitis features, where the agreement remains disappointing even after a consensus process[37].

For all these reasons there is no consensus on surgical treatment of PanIN lesions, and it is questionable whether finding of PanIN1-2 should be considered a success. However, one can assume that histological confirmed PanIN3 lesions should be resected. The extent of pancreatectomy for those patients is not defined, but a radical partial pancreatectomy seems to be the adequate option.

IPMNs are the most frequent finding detected during the screening of HRIs[35]. Even if the natural history of IPMNs in individuals with family history is not well defined, some data[38] suggest that the risk to progress to cancer is not higher than that of sporadic cases. However, the IAP guidelines for treatment and follow-up of cystic pancreatic lesions[8] suggest to shorten follow-up intervals in patients with BD-IPMN and FPC, and more recently the Italian guidelines[7] have suggested to consider surgery for all IPMNs in the setting of FPC in fit patients. Which surgical procedure should be performed in such cases is also unclear. Notably, it has been reported that in the setting of HRIs, BD-IPMNs are often associated with distant foci of PanIN3[36], and IPMNs are also frequently multifocal, thus a radical surgical treatment might be a total pancreatectomy. On the other hand, this may often result in an overtreatment. At any rate, such patients should be discussed in highly specialized centers and the indications should also take in consideration patient age and perception of the problem.

The surgical treatment of solid tumors of the pancreas (suspected pancreatic adenocarcinoma) in HRIs, should follow the rules of oncologic surgery[26]. The initial approach to these patients in Seattle was total pancreatectomy[16], but this is not supported by evidence and might only be considered in cases with diffuse multiple lesions in the pancreas (for example a solid tumor in the head and IPMN in the tail). Data on post-operative follow-up of HRIs are extremely scanty. It seems reasonable to follow-up HRIs diagnosed with cancer and resected as other sporadic cases. For patients operated for pre-malignant lesions, the pancreas remnant should be followed-up according to the surveillance program for HRIs[5].

AREAS FOR IMPROVEMENT

Screening for pancreatic cancer or its precursors has an indication in research settings only. As compared with other screening policies for cancers indeed, there are a number of issues that need to be clarified in order to consider screening worthwhile.

The overall yield of screening methods for pre-neoplastic or neoplastic pancreatic lesions in HRIs is of about 20% with EUS and 14% with MRI/MRCP. However, only 2% of the detected lesions might be considered a successful target of screening (Tables 1 and 2), and there are insufficient data demonstrating that resection

of benign or low grade lesions improves survival. Many patients in the published studies, indeed, seemed to have received an overtreatment by undergoing surgery.

In this view, it is crucial to better stratify the risk of malignancy individually, and to better define optimal screening intervals and methods. The use of a computerized risk assessment tool named PancPRO has been proposed and tested in incident cases of PDAC[39]; similar tools taking into account the role of family history and possibly other factors such as smoking, might help selecting patients at a substantially higher risk. In the future, application of novel methods of molecular analysis might help better select patients for screening, and provide the indication for surgical treatment. Eshleman *et al*[40] recently investigated the possible role of KRAS and GNAS mutations in the duodenal juice of PDAC patients and HRIs undergoing screening EUS. As expected, a high percentage of PDAC patients had KRAS mutations, but among screened individuals the presence of KRAS mutations did not discriminate between these with or without lesions. This is most likely due to the fact that KRAS mutations are an early event, already present in PanIN1, which is extremely common in HRIs and does not represent a target lesion for resection. Crnogorac-Jurcevic *et al*[41] analysed the gene expression profile of precursor lesions, PanIN2/3 obtained from prophylactic pancreatectomy specimens of FPC from the Seattle-Washington screening program. They found that transcriptomic changes occur during the progression of PanIN to PDAC, not only in the epithelium but also in the surrounding stroma. These findings support the view that early changes in familial cases are similar to those seen in sporadic cases, and might serve as a tool to predict the behaviour of pre-neoplastic changes in HRIs. The possible role of microRNAs, and other biomarkers, has been investigated by Slater *et al*[42]. They reported that serum levels of miR-196a and miR-196b were significantly higher in patients with PDAC as compared to controls, but notably, the serum levels of such miRs were also higher in HRIs screened for PDAC with PanIN2/3 lesions than in screened subjects without lesions or with PanIN1 lesions only. These results, if confirmed, might suggest that a panel of miRs might help selecting patients at higher risk of significant findings among screened individuals.

It is also uncertain whether EUS or MRI, or both, should be employed as screening tests, as few studies compared these two methods. It seems that the two techniques might be considered somehow complementary, with EUS being more accurate for solid lesions and MRI for cystic ones. Future studies should also take into account different subgroups of HRIs when establishing screening intervals and modalities. As an example, it has been reported that in individuals with FAMMM (p16 mutation carriers), cystic lesions are less frequent than in FPC, but solid lesions diagnosed as PDAC are far more frequent[43]. Thus, in p16 mutation carriers a screening with EUS and not with MRI, with closer intervals, might be preferred.

Another intriguing issue regards the diagnosis of other pancreatic lesions at screening. Pancreatic neuroendocrine tumours (PNETs) have been diagnosed in HRIs receiving screening for PDAC, with a prevalence apparently exceeding the expectations[24,25,27]. It is unclear whether these findings are just occasional, or if PNETs may represent a part of FPC phenotype, as possibly suggested by findings of similar risk factors for the occurrence of PNETs and exocrine neoplasms[44].

Finally, it also needs to be determined whether screening for pancreatic cancer in HRIs is really cost-effective. In a simulation considering a 20% prevalence of pancreatic "dysplasia" and 90% sensitivity of EUS and ERCP, endoscopic screening was calculated to be cost-effective, but this analysis most likely considered an excess of lesions now considered as successful targets of screening[45].

Future large collaborative studies are likely to give the answer to many of these open questions but, until then, screening for pancreatic neoplasms in HRI should be carefully performed within research protocols at experienced centres, offering involved individuals medical and psychological advice.

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EDITORIAL

Staple-line leak after sleve gastrectomy in obese patients: A hot topic in bariatric surgery

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Abstract

Laparoscopic sleeve gastrectomy is a surgical procedure that is being increasingly performed on obese patients. Among its complications, leaks are the most serious and life threatening. The placement of esophageal, covered, self-expandable metal stents in these cases has been performed by many authors but reports on the outcome of this procedure are limited and the technical aspects are not well defined. Stent migration is the main complication of the procedure and poses a challenge to the surgeon, with a limited number of options. Here we evaluate the technical and clinical outcome of a new, dedicated, self-expanding metal stent, comparing the advantages of this stent to those traditionally used to treat staple-line leak after sleeve gastrectomy. While published data are limited, they seem support the use of this kind of new stent as the best option for the stenting treatment of a staple-line leak after sleeve gastrectomy, over other kinds of stents. Further studies based on larger series are needed to better evaluate patient outcome.

Key words: Bariatric surgery; Leak; Obesity; Sleeve gastrectomy; Endoscopic stent; Therapy

Core tip: Laparoscopic sleeve gastrectomy (LSG) is a surgical procedure increasingly performed on obese patients with convincing outcomes. Among its complications, leaks are the most serious. The use of esophageal self-expandable metal stents in these cases has been performed by many authors but reports are limited and stent migration is the main complication of the procedure. Megastent®, a new stent dedicated to the treatment of leaks after LSG, seems to resolve most of the problems of the esophageal stents. While published data are limited, they seem support the use of Megastent® as the best option for the stenting treatment

of a staple-line leak after sleeve gastrectomy. Further studies on larger series are needed to better evaluate definitive outcomes.

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A HOT TOPIC IN BARIATRIC SURGERY: NEW DEDICATED STENTS TO IMPROVE TREATMENT

Laparoscopic sleeve gastrectomy (LSG), first described by Gagner[1] in 2003, has become a well standardized therapeutic option for the surgical treatment of different degrees of obesity[2-6]. Since its introduction, LSG has gained acceptance due to its technical simplicity and the convincing outcomes[7,8]. While specific complications have been reported, including staple-line bleeding and stricture, staple-line leaks are the most serious as they are associated with the greatest morbidity. The incidence of this type of leak after LSG varies in different series[9-11] and its management has been attempted using several different therapeutic approaches[7,10,12-21].

Staple-line leak after LSG reportedly develops in 2.5% of patients undergoing primary sleeve gastrectomies, with a range between 0.5% and 7% in the different series of dedicated bariatric surgeons[6,7,10,16,22,23]. Recently Gagner[24] reported that the incidence of staple-line leak after LSG is decreasing from a generally accepted rate of 2.5% initially to a now 1.1% leak rate in 2013 as reported in a large cohort of 46.133 sleeve gastrectomies, with more than 50% decreased incidence.

Nevertheless, in our opinion, the true rate is probably underestimated. A detailed review by the American Society for Bariatric and Metabolic Surgery reported an overall complication rate after LSG of 0%-24%, with the leakage occurring in 16%-20% of the cases in several series of different experienced surgeons[16] and in patients requiring re-operation after a previous gastric operation performed in no-dedicated to bariatric surgery centers[25].

The gastro-esophageal junction and the proximal stomach near the angle of His are, according to the literature, the most frequent origins of leaks[6,9,11,15], but the reason for this predominance is still unknown. Baker[26] suggested that staple-line leaks are secondary to an impaired healing process and may have multiple risk factors (impaired suture-line healing, poor blood flow, infection, poor oxygenation with subsequent ischemia), but these can be divided into two main categories: mechanical-tissue causes and ischemic causes.

A mechanical mechanism can be invoked when the intraluminal pressure, in association with a low compliance of the gastric tube, exceeds the strength of the staple line. This situation is more likely in patients with difficulties in gastric emptying due to a middle or a distal stenosis of the sleeve[27,28]. In order to reduce the possibility of mechanical failure, the use of buttress material associated with the stapler has been advised, but there is no statistical evidence to support this solution[29].

On the other hand, some Authors claim that most fistulas are not due to staple failure and dehiscence but to ischemia in the gastric wall next to the staple line, likely reflecting devascularization of the gastro-esophageal junction during liberation of the greater curvature or dissection of the greater curvature when electrocautery, Ultracision®, or the LigaSure® system is used[30,31].

Moreover, regardless of the mechanism (mechanical or ischemic) the physiology of the normal sleeve must be considered as well. Studies assessing volume and pressure after LSG[28,32] clearly demonstrated that the removed portion of the stomach (fundus and corpus) is indeed the most expandable, with an important reservoir function. The volume of the sleeve is less than 10% of the volume of the whole stomach and the mean pressure in the sleeve is higher (43 ± 8 mmHg *vs* 34 ± 6 mmHg, $P < 0.005$). Furthermore, the valve function of the cardia and pylorus persists in the gastric sleeve as does the pumping function of the antrum, both of which may further increase the intraluminal pressure.

For these reasons, in obese patients undergoing LSG, although the high intraluminal pressure resulting from the small volume and reduced distensibility of the sleeve confers early satiety, it is also a risk factor for dehiscence of the staple line.

The use of covered, esophageal, self-expandable metal stents (C-SEMS) in the treatment of staple-line leak after LSG has been supported by many authors in recent years[15,17,18,31] even if this is not a widely accepted treatment. C-SEMS permit the comfortable management of this complication, as the temporary fistula-bypass enables enteral nutrition (liquid hyperprotein diet progressing to a soft diet as tolerated) and, if the clinical situation is appropriate, allows the patient to return home temporarily[15]. Nevertheless, reports on the outcome of this procedure are limited and the technical aspects are not well defined.

To select candidates for this form of treatment, the following criteria should be observed: (1) Any abscess or intra-abdominal collection should be previously drained prior to stent placement[31]; (2) Leaks located at the proximal and mid part of the sleeve are the only ones amenable to stent treatment[10,11,17,18,21]; (3) The size of the leak should not exceed 2 cm[17]; (4) The stent should be chosen based on an evaluation of the gastric sleeve diameter, using a larger size in case of doubt, to prevent migration[17,18]; and (5) Late leaks (persisting for more than 4 wk) have the best outcome[15,33,34].

Most authors recommend leaving the stent in place

for a period of 6-8 wk.

In the literature, a highly variable success rate has been reported for this technique[21]. However, most of the published papers have been case reports or small surveys; statistically reliable data are, at this point, lacking.

Stent migration is the main complication of the procedure and it occurs in 30% of the cases in some series[14,17,18,33] and in as many as 42%-50% in others[15,20,35]. The highly variable stent migration rate can be explained by the following: (1) These stents are designed for use in esophageal stenosis and have therefore been adapted in a different site and to a different target; (2) The "abnormal" placement of the stent along the last portion of the esophagus and the gastric sleeve does not ensure proper containment of the stent; and (3) The coating of the stents prevents its integration into the stomach wall but reduces the grip on the wall and therefore allows migration along the gastric tube.

Regardless of the cause, failure of C-SEMS treatment poses a challenge to the surgeon, as successful management of the fistula is then very difficult, with a limited number of options.

Recently, Taewoong Medical Industries developed and marketed Megastent®, a new, fully covered stent dedicated to the treatment of leaks after LSG. Its features resolve some of the above-mentioned problems. The proximal and distal ends of the stent are slightly flared, with a high edge profile permitting good anchorage. The body of the stent is longer than that of other esophageal stents (15, 18 and 23 cm) thus allowing the distal end (with the same shape as the proximal one) to open into the duodenal bulb. The large diameter (24 or 28 mm) ensures optimal adherence of the stent to the sleeve wall, even in the antral segment, conferring adequate radial strength to dilate a possible stenosis. The entire stent is coated, which prevents its integration into the stomach wall due to a granulomatous reaction while the flexibility of the stent nets is sufficient to allow adaptation of the stent to the post-operative anatomy of the gastric sleeve.

In our experience[36], stents 230 cm long and 24 mm in diameter were chosen. The shape of the proximal end of the stent and its angle with respect to the stent body allowed complete coverage of the leak, thus promoting healing. Moreover, the total length of the stent facilitated delivery of the proximal end into the distal esophagus and the distal end into the duodenal bulb, such that the stent body extended through the entire sleeve. In our opinion, this is the main advantage of the Megastent®, as this feature eliminates the pressure gradient in the gastric sleeve. Thus, by establishing a communication with the esophagus and the duodenum, the Megastent® completely resolved the high-pressure condition that had developed in the gastric sleeve, thus promoting healing of the leak hole. The absence of stent migration was likely due to the fact that the length and diameter of the stent allow it to firmly grip the entire gastric sleeve, despite its full-length coating.

In our patients one week after the stent placement a liquid high protein diet was started, followed by a soft diet and discharge 3 d later. The stent was removed after 8 or 9 wk and an upper endoscopy documented complete healing of the leak.

While the procedure described herein was successful, two problems arose during and after stent placement. The first was biliary vomiting, which the patient experienced during the treatment. Pharmacologic therapy with domperidone was mandatory, to reduce the symptoms, which were due to esophageal biliary reflux. The second problem occurred after stent removal: a decubitus lesion in the duodenal bulb that arose, in our opinion, from the decubitus of the free edge of the distal end of the stent, strained by the radial strength of the net.

In conclusion, we recommend that the complicated multi-disciplinary management of patients with gastric leakage treated by stent graft should be confined to specialized centers. Stent placement, in appropriately selected patients, is a safe and effective treatment for staple-line leaks after LSG. This minimally invasive technique has an acceptable complication rate and causes little discomfort to the patient, who avoids the need for more invasive procedures or even total gastrectomy.

Published data about Megastent® are limited but very interesting and encouraging. I like to close this article citing the words by Gagner[24] on a his recent editorial: "I project that staple line leaks will continue to decrease. However, it may never be eliminated completely and nonoperative treatment with endoscopic fully covered metallic stent placement will continue to be the best method in leaks < 12 wk. If the long stents advoked by Galloro *et al*[36] will solve the migration problem seen in earlier series, as well as take care of the mid-body stricture often associated, then we might see less fistula-jejunostomies in the near future".

Obviously, further studies based on larger series are needed to better evaluate patients outcome.

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REVIEW

Endoscopic therapy for weight loss: Gastroplasty, duodenal sleeves, intragastric balloons, and aspiration

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Abstract

A new paradigm in the treatment of obesity and metabolic disease is developing. The global obesity epidemic continues to expand despite the availability of diet and lifestyle counseling, pharmacologic therapy, and weight loss surgery. Endoscopic procedures have the potential to bridge the gap between medical therapy and surgery. Current primary endoscopic bariatric therapies can be classified as restrictive, bypass, space-occupying, or aspiration therapy. Restrictive procedures include the USGI Primary Obesity Surgery Endolumenal procedure, endoscopic sleeve gastroplasty using Apollo OverStitch, TransOral GAstroplasty, gastric volume reduction using the ACE stapler, and insertion of the TERIS restrictive device. Intestinal bypass has been reported using the EndoBarrier duodenal-jejunal bypass liner. A number of space-occupying devices have been studied or are in use, including intragastric balloons (Orbera, Reshape Duo, Heliosphere BAG, Obalon), Transpyloric Shuttle, and SatiSphere. The AspireAssist aspiration system has demonstrated efficacy. Finally, endoscopic revision of gastric bypass to address weight regain has been studied using Apollo OverStitch, the USGI Incisionless Operating Platform Revision Obesity Surgery Endolumenal procedure, Stomaphyx, and endoscopic sclerotherapy. Endoscopic therapies for weight loss are potentially reversible, repeatable, less invasive, and lower cost than various medical and surgical alternatives. Given the variety of devices under development, in clinical trials, and currently in use, patients will have multiple endoscopic options with greater efficacy than medical therapy, and with lower invasiveness and greater accessibility than surgery.

Key words: Weight loss; OverStitch; Aspire; Transoral outlet reduction; Gastric balloon; Orbera; EndoBarrier; Apollo; Primary Obesity Surgery Endolumenal; Gastric bypass; Duodenal sleeve; Intragastric

Core tip: A broad array of endoscopic procedures and

devices will be approved to treat obesity and its metabolic comorbidities in the coming years. A robust body of safety, efficacy, and cost effectiveness data will continue to develop. Endoscopists should have familiarity with target population, benefits, contraindications, and adverse events for each device or procedure. Furthermore, the use of these devices and procedures in the context of a diet and lifestyle management program will be important to ensure success.

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INTRODUCTION

A new paradigm is developing in the treatment of obesity and metabolic disease. Endoscopic procedures in development, in trials, and in use have the potential to bridge the gap between medical therapy and weight loss surgery. Obesity and its comorbidities - diabetes, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease, have become a global epidemic[1]. Dietary modification, exercise, and pharmacologic therapy have been ineffective in arresting the spread of obesity at the population level. Bariatric surgery, which is effective and is utilized by hundreds of thousands of patients each year, can only be performed on a fraction of eligible patients given the current number of practicing surgeons[2]. Endoscopic therapies for weight loss are potentially less invasive, reversible, and lower cost; they may also be repeatable as necessary. These characteristics mean that various endoscopic procedures may play a role as primary therapy, as a bridge to bariatric surgery, or as a revisional procedure after bariatric surgery. Current primary endoscopic bariatric therapies can be classified as restrictive, bypass, space-occupying, or aspiration therapy. These procedures, as well as endoscopic revision of gastric bypass, are discussed herein.

RESTRICTIVE PROCEDURES AND DEVICES

Restrictive procedures remodel the stomach *via* suturing, stapling, or tissue anchor placement to reduce gastric volume.

Incisionless Operating Platform for Primary Obesity Surgery Endolumenal

The Incisionless Operating Platform (IOP) [USGI Medical, San Clemente, California (CA)] can perform full-thickness tissue plication. The platform of the IOP is the four-channel TransPort, which is steerable in four directions and has a 73 cm insertion length. A 4.9-mm endoscope is passed through one channel for endoscopic visualization. The g-Prox, which is capable of 360-degree rotation, has 33-mm stainless steel jaws at its tip to grasp tissue. A helix, called g-Lix, is passed through one channel to grasp tissue and pull it into the jaws of the g-Prox. The g-Cath is advanced through the g-Prox and used to deploy suture anchors. The g-Prox is able to cut suture. The device can be reloaded *in vivo*.

The device has been used to perform the Primary Obesity Surgery Endolumenal (POSE) procedure. To perform POSE, eight to ten plications are created in the gastric fundus (in retroflexion) in two parallel ridges until the fundic apex is brought down to the level of the gastroesophageal junction. The device is then straightened so that the distal gastric body is visualized. A tissue ridge is created with three or four plications in the distal gastric body across from the incisura. Care should be taken to avoid deep g-Lix insertion in this area, in order to avoid injury of adjacent viscera. After the procedure, patients advance from a clear liquid diet to soft pureed diet during the first month, and then to solid food by six weeks. A study of 45 patients with average body mass index (BMI) 36.7 ± 3.8 kg/m^2 reported six-month weight loss of 16.3 ± 7.1 kg or 15.5% ± 6.1%[3]. BMI decreased by 5.8 ± 2.5 kg/m^2 over six months. Adverse events associated with the procedure included one case of low-grade fever and one case of chest pain. POSE is currently being studied in the ongoing randomized sham-controlled ESSENTIAL trial.

OverStitch for endoscopic sleeve gastroplasty

The Apollo OverStitch (Apollo Endosurgery, Austin, TX) can place full-thickness stitches in a variety of interrupted or running patterns. Sutures can be reloaded without endoscope removal. The OverStitch includes a curved needle driver attached to the tip of the endoscope, a catheter-based suture anchor, and an actuating handle attached near the endoscope controls. A double-channel endoscope is necessary.

The OverStitch can be used to perform endoscopic sleeve gastroplasty (Figure 1). Initial human cases were performed in a three-center study: a pilot study of five patients to establish procedure technique, safety, and feasibility followed by 23 cases to study efficacy[4]. Gastroplasty was performed by placing running stitches in a triangular configuration starting in the antrum and working proximally. Each suture was used to create two conjoined triangles. Between 8 and 14 sutures were placed in this fashion. The procedure included fundic reduction in retroflexion. The sleeve was reinforced with interrupted stitches. BMI in the 23 patients studied for efficacy decreased from 34.2 ± 1.1 kg/m^2 to 29.4 kg/m^2. Gastroplasty using a different method was studied in a single-center pilot trial including four patients with average BMI of 35.9 ± 1.2 kg/m$^{2[5]}$. This technique employed two parallel rows of interrupted plications to create a gastric sleeve. The trial established technical feasibility. The multicenter Primary Obesity Multicenter

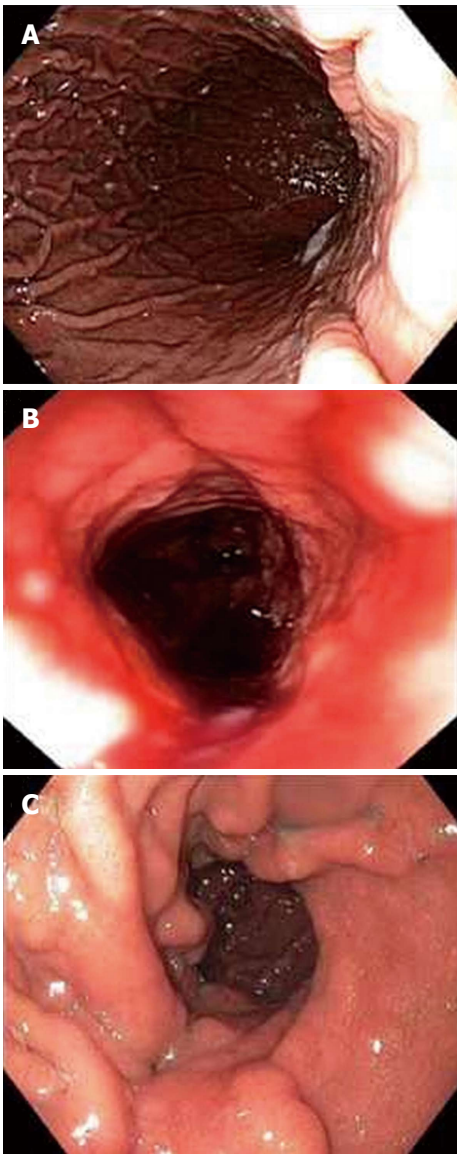

Figure 1 Endoscopic sleeve gastroplasty using Apollo OverStitch: before (A), after (B), and at three months (C)[5].

Incisionless Suturing Evaluation trial to study efficacy of endoscopic sleeve gastroplasty using OverStitch is ongoing in the United States.

EndoCinch for endoscopic gastroplasty

The EndoCinch [Davol, Murray Hill, New Jersey (NJ)] is a superficial-thickness endoscopic suturing system. EndoCinch uses suction to acquire tissue in a hollow capsule, and then passes a needle through the tissue. EndoCinch has been studied for endoscopic gastroplasty in adolescents and adults. A study of gastroplasty in 64 patients with average BMI of 39.9 kg/m^2 reported no serious adverse events[6]. Weight loss of 58.1% ± 19.9% Excess Weight Loss (EWL) was reported after one year. A study of the same procedure in 21 adolescents (age 13-17) with average BMI of 36.2 kg/m^2 reported 67.3% EWL after one year and 61.5% EWL after 18 mo[7]. The device was then modified and named the RESTORe (Davol, Murray Hill, NJ), and was capable of both full-thickness suturing and suture reloading *in vivo*. This device was studied in a two-site trial including 18 patients[8]. There were no significant adverse events. One-year mean weight loss was 11.0 ± 10 kg, or 27.7% ± 21.9% EWL. Half of the patients lost more than 30% of excess weight. Average waist circumference declined by 12.6 ± 9.5 cm. Blood pressure decreased significantly (systolic -15.2 mmHg, diastolic -9.7 mmHg). However, follow-up endoscopy revealed partial or complete release of plications in 13 of 18 patients.

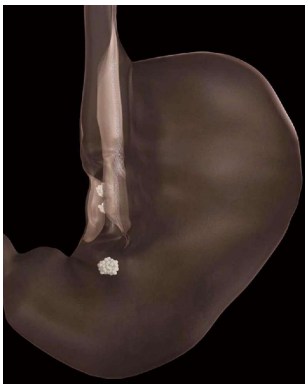

Figure 2 Creation of sleeve using TransOral GAstroplasty[9].

TransOral GAstroplasty

The TransOral GAstroplasty device (TOGA; Satiety Inc, Palo Alto, CA) is a flexible endoscopic stapler capable of full-thickness tissue apposition. The device comprises a stapler and a restrictor. The sleeve stapler comprises a handle and a long but flexible shaft. It also has a short rigid capsule with stapler assembly, two vacuum pods, and a septum at the end. An 8.6 mm endoscope can be passed through the device and retroflexed to visualize the procedure. The stapler creates a vertical sleeve approximately 8 cm long and 2 cm in diameter along the lesser curvature. The restrictor has a long flexible shaft and a short rigid capsule with stapler. It reduces the sleeve outlet to 10-15 mm in diameter. The procedure begins with dilation of the esophagus to 60F with a Savary dilator[9]. The device is inserted into the stomach over a guidewire. Once in position, vacuum apposes the gastric walls, acquiring tissue into the device. Firing the stapler creates a 4.5 cm sleeve around the stapler using titanium staples. The device has to be removed for reloading, and the firing process is repeated once more distally, overlapping the first sleeve. The restrictor is inserted over the guidewire, with the endoscope adjacent to the device. Vacuum acquires tissue into the device at the distal sleeve, and firing the restrictor creates a 2.5 cm long stapled narrowing at the outlet of the sleeve.

TOGA has been studied for endoscopic gastroplasty (Figure 2). A study of 21 patients (average BMI 43.3 kg/m^2) used the first-generation device[10]. There were no serious adverse events, although pain, nausea, vomiting, and temporary dysphagia were reported. Average 6-mo weight loss was 12 kg (24.4% EWL). Endoscopy at that

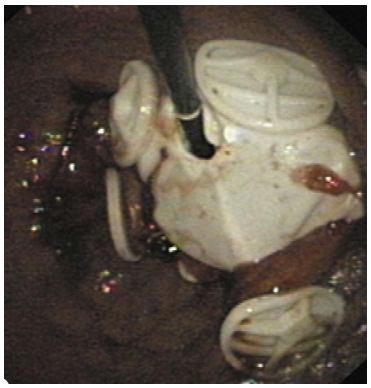

Figure 3 Transoral Endoscopic Restrictive Implant System restrictive diaphragm[14].

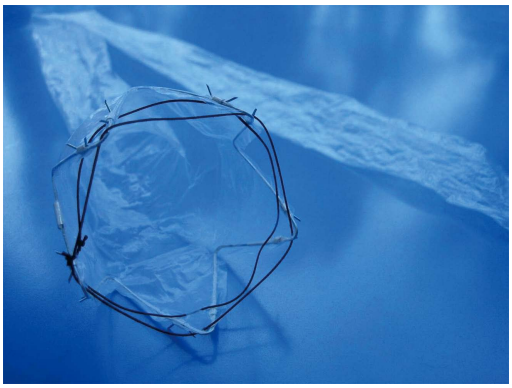

Figure 4 EndoBarrier duodenal-jejunal liner[16].

time found staple line gaps in 13 patients, although every patient had at least a partial sleeve. The second-generation device was studied in 11 patients[11]. In this study, additional distal restrictions were created during retreatment if necessary. No significant adverse events were reported. Six-month weight loss was an average 24.0 kg, and average BMI decreased from 41.6 to 33.1 kg/m^2. A multicenter study of 67 patients reported adverse events including respiratory insufficiency in one case and asymptomatic pneumoperitoneum in another[9]. At one year, patients with BMI $\geqslant$ 40 had 52.2% EWL and patients with BMI < 40 had 41.3% EWL. There were significant improvements in hemoglobin A1c (decline from 7.0% to 5.7%), HDL and triglycerides. A single-center study of 29 patients reported mean BMI decline from 41.7 kg/m^2 to 35.5 kg/m^2 over two years[12]. Average weight loss was 16.8 kg, or 14.9% total body weight loss.

ACE stapler

The ACE stapler (Boston Scientific Corporation, Natick, MA) is an endoscopic stapler with a head capable of both 360-degree rotation and complete retroflexion. A 5-mm endoscope enables visualization; the device is 16 mm in diameter. The stapler head acquires gastric tissue using vacuum suction; firing the stapler creates a full-thickness plication using a 10-mm plastic ring with 8 titanium staples. For gastric volume reduction, up to 8 plications are made in the fundus. Two plications are created in the antrum, which may delay gastric emptying. A prospective safety and feasibility study of gastric volume reduction in 17 patients (median BMI 40.2 kg/m^2) reported median procedure time of 123 min[13]. The most common adverse event was abdominal pain (7 patients); sore throat, diarrhea, nausea, constipation, and vomiting were also reported. All were self-limited. Median EWL was 34.9% (interquartile range 17.8-46.6). Endoscopy performed at 12 mo (in 11/17 patients) revealed 6-9 plications in all participants, as well as durability of gastric volume reduction.

Transoral Endoscopic Restrictive Implant System

Unlike the aforementioned devices, Transoral Endoscopic Restrictive Implant System (TERIS) (Barosense, Menlo Park, CA) is an implanted device. A gastric pouch is created by implanting a diaphragm with a 10-mm orifice. This is attached to the cardia (Figure 3). For implantation, a 22-mm endogastric tube is inserted. A gastroscope with a stapling device is retroflexed, and a full-thickness plication is created in the cardia. An anchor is attached to the plication. This is repeated until five anchors have been implanted. The restrictive diaphragm is then attached to the anchors. A study of TERIS in 13 patients reported three adverse events: One gastric perforation and two cases of pneumoperitoneum[14]. The procedure was modified after these events, and no further adverse events occurred. In total, 12 of 13 implantation procedures were successful. Procedure time was 142 min on average. Weight loss at three-month follow-up was 16.9 kg or 22.2% EWL; median BMI fell from 42.1 to 37.9 kg/m^2.

BYPASS DEVICES AND PROCEDURES

Bypass of the small intestine is thought to have a significant role in the weight loss and metabolic benefits experienced after certain bariatric surgeries. Animal models suggest that duodenal exclusion and accelerated arrival of partially-digested meals to mid-jejunum and ileum are partially responsible for the salutary effects of gastric bypass in diabetes and obesity. Endoscopically implanted devices have been developed to reproduce this effect.

EndoBarrier duodenal-jejunal bypass liner

The EndoBarrier duodenal-jejunal bypass device (GI Dynamics, Lexington, MA) comprises a nickel-titanium implant attached to a 60 cm polymer sleeve (Figure 4). The sleeve extends from the duodenal bulb into the jejunum. It prevents food from contacting the mucosa of the small intestine, but allows pancreaticobiliary secretions to move along the outside of the device to the jejunum. Additionally, it allows food to reach the mid-jejunum earlier. The device is placed endoscopically, with fluoroscopic guidance, under general anesthesia. A guidewire is advanced into the duodenum. The sleeve

and anchor are enclosed in a capsule, which is advanced over the guidewire. The sleeve is deployed in the intestine; once it is fully extended, the anchor is deployed in the duodenal bulb approximately 5 mm distal to the pylorus. Device removal is also performed under general anesthesia. A foreign body hood is placed at the tip of the endoscope, and the device is removed by securing the anchor with a procedure-specific grasping device.

A multicenter randomized trial compared 30 EndoBarrier patients (BMI 48.9 kg/m^2) with 11 controls (BMI 47.4 kg/m^2)[15]. No serious adverse events were reported. However, four of 30 EndoBarrier patients required removal due to migration, obstruction, pain, or anchor dislocation. The EndoBarrier group had significantly higher weight loss at three months, with BMI decrease of 5.5 kg/m^2 *vs* 1.9 kg/m^2 in control patients. Notably, 7 of 8 diabetics in the EndoBarrier group had improvement in diabetes.

A multicenter randomized trial including 25 patients reported successful EndoBarrier implantation in 21 patients, with implantation failure in patients with small duodenal bulb[16]. Adverse events resulted in device explantation in seven of 21 implanted patients, including three cases of bleeding that presented as hematemesis. There was significantly more weight loss in the EndoBarrier group: (8.2 ± 1.3 kg *vs* 2.0 ± 1.1 kg).

A randomized trial of 39 patients assigned 25 patients to EndoBarrier and 14 patients to the control group[17]. At 3 mo, the EndoBarrier group had 22% EWL *vs* 5% EWL in controls. The adverse event rate, including bleeding, migration, and obstruction, was 20%.

A multicenter randomized controlled trial including 77 patients with obesity and type Ⅱ diabetes included 31 patients who completed EndoBarrier therapy and 35 controls who completed dietary intervention[18]. The EndoBarrier group experienced 32.0% EWL *vs* 16.4% in the control group; the EndoBarrier group also had a significantly larger improvement in hemoglobin A1c (P < 0.05 for both). After the EndoBarrier had been removed for 6 mo, EWL was 19.8% *vs* 11.7% in controls (P < 0.05).

A one-year prospective open-label trial of 42 patients reported that 39 patients were successfully implanted[19]. Premature explantation was necessary in 15 patients due to anchor movement in 8 patients, device obstruction in 3 patients, abdominal pain in 2 patients, acute cholecystitis in 1 patient, and one patient request. Initial average BMI was 43.7 ± 5.9 kg/m^2. At 1 year, the 24 patients with EndoBarrier in place experienced weight loss of 22.1 ± 2.1 kg or 47.0% ± 4.4% EWL, and BMI decline of 9.1 ± 0.9 kg/m^2. Waist circumference decreased significantly, from 120.5 ± 6.8 cm to 96.0 ± 2.6 cm. Statistically significant improvements were also reported in blood pressure, hemoglobin A1c, cholesterol, low-density lipoprotein, triglycerides, and prevalence of metabolic syndrome.

A modified EndoBarrier with a 4-mm flow-restriction orifice was implanted in 10 patients with average BMI of 40.8 kg/m^2[20]. Eight of 10 patients in the trial developed abdominal pain, nausea, and vomiting; they required balloon dilation of the restrictive orifice. Weight loss at three months was 16.7 ± 1.4 kg.

SPACE-OCCUPYING DEVICES

Space-occupying devices displace volume and induce gastric distention, but may also alter gastrointestinal motility, nutrient transit, and hormone levels[21]. One space-occupying device, the intragastric balloon, was described in 1982 and approved for American use in 1985[22]. In the intervening decades, balloons have built a track record of safety and efficacy in Europe, and are likely to reappear in the United States. The intragastric balloon has found a role as a bridge to bariatric surgery in patients with high risk for anesthesia, temporary use in patients eligible for bariatric surgery but unwilling to undergo it, and temporary use in patients not eligible for bariatric surgery as part of an integrated medical weight loss program[23]. Space-occupying devices other than balloons are in clinical trials.

Orbera intragastric balloon

The Orbera (formerly BioEnterics) intragastric balloon (Apollo Endosurgery, Austin, TX) is an endoscopically implanted spherical silicone elastomer device. The balloon is placed in the stomach and then filled with saline (and where allowed, methylene blue dye, which alters urine color in case of balloon perforation). The balloon is resistant to gastric acid, and is indicated for insertion for up to six months. The device is inflated in the gastric fundus during endoscopic visualization using 500-750 mL saline and 10 mL methylene blue.

Orbera balloon placement was studied in a meta-analysis of 3698 patients[24]. Early device removal was required in 4.2% of patients; reported adverse events included nausea, vomiting, bowel obstruction (0.8%), and gastric perforation (0.1%). Average weight loss after six months was 14.7 kg or 32.1% EWL, with drop in BMI of 5.7 kg/m^2. The largest study in the meta-analysis, which included 2515 patients, reported average decrease in BMI of 9.0 kg/m^2 over six months[25]. Notably, statistically significant improvement was reported in blood pressure, fasting glucose, and lipid profile. Significant decrease in or normalization of hemoglobin A1c was reported in 87.2% of the 488 diabetic patients in the study. Two instances of mortality were reported, both in patients with prior gastric surgery.

The long-term weight loss trend after removal of the Orbera balloon was studied in 500 patients[26]. Average BMI before therapy was 43.7 kg/m^2. Success was defined as ⩾ 20% EWL. At the time of balloon removal, 83% of patients had reached this threshold, with average loss of 23.9 ± 9.1 kg and BMI loss of 8.3 kg/m^2. In the 41% of patients available five years after balloon removal, the successful group had average loss of 7.3 ± 5.4 kg and average BMI loss of 2.5 kg/m^2.

The effectiveness of a second Orbera balloon place-

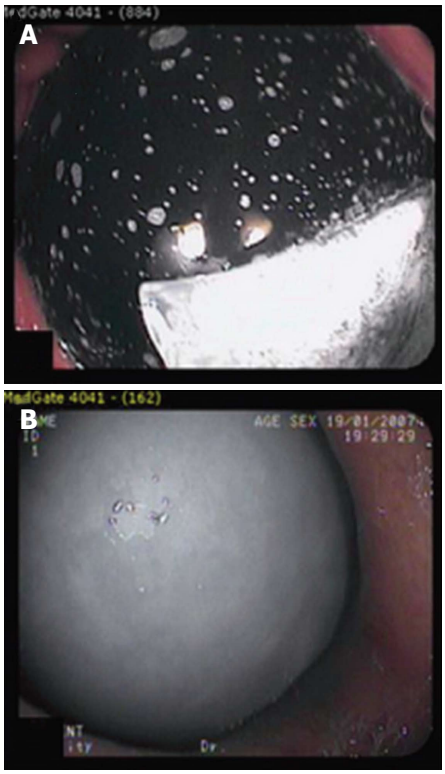

Figure 5 The Orbera intragastric balloon (A) and Heliosphere BAG (B)[34].

ment was studied in a prospective trial of 118 patients[27]. The balloon was replaced immediately in 8 patients, replaced after a balloon-free interval in 11 patients, and not replaced in 99 patients. Those patients undergoing a second balloon placement with a balloon-free interval regained 13.6 kg on average during that interval. The second balloon therapy did result in weight loss, although its magnitude was smaller than that of the initial therapy (9.0 kg *vs* 14.6 kg, or 18.2% EWL *vs* 49.3% EWL). The effect of second balloon placement dissipated by the third year of follow-up. A study of 112 patients undergoing a second Orbera balloon placement within one month of removing the first balloon found average BMI loss of 2.5 kg/m^2 with the second balloon in addition to BMI loss of 6.5 kg/m^2 with the first balloon[23].

The utility of the Orbera balloon as a bridge to gastric bypass was studied in 60 consecutive super-super obese subjects with average BMI of 66.5 ± 3.4 kg/m^2[28]. The balloon was placed in 23 patients, while 37 patients went to surgery without prior balloon therapy. In the Orbera group, the balloon was in place for 155 ± 62 d. The balloon group achieved BMI loss of 5.5 ± 1.3 kg/m^2 at the time of gastric bypass, as well as statistically significant decreases in systolic blood pressure and gamma-glutamyl transpeptidase. The operative time for performance of gastric bypass was shorter in the Orbera group (146 ± 47 *vs* 201 ± 81 min). The Orbera group also experienced significantly fewer major adverse events (defined as conversion to laparotomy, ICU stay longer than 2 d, and total hospital stay longer 2 wk): 2 events *vs* 13 in patients who did not have balloon placement. Weight loss was similar between groups one year after gastric bypass.

The metabolic effects of Orbera balloon placement were examined in a prospective trial including 130 patients (average BMI 43.1 kg/m^2)[29]. Premature balloon explantation was required in ten patients due to intolerance, abdominal pain, or vomiting. Patients were maintained on a 1000-1200 daily kilocalorie diet during the 6-mo balloon therapy period. Average weight loss was 13.1 kg, with decrease in prevalence of class Ⅳ obesity from 23% to 8%. Metabolic effects included decrease in the prevalence of hyperglycemia from 50% to 12%, and hypertriglyceridemia from 58% to 19%. Patients with decrease in BMI of greater than 3.5 kg/m^2 experienced a significant decrease in the prevalence of severe hepatic steatosis from 52% to 4%. Weight regain occurred in 50% of the patients in the follow-up period (median 22 mo) after balloon removal.

Dietary counseling during Orbera balloon therapy was been found to be beneficial in a study of 28 patients[30]. Patients saw a dietitian weekly for two weeks, every two weeks for one month, and then monthly while the balloon was in place. BMI declined from 32.4 ± 3.7 kg/m^2 to 28.5 ± 3.7 kg/m^2 with therapy. Of the patients who achieved at least 20% EWL, 85% had attended at least half of dietitian appointments. Of patients failing to reach 20% EWL, 75% had missed at least half of dietitian appointments.

Orbera balloon therapy is associated with mental health benefits in patients with depression[31]. In this study, 100 consecutive female patients were characterized as depressed (65 patients) or non-depressed (35 patients) using the Beck Depression Inventory score. Other characteristics were similar between groups. Weight loss was similar between groups (39.3% EWL in depressed patients *vs* 36.1% EWL in non-depressed patients). The Depression Inventory score improved from 20.3 ± 8.5 to 7.9 ± 5.6 during balloon therapy. Resolution of depression occurred in 70.8% of the depressed patients, with a decrease in the prevalence of severe depression (27.7% to 1.5%).

Heliosphere BAG

The Heliosphere BAG is filled with 950 mL of air rather than fluid. The Heliosphere BAG has been compared with the Orbera balloon (Figure 5)[32]. Sixty patients with average BMI of 46.3 kg/m^2 were randomly assigned. The Heliosphere group achieved BMI decrease of 4.2 kg/m^2, *vs* 5.7 kg/m^2 in the Orbera group. The Heliosphere group had significantly longer extraction procedure time and significantly more discomfort during extraction.

A prospective study of 91 patients compared the Orbera balloon (73 patients) with Heliosphere BAG (18 patients, mean BMI 45.2 kg/m^2)[33]. Balloons were implanted for six months, and 13.2% were removed early due to intolerance. Average weight reduction at six months was 13.3 kg, and BMI reduction was 5 kg/m^2; 88% of weight reduction occurred in the first three

months. Weight loss was similar between balloon types. The Heliosphere BAG deflated and passed spontaneously in 2 cases. Balloon extraction was difficult in 8 cases, and a rigid esophagoscope as required in 4 cases; laparoscopic surgery was required to remove BAG in 1 case. BAG was significantly more likely to result in retrieval complications.

A nonrandomized study compared Heliosphere BAG with the Orbera balloon in patients who failed six months of medical and dietary weight loss therapy[34]. The Orbera balloon was placed in 19 patients (BMI 45.6 ± 9 kg/m^2), and the Heliosphere BAG was placed in 13 patients (BMI 45.0 ± 8 kg/m^2). The Orbera balloon was more effective, with weight loss of 19.0 kg *vs* 13.0 kg for Heliosphere BAG. One patient with the Orbera balloon required removal for persistent nausea and vomiting at one month. There was one mortality in the Orbera group 13 d after placement.

Reshape Duo intragastric balloon

The Duo intragastric balloon (Reshape, San Clemente, CA) contains two silicone spheres filled with a total of 900 mL of saline, which prevents migration if one balloon deflates. A prospective trial of Duo included 30 patients at three centers (21 Duo *vs* 9 controls)[35]. Both groups received diet and exercise counseling. Four of the 21 Duo patients were readmitted for nausea, and two patients were found to have gastritis at the time of balloon removal. After 48 wk, 30% of the Duo patients achieved 25% EWL, *vs* 25% of the control patients.

Obalon intragastric balloon

The Obalon intragastric balloon (Obalon Therapeutics, Carlsbad, CA) is a 250-mL gas-filled balloon which is swallowed under fluoroscopic visualization rather than inserted endoscopically. The balloon is enclosed in a capsule. A catheter, which extends through the esophagus and outside the mouth, is used to fill the balloon with gas. The balloon is removed endoscopically; it is punctured and then grasped with forceps for extraction. If the balloon is tolerated and induces weight loss, a second balloon can be swallowed at 4 wk and a third balloon at 8 wk. A study including 17 patients with BMI ranging from 27 to 35 kg/m^2 reported that 98% of balloons were swallowed successfully[36]. Abdominal pain (in 76%) and nausea (in 41%) were the most frequent adverse events. All balloons were removed endoscopically, under conscious sedation, at 12 wk.

Transpyloric Shuttle

The Transpyloric Shuttle (BAROnova, Goleta, CA) is made of a large spherical bulb attached to a smaller cylindrical bulb by a flexible tether. The cylinder is small enough to enter the duodenal bulb with peristalsis, and pulls the spherical bulb to the pylorus. The spherical bulb is too large to traverse the pylorus, but occludes it intermittently to reduce gastric emptying. The device is delivered transorally *via* catheter and removed endoscopically. A single-center nonblinded prospective trial of 20 patients with average BMI of 36.0 kg/m^2 reported loss of 8.9 ± 5.2 kg, or 31.3% ± 15.7% EWL, at 3 mo[37]. Six-month weight loss was 14.6 ± 5.7 kg, or 50.0% ± 26.4% EWL. Two patients required early removal due to persistent ulcer.

SatiSphere

The SatiSphere (Endosphere, Columbus, OH) is made from a preformed memory wire with curled ends that conforms to the shape of the duodenum. The device anchors itself in the distal stomach and in the duodenum. Several mesh spheres are mounted along the wire. SatiSphere slows duodenal transit of food, which may alter satiety hormones levels and glucose metabolism. A trial of 31 patients with average BMI of 41.3 kg/m^2 compared 21 SatiSphere patients with 10 controls[38]. Device migration was reported in 10 of 21 implanted patients. Emergency surgery was necessary in two patients. Of patients completing the trial, three-month weight loss was 6.7 kg in the SatiSphere group *vs* 2.2 kg in controls. SatiSphere was associated with delayed glucose absorption, delayed insulin secretion, and altered glucagon-like peptide-1 kinetics.

ASPIRATION THERAPY

AspireAssist

The AspireAssist (Aspire Bariatrics, King of Prussia, PA) is a modified percutaneous endoscopic gastrostomy tube with an external accessory capable of aspirating a portion of ingested caloric intake. The device includes a large-bore gastrostomy tube with holes in the intragastric portion; this is attached to a skin port with a connector and valve placed at the skin (Figure 6). A 600-mL reservoir allows for flushing and aspiration of gastric contents after meals.

A randomized trial of 18 patients assigned 11 to AspireAssist and 7 to the control group; all patients underwent a 15-session diet and behavioral education program[39]. At one year, 10/11 Aspire patients and 4/7 control patients remained in the trial. Weight loss was 18.6% ± 2.3% of total body weight in Aspire patients *vs* 5.9% ± 5.0% in controls. Of the ten Aspire patients in the trial at one year, seven chose to continue for another year; this group reached 20.1% ± 3.5% total body weight loss. Notably, there was no evidence of increased food intake to compensate for the aspirated food. Reported adverse events included abdominal pain at the aspiration tube site, which improved after the device was redesigned; infection in three patients requiring topical medication or oral antibiotics; and persistent gastrocutaneous fistula (which eventually closed spontaneously) in one of the four patients who underwent aspiration tube removal. A prospective multicenter clinical trial, PATHWAY, is ongoing.

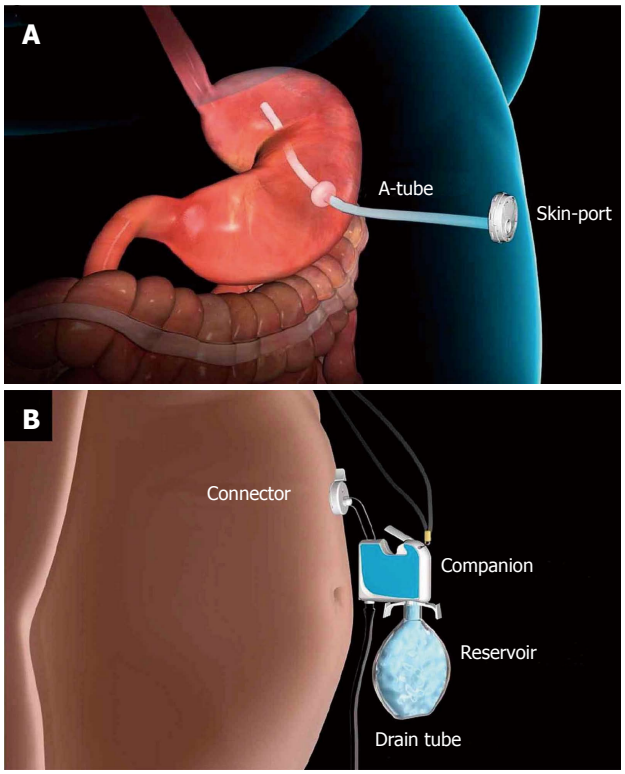

Figure 6 The Aspire aspiration tube (A) and AspireAssist (B)[39].

ENDOSCOPIC REVISION OF GASTRIC BYPASS

Roux-en-Y gastric bypass can induce 56.7%-66.5% EWL during the two years after surgery[40]. Comorbidities associated with obesity, including hypertension, diabetes, obstructive sleep apnea, and hyperlipidemia, often improve or resolve. It is postulated that small gastric pouch size and gastrojejunal anastomosis aperture create a restrictive effect. A weight plateau typically occurs as equilibrium in energy balance is reached 12 to 18 mo after gastric bypass[41]. However, approximately 20% of patients fail to achieve 50% EWL in the first year after gastric bypass. Additionally, 30% of patients regain weight by 18 to 24 mo after bypass; average regain of 18 kg has been reported at 2 years[42,43]. The long-term outcome of gastric bypass is affected by a number of factors, including preoperative BMI and postoperative diet and lifestyle[44]. Weight regain may be induced by neuroendocrine-metabolic dysregulation resulting in a starvation-like response[45,46]. Anatomic factors may also play a role: increased gastrojejunal anastomotic aperture may result in loss of restriction, and has been associated with weight regain in a linear fashion[5,47,48].

Surgical procedures, including reconstruction of the gastrojejunal anastomosis, placement of an adjustable gastric band over the gastric pouch, surgical revision of the pouch, and distal gastric bypass, are available to treat weight regain; however, few patients undergo surgical revision. Revision surgery is challenging in the context of older patients, altered anatomy, scarring, and adhesions; complication and mortality rates are higher than that of primary gastric bypass[49,50]. Endolumenal revision is an attractive option in this patient set. Endoscopic suturing, plication, and sclerotherapy are discussed here.

EndoCinch for transoral outlet reduction

The EndoCinch (Bard Davol, Murray Hill, NJ), as described above for endoscopic gastroplasty, is a superficial-thickness suturing device which uses suction to acquire tissue. The EndoCinch has been used to perform transoral outlet reduction (TORe), or endoscopic revision of gastric bypass. First, the entire gastric margin of the gastrojejunal anastomosis is ablated with argon plasma coagulation. The aperture of the gastrojejunal anastomosis is then reduced by placing interrupted stitches at the anastomotic margin, across the anastomotic opening. Cinching the sutures apposes the anastomotic margin, reducing the diameter of the anastomosis. The volume of the gastric pouch can be reduced by creating ridges and suturing them together.

Use of the EndoCinch for TORe was first reported in 2004[51]. The device was used in RESTORe, a randomized sham-controlled double-blinded multicenter trial which resulted in level 1 evidence for the effectiveness of endoscopic suturing in revision of gastric bypass[52]. Seventy-seven patients with gastrojejunal anastomosis aperture larger than 20 mm were randomized to TORe or to sham endoscopy. Average BMI was 47.6 kg/m^2. Anastomotic aperture of < 10 mm was achieved in 89% of TORe patients. There was no difference in the adverse event rate between groups, and no perforations occurred. In the intent-to-treat analysis, total body weight loss was 3.8% in TORe patients *vs* 0.3% in the sham group (P = 0.02). Weight stabilization or weight loss was achieved in 96% of TORe patients during the 6-mo follow-up period.

OverStitch for TORe

Apollo OverStitch, as described in detail above for endoscopic sleeve gastroplasty, is reloadable *in vivo* and is capable of placing full-thickness sutures in a variety of stitch patterns. After TORe is performed to reduce the aperture of the gastrojejunal anastomosis, gastric pouch size can be reduced and fistulas can be closed during the procedure. TORe should be performed using general anesthesia, endotracheal intubation, and carbon dioxide insufflation. An overtube should be placed. Upper endoscopy is performed to ablate the margin of the gastrojejunal anastomosis. This can be performed using end-firing argon plasma coagulation (at 30 watts) to create a ring 5-10 mm thick around the margin of the anastomosis, or performance of endoscopic mucosal resection around the anastomosis. Anastomotic reduction can be performed using an interrupted technique, in which stitches are placed across the anastomosis and then cinched to appose its margins. Alternatively, a pursestring suture technique can be used (Figure 7). The pursestring technique potentially confers a number of benefits compared with the interrupted technique. It

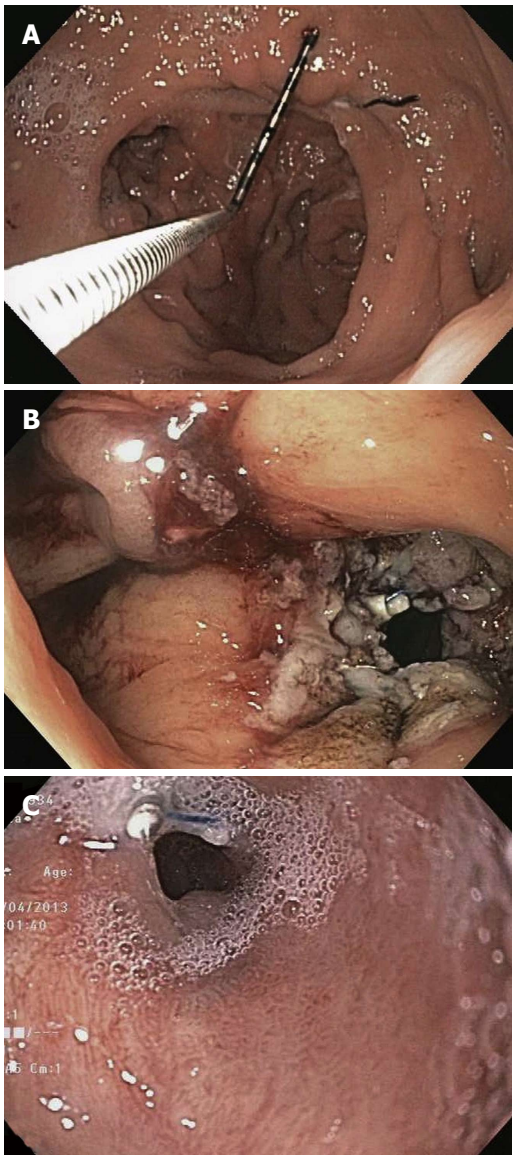

Figure 7 Gastrojejunal anastomosis before (A), immediately after (B), and six months after (C) TORe using Apollo OverStitch[54].

allows the use of a sizing balloon, which ensures precise control of final anastomosis aperture. It reinforces the entire circumference of the anastomosis against future dilation, and against transient compliant dilation during meals. In contrast, the interrupted technique closes part of the lumen entirely, but does not reinforce the remaining anastomotic margin, and the final anastomotic diameter cannot be precisely controlled. To perform anastomotic reduction using the pursestring technique, a running pursestring suture is placed around the anastomosis. A controlled radial expansion balloon is passed through the second channel of the endoscope and inflated to 8-10 mm. The pursestring is tightened around the balloon, and the suture is cinched. A second pursestring can be placed around the anastomosis for reinforcement.

Endoscopic revision of gastric bypass using OverStitch proved effective in a study of 25 patients[53]. Gastrojejunal anastomosis aperture was reduced from 26.4 mm to 6 mm on average. No significant adverse events were reported. Patients lost an average 11.7 kg during the 6-mo follow-up period, or 69.5% of regained weight. Endoscopic revision of gastric bypass using the superficial-thickness EndoCinch and full-thickness OverStitch were directly compared in a matched cohort study[54]. The interrupted stitch technique was used in both groups, and the technique used in the EndoCinch patients was the same technique used in the RESTORe trial. One hundred eighteen patients (59 in each group) were sequentially matched by gastrojejunal anastomosis aperture, then BMI, and then age. Average weight loss at six months was significantly higher in patients undergoing full-thickness suturing (4.4 ± 0.8 kg with EndoCinch *vs* 10.6 ± 1.8 kg with OverStitch, $P < 0.01$). One-year weight loss was also significantly higher in the OverStitch group (2.9 ± 1.0 kg with EndoCinch *vs* 8.6 ± 2.5 kg with OverStitch, $P < 0.01$).

IOP for Revision Obesity Surgery Endolumenal

The IOP (USGI Medical, San Clemente, CA), as described in detail above for the POSE procedure, is capable of performing full-thickness tissue plication by placement of tissue anchors. The platform has been optimized specifically for endoscopic revision of gastric bypass, called Revision Obesity Surgery Endolumenal (ROSE). ROSE entails reduction of dilated gastric pouch and gastrojejunal anastomosis aperture. A prospective study included 20 patients with weight regain[55]. The procedure was technically successful in 85%, with reduction of anastomotic aperture by an average of 65% and reduction of gastric pouch length by 36%. Anastomotic aperture was reduced to an average of 16 mm. Average weight loss was 8.8 kg after 3 mo. A subsequent iteration of the device was studied in five patients, with all five patients losing weight (average weight loss was 7.8 kg)[56]. A prospective multicenter trial of 116 patients with dilated gastrojejunal anastomosis and gastric pouch achieved technical success in 97%[57]. Gastrojejunal anastomosis aperture was reduced by an average of 50%, and the gastric pouch was shortened by an average of 44%. No significant procedural complications occurred; three patients had superficial esophageal tears, one of which required placement of an endoscopic clip. Pharyngitis was reported in 41% of patients, nausea and vomiting in 12%, and abdominal pain in 11%. During the 6-mo follow-up period, patients lost 32% of the weight regained after Roux-en-Y gastric bypass. Patients with anastomotic aperture of less than 10 mm at the end of the procedure experienced 24% EWL. The device has since been further optimized for revision of gastric bypass.

StomaphyX

StomaphyX (EndoGastric Solutions, Redmond, Washington) is a full-thickness tissue plication platform capable of endoscopic revision of gastric bypass. It uses vacuum to acquire a fold of the gastric pouch.

Polypropylene H-fasteners are passed through the tissue to create full-thickness plications. Without removal of the device, 3 to 4 rows with 4 to 6 plications each (a total of 12-24) are created circumferentially around the margin of the anastomosis.

A study of StomaphyX in 39 patients with average BMI of 39.8 kg/m^2 reported no adverse events[58]. EWL was 13.1% after 3 mo and 19.5% after 1 year. A subsequent study of 64 patients with average BMI of 39.5 kg/m^2 reported placement of an average 23 plications, resulting in reduction of anastomotic diameter from 22 mm to 9 mm[59]. One patient had bleeding that did not require transfusion; no other significant adverse events were reported. During follow up (average 5.8 mo), patients lost an average 7.6 kg. A retrospective study of 59 patients with mean BMI of 36.1 kg/m^2 reported mean weight loss of 3.8 kg and 11.5% EWL after 6 mo[60]. However, endoscopy in 12 patients at an average of 18 mo after revision showed no sustained reduction in pouch or anastomosis size. Mean follow-up duration was 41 mo, with average loss of 1.7 kg; 35.8% of patients had actually gained weight by this point. A randomized sham-controlled single-blind trial of StomaphyX revision with SerosFuse fasteners was terminated prematurely due to failure to reach preliminary efficacy targets. There was one adverse event in the StomaphyX group, and laparoscopic exploration and repair were necessary. A total of 45 StomaphyX patients and 29 sham patients completed 1-year follow-up. Of these, 22.2% of the StomaphyX patients and 3.4% of the sham patients achieved 15% excess BMI loss ($P < 0.01$). The StomaphyX group had significantly more weight loss at 6 and 12 mo ($P \leqslant 0.05$).

Endoscopic sclerotherapy

Endoscopic sclerotherapy entails injection of a sclerosant, such as sodium morrhuate, around the gastrojejunal anastomosis to reduce compliance and aperture. The procedure can be performed under conscious sedation in many patients. The anastomotic aperture should be measured prior to injection, as measurement afterwards will be inaccurate due to transient edema. A test dose of the sclerosing agent should be injected at the rim of the anastomosis, and the patient should be monitored for an adverse reaction before further injection. Approximately 2 mL should be injected into the submucosa at the margin of the gastrojejunal anastomosis until a bleb forms. Several such injections are performed around the anastomotic margin, for a total of 10-25 mL[61]. Overinjection is indicated by dark red or black discoloration and subsequent overt bleeding. Intravenous ciprofloxacin should be given as prophylaxis prior to the procedure, followed by a five-day course of liquid ciprofloxacin or trimethoprim-sulfamethoxazole. The patient should can start a liquid diet the day after the procedure and advance to a regular diet during the month after the procedure. Sclerotherapy can be repeated every 3-6 mo until the anastomosis aperture has reached a target of 12 mm; two or three sessions are often necessary[62]. The development of scar tissue after each sclerotherapy session can eventually make submucosal injection difficult.

Endoscopic sclerotherapy has proven effective in arresting weight regain after gastric bypass. One study including 28 patients reported that most patients (64%) lost more than 75% of regained weight[62]. An average of 2.3 sessions was required. Notably, patients with anastomotic aperture larger than 15 mm did not benefit. A study of 32 patients reported arrest or reversal of weight regain in 91.6% of patients at 1 year[61]. A study of 71 patients reported arrest or reversal of weight regain in 72% of patients after 1 year[63]. A recent study of 48 patients undergoing sclerotherapy reported average loss of 1.45 kg during a follow-up period averaging 22 mo[64]. Although weight regain was arrested, weight loss after sclerotherapy was not significant. The largest published series included 231 consecutive patients with mean anastomosis diameter of 19 mm undergoing 575 sclerotherapy sessions[65]. Weight regain was arrested in 78% of patients at one year after sclerotherapy. Average weight loss at six months was 4.5 kg. Bleeding occurred in 2.4%, with 57% of those requiring endoscopic clip placement. Transient elevation in blood pressure was observed in 15%, and was associated with higher injection volume. Small ulcerations were found on follow-up endoscopy in 1%.

CONCLUSION

The global obesity epidemic has continued to expand despite the availability of diet and lifestyle counseling, pharmacologic therapy, and bariatric surgery. Endoscopic therapies for weight loss have the potential to transform the treatment of obesity. Given the variety of devices under development, in clinical trials, and in use, patients will have multiple options with greater efficacy than medical therapy, and with lower invasiveness and greater accessibility than bariatric surgery. Endoscopic therapies have also proven safe and effective for revision of bariatric surgery. As data for safety, efficacy, and cost effectiveness of endoscopic therapies accumulates over the coming years, endoscopists will play a leading role in the management of obesity and metabolic disease.

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REVIEW

Serrated polyps of the colon and rectum: Endoscopic features including image enhanced endoscopy

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Abstract

In this review, I outline the characteristic endoscopic findings of serrated lesions of the colorectum based on image enhanced endoscopy (IEE). Histopathologically, lesions with serrated structures are typically classified into the following three types based: hyperplastic polyps (HPs), traditional serrated adenomas (TSAs), and sessile serrated adenoma/polyps (SSA/Ps). Both HP and SSA/P often present as dark-green colors on auto fluorescence imaging (AFI) colonoscopy that are similar to the normal surrounding mucosa. In contrast, TSAs often have elevated shapes and present as magenta colors that are similar to the tubular adenomas. The superficial type of TSA also includes many lesions that present as magenta colors. When SSA/Ps are associated with cytological dysplasia, many lesions present with magenta colors, whereas lesions that are not associated with cytological dysplasia present with dark-green colors. When observed *via* narrow band imaging (NBI), many SSA/P include lesions with strong mucous adhesions. Because these lesions are observed with reddish mucous adhesions, we refer to them as "red cap sign" and place such signs among the typical findings of SSA/P. Because the dilatation of the pit in SSA/P is observed as a round/oval black dot on magnified observations, we refer to this finding as Ⅱ-dilatation pit (Ⅱ-D pit) and also positioned it as a characteristic finding of SSA/P. In contrast, dilatations of the capillary vessels surrounding the glands, such as those that occur in tubular adenoma, are not considered to be useful for differentiating HPs from SSA/Ps. However, in cases in which SSA/P is associated with cytological dysplasia, the dilatation of capillary vessels is observed in the same area. When submucosal layer invasion occurs in the same area, the blood flow presents with irregularities that are similar to those of common colorectal cancer at an early stage and disappears as the invasion proceeds deeply. The surface pattern of invasive cancer that is observed at the tumor surface is also likely to disappear. Based on the above results, we considered that the differentiations between HP and TSA, between TSA and SSA/P, and between HP and SSA/P might become easier due to the concomitant use of white light observation and IEE. We

also concluded that AFI and NBI can be useful modalities for SSA/P lesions associated with cytological dysplasia.

Key words: Image enhanced endoscopy; Hyperplastic polyp; Early colon cancer; Traditional serrated adenoma; Sessile serrated adenoma/polyp

Core tip: Histopathologically, "serrated lesions" are categorized by the World Health Organization into three groups: (1) hyperplastic polyp; (2) traditional serrated adenoma; and (3) sessile serrated adenoma/polyp (SSA/P). I have discussed the findings associated with each lesion type as observed on image enhanced endoscopy. Regarding HPs and SSA/Ps, it is easy to differentiate both lesions. Especially, dilatations of the gland orifices are frequently observed in SSA/P and appear as blackish dotted orifices. And a thick mucous adhesion referred to as a "mucous cap" can be confirmed as red mucus on narrow band imaging observation and can be recognized when it adheres to the surface of a "red cap" polyp in SSA/P.

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INTRODUCTION

Among colon polyps, hyperplastic polyps (HPs) have previously been defined as non-neoplastic lesions and are not considered to be lesions that are indicated for endoscopic treatment[1]. However, since the mid-1980's, reports on HP lesions associated with neoplastic changes have become more common[2,3] and it has been suggested in 1990 that the serrated lesions that are associated with neoplastic changes be referred to as serrated adenomas[4] to differentiate them from HPs. Later, in 2003, there was a report of a lesion with a gland structure that was an extremely similar to that of HP, and this lesion invaded into the submucosal layer (SM) primarily in the right colon[5].

Therefore, several guidelines for colon polyps have been published regarding the indications for the endoscopic treatment of sessile serrated lesion in the past several years[6-9]. However, the details of the endoscopic characteristics of sessile serrated lesions (SSLs) have obviously never been described in terms of guidelines. Particularly, the macroscopic appearances of SSLs present as flat elevations in the proximal colon, and it has been suggested that proximal serrated lesions, which can be more difficult to find than lesions in the distal portion due to the fold, might have an important role in this limitation[10-13]. Thus, Butterly *et al*[14] recommended that more time should be taken to withdraw to enable the detection of SSLs in the proximal colon.

Here, we would like to illustrate the characteristic endoscopic findings from these serrated lesions of the colorectum, particularly as observed with image enhanced endoscopy (IEE). These endoscopic images are observed with a Lucera Elite system® (Olympus Medical Science, Tokyo Japan).

ENDOSCOPIC FEATURES WITH PATHOLOGICAL FINDINGS

Histopathologically, "serrated polyps" can be categorized into the following three types according to the World Health Organization (WHO) classification[15] (Table 1): (1) HPs; (2) traditional serrated adenomas (TSAs); and (3) sessile serrated adenoma/polyps (SSA/Ps). All of these lesions have serrated structures within the crypts from the histological perspective: however, the extent to which these tissue diagnostic standards have become widespread and commonly understood among gastroenterological pathologists across the world remain unclear[16]. Especially, the definition of all sessile serrated adenomas and sessile serrated polyps are not as neoplastic changed lesions despite of the usage of "adenoma". Therefore there is a strong possibility to confuse whether neoplastic or non-neoplastic lesions for SSA/Ps.

Here, the conventional endoscopic features, including those from magnified examinations, related to SSLs are reviewed based on previous reports[9,17-19].

HP (Figure 1)

HPs can be categorized into the following three subtypes based on histological findings: (1) microvesicular HPs: MVHPs (Figure 1A); (2) goblet-cell rich HPs: GCHPs (Figure 1B); and (3) mucin-poor HPs: MPHPs (Figure 1C). Of these, MVHPs are thought to often be found often in the right side of the colon, and GCHPs are often found in the left side of the colon. The incidence of MPHPs is low[20-23]. All of these lesions are small in diameter and treated as non-neoplastic lesions[24].

The characteristic endoscopic findings of these HPs are that they generally present with pale colors and the boundaries with the normal surrounding mucosa are occasionally obscure. Adhesions of the mucus are also commonly observed on the surface. Large tumors are often found in the right side of the colon and differentiation between the above-mentioned MVHPs and SSA/Ps can be necessary. HPs characteristically presents with primarily asteroid shaped pits (type Ⅱ pits) on magnifying endoscopy (ME).

SSA/P (Figures 2-4)

Prior to the proposal of a definition of SSA/Ps based on pathological criteria, SSA/Ps were termed "large HPs[25]", "giant HPs[26]", *etc.* Therefore, these sessile serrated lesions thought to be defined as a single entity.

SSA/Ps are primarily located in the right side of the colon and account for 3%-9% of all of the colorectal

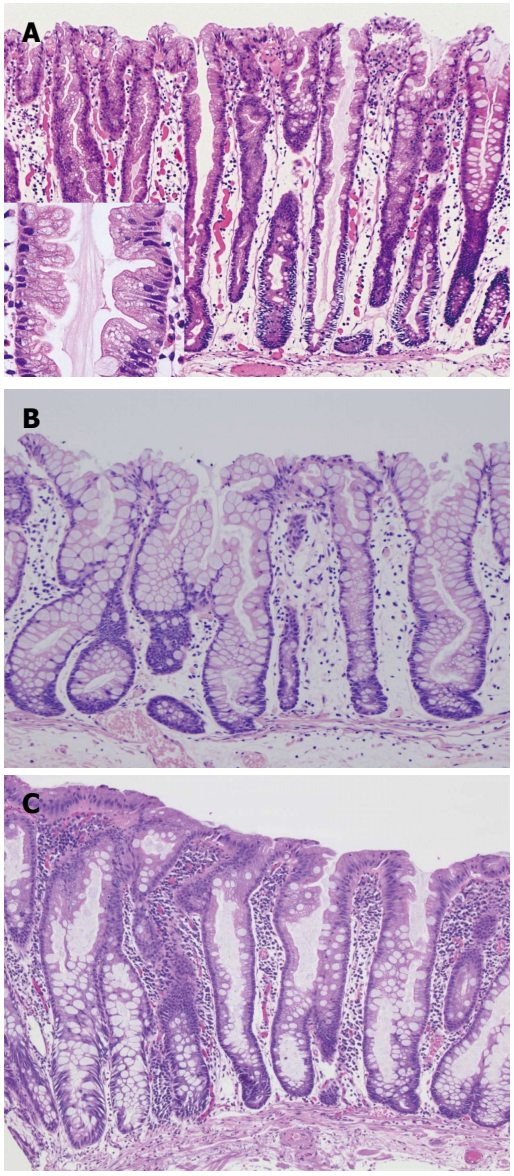


Figure 1 Histological findings of hyperplastic polyps. A: Microvesicular hyperplastic polyp (MVHP): The crypts and surface epithelium showing a serrated appearance with micro-goblet cells increased. High power view is shown at left side bottom. Many small droplet (microvesicular) mucin within the cytoplasm at the epithelial layer is specific findings as shown the picture; B: Goblet-cell rich HP: In contrast to MVHP, this type polyp is showing a much less serrated appearance inside the surface epithelium of crypts. And showing a preponderance of goblet cells without microvesicular mucin; C: Mucin-poor HP (MPHP): MPHP is rare, and little is known about their molecular features and natural history. The histological features are showing no cytoplasmic mucin with a luminal serration pattern. And also showing increased nuclear atypia without pseudostratification.

polyps[10,15,21,23,27]. The most important histological findings of SSA/Ps are characterized by the shapes of the growth pattern within the serrated glands as follows: (1) crypt dilatation; (2) irregularly branching crypts; and (3) horizontally arranged crypts in the basal portion that have boot-like shapes (*i.e.*, inverted T- and/or L-shaped crypts) (Figure 2H and I, 3H, 4J)[5,15,28-30].

The histological characteristics of SSA/Ps can be differentiated from those of HPs based on the histological criteria advocated by the WHO. SSA/Ps are also sub-

Table 1 Classification of serrated lesion World Health Organization (2010)

Hyperplastic polyp
Microvesicular hyperplastic polyp
Goblet cell rich hyperplastic polyp
Mucin poor
Sessile serrated adenoma/polyp
Without cytological dysplasia
With cytological dysplasia
Traditional serrated adenoma

categorized into the following two types based on cellular dysplasia (Table 1); *i.e.*, those without and with cytological dysplasia (Figures 2-4). As shown in the Figure 3 and 4, SSA/Ps with cytological dysplasia comprise two types of lesion; the first is confined within the mucosa (Figure 3), and the second invades further into the SM layer (Figure 4).

Conventional SSA/P endoscopic findings have revealed superficial types of lesions with a pale color that is similar to that of HPs. Notably, the characteristic tumor sizes of such lesions are greater than 10 mm and these lesions adhered with a yellowish thick mucus. Some studies have termed this mucus a "mucous cap"[19,31,32]. When observed with crystal violet staining under magnification, the orifices can be seen to be widely opened and are referred to as Ⅱ-open pit[19,32,33]. However, these findings are often also found in associated with HPs and thus not suitable for differentiation at present.

Traditional serrated adenoma (Figure 5)

Traditional serrated adenoma (TSA) is an additional name for "serrated adenoma" that was previously advocated and is currently user to differentiate TSAs from SSA/Ps as further discussed below. Although this type of lesions is primarily observed on left side of the colon[17,18] and these lesions are primarily of the protruded type (Figure 5), there are also some superficial types of lesion. The characteristic pathological findings as a serrated adenoma are the following: (1) the presence of goblet cell; (2) upper zone mitoses; (3) prominent of nucleoli; and (4) the absence of a thickened collagen table[4]. Based on the above observations, the characteristic pathological findings of SSA/Ps are not observed among the above-mentioned four findings.

The characteristic endoscopic findings of TSAs reveal that the protruded type is composed of enhanced-reddish villous lesions that are often associated with a type Ⅱ pit pattern at the base[17]. The macroscopic gross type is characterized as "pine cone-shaped" or "coral-shaped" *via* conventional observation[34]. Magnifying endoscopic findings also reveal that the type Ⅳ pit pattern is often present and that differentiation from traditional adenomas is easy. In contrast, differentiation of superficial type lesions from SSA/Ps based on endoscopy is considered difficult due to the similar pit patterns. Some endoscopists have used the terms types ⅢH and ⅣH pits or type Ⅳ-serrated pit pattern to differentiate

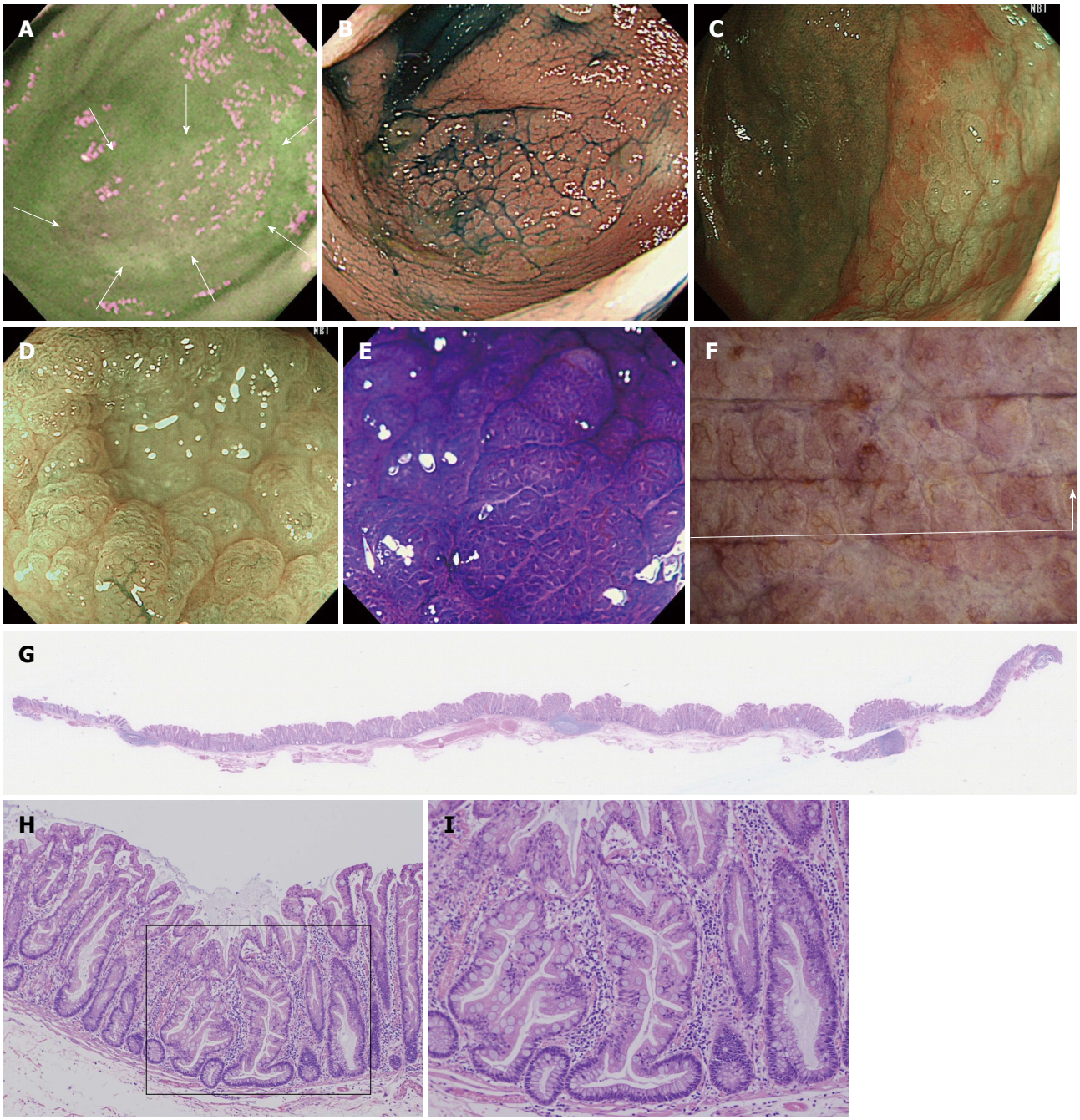


Figure 2 A case of sessile serrated adenoma/polyp without cytological dysplasia (scope: CF: FH260AZI). A: AFI imaging. The flat elevated polyp is approximately 37 mm in diameter as is located in cecum. No change to magenta of the tumor relative to the surrounding normal mucosa can be observed (inside white arrows); B: Indigocarmine spraying endoscopic finding. The structure of the granular surface is clearly revealed by chromoendoscopy; C: NBI observation, non-magnified. A red cap is covering the surface of the tumor; D: NBI observation, magnified. Small black dots can be observed in the tumor. This finding indicates that this tumor possesses the characteristic of SSA/P; E: Crystal violet staining under magnified observation. Type Ⅱ open pits (Ⅱ-O pits) containing T normal type Ⅱ pits are shown in the tumor; F: Stereoscopic finding. The tumor was excised by the ESD method. The tumor was cut into12 pieces; G: HE staining, whole specimen findings from section #4; H: Low power view of the HE staining findings. The tumor contains serrated glands in the mucosal layer; I: High power view of the HE staining findings. Typical histological findings for SSA/P. The crypt exhibits an "inverted T" type. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp; AFI: Auto fluorescence imaging.

conventional villous adenomas (Figure 4E and F)[18,19,33,34].

ENDOSCOPIC FEATURES ON IEE

According to the endoscopic imaging-object-oriented classification[35,36], IEE can be classified into three major categories: auto fluorescence imaging (AFI); narrow band imaging (NBI); and infra-red imaging. In this review, I will describe the characteristic endoscopic findings of AFI and NBI observations in details.

HP

Most of HPs are visualized as dark-green colors on AFI that are similar to the normal surrounding mucosa. We

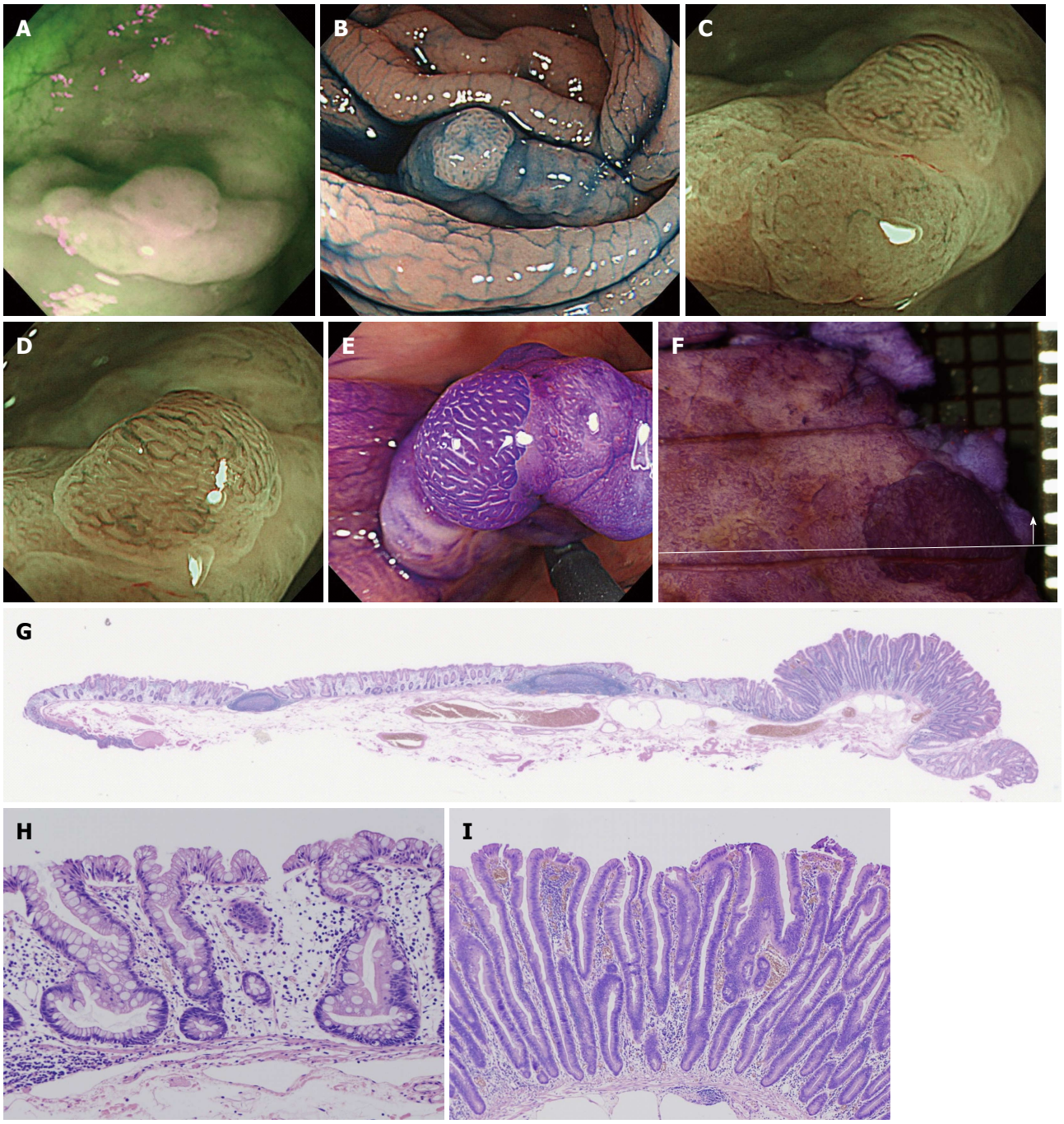
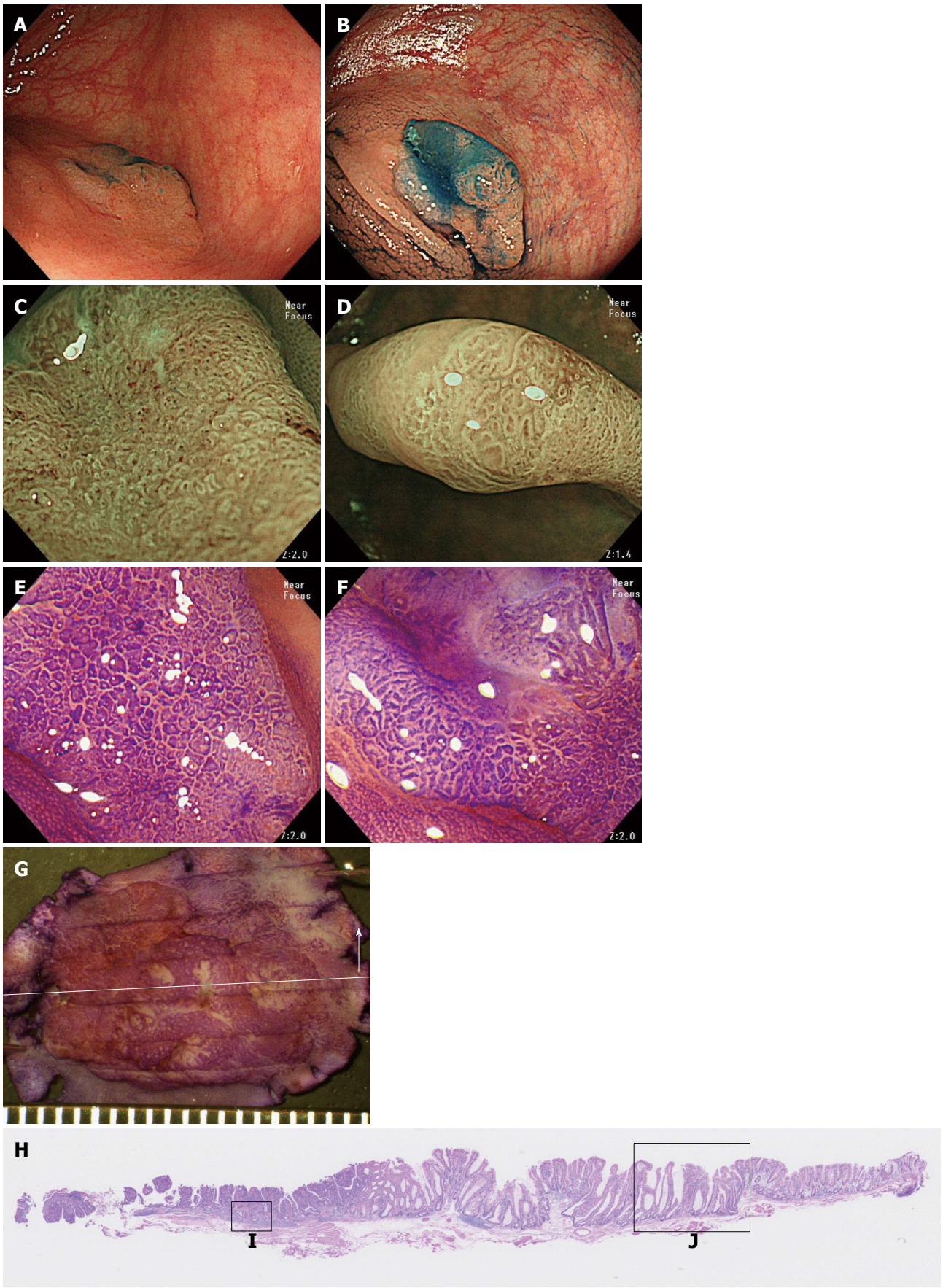


Figure 3 A case of sessile serrated adenoma/polyp with cytological dysplasia (scope: CF: FH260AZI). A: AFI imaging. The polyp is shown as a flat elevated lesion with a small nodule and is located in the ascending colon. A slightly change to a magenta color can be seen localized to a small elevated lesion in the tumor; B: Indigocarmine spraying endoscopic finding. The small elevated nodule in the tumor can be seen observed following dye spraying; C: Magnified NBI observation. In the tumor lesion, whitish mucosa with II-D pits can be observed. The microcapillary vessels are not dilated in the tumor; D: Magnified NBI observation. In contrast, the microcapillary vessels are dilated surrounding the tumor pits at the small elevated nodule. Moreover, a III$_L$ pit (white line) can be indirectly observed; E: Magnified crystal violet staining observation. Type II open pits (II-O pits) containing normal type II pits are shown in the tumor; F: Stereoscopic finding. The tumor was excised by the ESD method. The tumor was cut eight pieces; G: HE staining, whole specimen findings from section #4 including a small nodule; H: High power view of the HE staining finding. A part of an SSA/P is shown in the picture; I: High power view of the HE staining finding. The small elevated lesion is shown as a neoplastic change. Low grade cytologic dysplasia is present with nuclear hyperchromasia and pseudostratification. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp; AFI: Auto fluorescence imaging.

have previously reported that HPs can also be observed to exhibit dark-green colors[36,37]. Unlike neoplastic lesions, dilatation of the capillary vessels surrounding the glands cannot be observed *via* NBI magnifying endoscopy (NBI-ME)[38-42], and the type Ⅱ pit pattern can be indirectly observed. Basically, as visualized by IEE, HPs appear to be similar to the normal colon mucosa.

SSA/P (Figure 6)

Currently, satisfactory analysis based on AFI has not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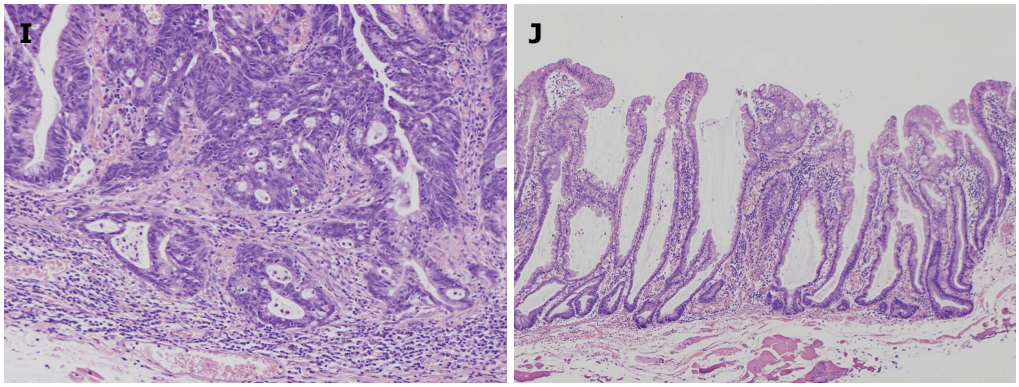

Figure 4 A case of an sessile serrated adenoma/polyp that has invaded the submucosal layer (scope: CF: HQ290I). A: Conventional white light observation. A flat elevated polyp of approximately 20 mm with a reddish depressed area can be observed in the ascending colon; B: Indigocarmine spraying endoscopic finding. Chromoendoscopy revealed this lesion, which is clearly composed of lesions. One edge area is covered with thick mucus; C: Magnified NBI observation. Firmly attached mucus can be observed on the tumor. A II-D pit that is indicative are markedly dilated crypts can be seen in this area; D: Magnified NBI observation. A granular surface pattern with dilated microcapillary vessels can be observed on this tumor in the absence of a thick mucous adhesion; E and F: Magnified crystal violet staining observation; G: Stereoscopic finding. The tumor was excised by the EMR method. The tumor was cut into seven pieces; H: HE staining, whole specimen finding from #4; I: High power view of the HE staining. The neoplastic glands have invaded into the SM layer to a depth of approximately 400 μm. The glands exhibit high grade dysplastic change; J: Low power view of the HE staining. This polyp is composed of SSA/P glands with markedly dilated crypts. NBI: Narrow band imaging; SSA/P: Sessile serrated adenoma/polyp.

been achieved[43,44]. However, in a single study from our group, we identified substantial difference between SSA/Ps with and without cytological dysplasia based on further prospective study prior to resection.

Specifically, the frequency with which the color changed to magenta color in SSA/Ps with dysplasia was higher than that of the SSA/Ps without dysplasia (Figures 2A and 3A). Moreover, the frequency of color changes among SSA/Ps is also higher than that among HPs[43]. Specifically, highly dysplastic lesions were strongly visualized. In contrast, 26 out of 46 SSA/P lesions (56.5%) presented with dark-green colors. Additionally, 17 out of 25 HP lesions (68.0%) presented with dark-green colors. Based on the above results, AFI observations can be considered useful for diagnoses in terms of whether SSA/Ps are associated with neoplastic changes.

When the above-mentioned "mucous cap" is observed on NBI, the bile is visualized in a red color tone; therefore, we reported this observation as the "red cap sign" (Figure 6A) and considered it to be useful in the differentiation of SSA/Ps. Additionally, because the orifices of the glands are frequently found to be wide open on magnified NBI observation, such orifices are referred to as type Ⅱ dilatation pits (Ⅱ-D pits) to differentiate them from Ⅱ-open pits[19,33] (Figure 6B).

Also in this study, Ⅱ-D pits were observed in 37 of 46 SSA/Ps without dysplasia lesions (80.4%), and HPs were found in approximately half of the lesions (7/25, 28.0%). Regarding SSA/Ps with dysplasia, only 4 of the 15 lesions presented type Ⅱ pits or Ⅱ-D pits, and 11 of these lesions presented with type Ⅲ to Ⅴ pits (Figure 4D). Based on the above results, differentiation can be considered to the possible based on observation of magenta color on AFI and the neoplastic pit pattern (with the exception of type Ⅱ pits) on magnified NBI observations when SSA/Ps are mixed with neoplastic changes.

Additionally, one, study has also reported that the presence of varicose microvascular vessels is useful for the differentiation of HPs based on magnified NBI observations of SSA/P lesions[45]. Unlike the blood vessels around the glands of the superficial mucosal layer, this finding is characterized by the observation of blood vessels running throughout the deep mucosal layer.

Dilatations and irregularities of the capillary vessels that are similar to those that develop from conventional adenomas are observed in polyp sites of SSA/Ps with dysplasia, but the disappearance of blood vessels and the superficial structures have been confirmed in invasive lesions that are deep into the SM layer (Figure 4D).

TSA (*Figure 5*)

Unlike HPs, TSAs can be visualized as magenta colors when observed on AFI, and this change is indicative of a neoplastic lesion. Protruded type TSAs primarily present with villous structures[17,18] and can be visualized as a color that is a mix of magenta and dark-green (Figure 5A). In contrast, superficial type TSAs can be identified although the intensity of the visualization of the magenta color varies depending on the degree of histological dysplasia.

In contrast, lesions that present with red color under white light observation can be observed to exhibit brownish color on NBI. Regarding the protruded type, the orifices of the glands and the interstitial capillaries can be observed in whitish and in blackish-brown color, respectively, on NBI magnifying observations; thus, their appearances are similar to those of normal villous tumors (Figure 5D). The superficial type of TSA can also be indirectly observed to exhibit a relatively villous

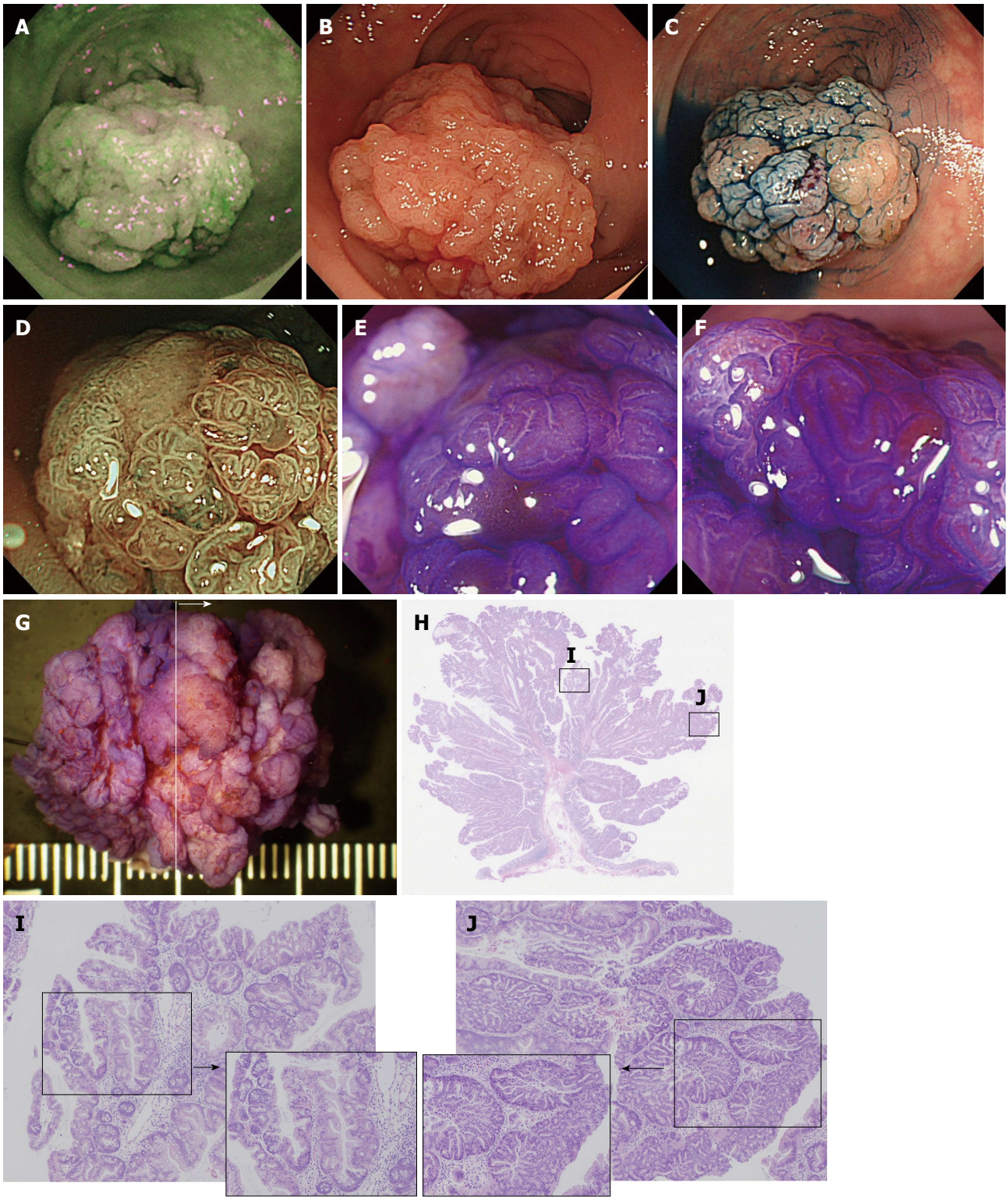

Figure 5 A case of a traditional serrated adenoma with conventional dysplasia (scope: CF: FH260AZI). A: AFI imaging. A dark green tone that is nearly the same as the surrounding normal colon mucosa can be observed in the tumor; B: Conventional white light observation. A large (approximately 30 mm) semipedunculated polyp exhibiting a slightly reddish change can be observed at the rect-sigmoid junction. There are no findings suggestive of submucosal invasion of the cancer; C: Indigocarmine spraying endoscopic findings. The structure of the nodular surface pattern is clearly revealed; D: NBI observation, magnified. A granular surface pattern with dilated microcapillary vessels can be observed in the tumor; E and F: Magnified crystal violet staining with observation. A type III_{H} or IV_{H} pit pattern is shown in the tumor; G: Stereoscopic finding. The tumor was excised by the EMR method. The tumor was cut into 4 pieces; H: HE staining, whole specimen finding from section #2; I: Histological findings from the HE staining. The tumor contains serrated glands in the mucosal layer. Dysplastic change is not observed; J: Histological findings of the HE staining. At several points, TSAs with conventional epithelial dysplasia exhibiting enlarged crowding and pseudostratification of the nuclei with crypt structure dysplastic changes can be observed. TSA: Traditional serrated adenoma; NBI: Narrow band imaging; AFI: Auto fluorescence imaging.

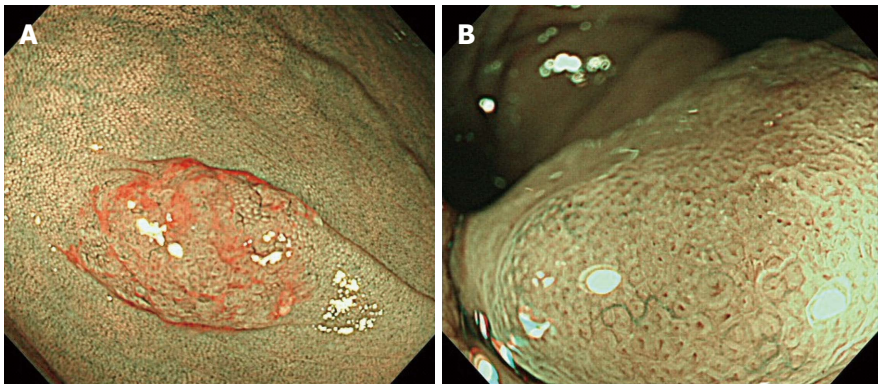

Figure 6 Endoscopic characteristics on narrow band imaging observation. A: Red cap sign – positive case; B: A finding of showing Ⅱ-D pit.

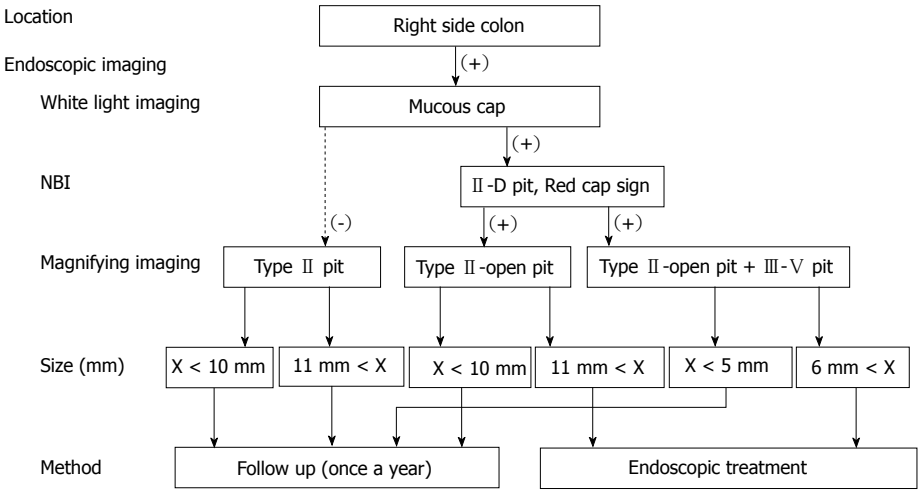

Figure 7 Flow chart for endoscopic treatment about sessile serrated adenoma/polyp. NBI: Narrow band imaging.

structure that is characteristic of a lack of associated with vasodilatation in contrast to the protruded type. However, within the lesion, a blackish dotted orifice of the crypt that is similar to that of SSA/Ps is often observed as discussed later (Figure 2B); this similarity makes, differentiation difficult.

INDICATIONS FOR ENDOSCOPIC TREATMENT

Currently, there is no established indication for endoscopic treatment about serrated polyps. However, according to the guidelines of management published by the ASGE[6,11,31] or ESGE[46], a five-year follow-up period is recommended for SSA/Ps without dysplasia that are 10 mm or less in size, and a follow-up with a three-year intervals is recommended for SSA/Ps with dysplasia of that are 10 mm or more in size. Notably, a biennial follow-up is recommended for serrated polyposis.

However, we summarized about the indication for endoscopic treatment of serrated polyps as a flow chart in Figure 7. Especially, the indication of endoscopic treatment for SSA/Ps is complicated. As we mentioned above, it is recommended to use the ME with NBI method and chromoendoscopy for diagnosis of characterized findings. At first, it is recommended to do the endoscopic treatment for greater than 6 mm sized polyps with Ⅱ-D pit and neoplastic changes (type Ⅲ-Ⅴ pit pattern) on right side colon. In contrast, small sized polyps smaller than 10 mm are should be follow up, even if shown to the mucous cap and Ⅱ-D pit. And also most of small sized HPs at sigmoid colon and/or rectum are not indication for endoscopic treatment. However TSAs, which are shown to type Ⅲ-Ⅳ pit pattern in left side colon are indication for endoscopic treatment.

In terms of numbers of lesions, once every-five-year follow-ups are recommended when SSA/Ps and TSAs greater than 10 mm are found at three or more sites, and once every-three-year follow-ups are similarly recommended for SSA/Ps and TSAs greater than 10 mm according to guideline. In contrast, once every-three-year follow-ups are recommended when SSA/Ps and TSAs of 10 mm or less are found at three or fewer sites, and one to three year follow-ups are recommended when lesions of 10 mm or more are found at two or more sites. The same follow-up schedule is recommended when associated cytological dysplasia is found.

Although the above mentioned guidelines recommend

a once every-three-year follow-ups for lesions that are associated with dysplasia and are 10 mm or more in size (regardless whether they are SSA/Ps or TSAs), we recommend endoscopic resection such conditions in our department. We made this recommendation because some lesions will develop SM invasion even if they are less than 10 mm sized polyp. Lesions with tumors that are 20 mm or greater are particularly recommended for endoscopic resection even when endoscopic findings of obvious dysplasia are absent.

CONCLUSION

Histopathologically, "serrated lesions" are categorized by the WHO into three groups[15]: (1) HPs; (2) TSAs; and (3) SSA/Ps. I have discussed the findings associated with each lesion type as observed on IEE and provided a particular focus on such associated findings on magnified, AFI and NBI[43]. The differentiation between HP and TSA or SSA/P based on AFI is possible to some extent based on changes in color tone. However, similarly to HPs, more than half of SSA/Ps exhibit no change in color. In contrast, 90% lesions of SSA/P with cytological dysplasia changed in magenta color tone; therefore, AFI might be a useful method for determining the presence of neoplastic characteristic of SSA/Ps.

Regarding HPs and SSA/Ps, differentiation is impossible based only on the presence or absence of dilated microcapillary vessels because such dilatation is not observed around the glands on magnified NBI observation. However, dilatations of the gland orifices are frequently observed in SSA/P and appear as blackish dotted orifices (Figure 6B). Additionally, a thick mucus adhesion referred to as a "mucous cap" can be confirmed as red mucus on NBI observation and can be recognized when it adheres to the surface of a "red cap" polyp (Figure 6A). According to our data, it is concluded to possible to differentiate between SSA/Ps and another serrated polyps. When AFI color changes were used to differentiate from HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 43%, 68%, 71%, 40%, and 52%, respectively. In contrast, NBI method with using magnifying observation is also usefulness. When the red cap sign was used to differentiate between HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 94%, 40%, 74%, 77%, and 75%, respectively. And the existence of Ⅱ-D pit in magnifying observation is also important. When the Ⅱ-D pit was used to differentiate between HPs and SSA/Ps, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of SSA/P diagnosis were 80%, 72%, 84%, 67%, and 78%, respectively.

Based on the above findings, the differentiation of HPs and SSA/Ps is likely possible. In contrast, the superficial type of TSA is considered to be difficult to differentiate from SSA/Ps. However, further studies should be conducted because the histopathological diagnoses of both HPs and SSA/Ps have ambiguities that have yet to be resolved.

Additionally, SSA/Ps with dysplasia are observed to be associated with dilatation of the microcapillary vessels at the tumor site, and the same finding as been observed to be associated with traditional neoplastic change (Figure 4D).

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REVIEW

Recent development of optical coherence tomography for preoperative diagnosis of esophageal malignancies

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Abstract

Endoscopic diagnosis with histological evidence is necessary to decide the best strategy for treating esophageal squamous cell carcinoma and Barrett's-associated neoplasia, and the recent development of endoscopic technologies have made possible real-time information of malignant hallmarks. We focused on the development of optical coherence tomography (OCT), the only technology that can depict real-time cross-sectional images with high resolution. With the improvements in image resolution, acquisition rate and demonstrable area of three-dimensional devices with Doppler capability, OCT imaging was shown to enable visualization of structural/functional alterations in the mucosal/submucosal tissue of the esophagus, resulting in more accurate preoperative diagnosis of such malignancies. Moreover, it approved to be useful for targeting malignant areas for biopsy and treatment as well as for predicting the treatment effects. Therefore, further development of this technology is expected to overcome the current clinical issues in management strategies of esophageal malignancies.

Key words: Optical coherence tomography; Barrett's esophagus; Esophageal squamous cell carcinoma

Core tip: Optical coherence tomography (OCT) provides real-time cross-sectional images with extremely high resolution. We previously reported that OCT provided significantly more accurate preoperative staging of esophageal squamous carcinoma (ESCC) than endosonography. With remarkable improvements in this technology, such as three-dimensional devices with Doppler capability, for the detection of Barrett's-associated neoplasia, the diagnostic accuracy gradually became better through enhanced visualization of structural/functional alterations in mucosal/submucosal tissue. Recent reports suggested its usefulness for targeting malignant lesions for endoscopic intervention and for predicting treatment effects. Therefore, further development of OCT should promote improved management strategies for esophageal malignancies, including ESCC.

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coherence tomography for preoperative diagnosis of esophageal malignancies. *World J Gastrointest Endosc* 2015; 7(9): 872-880 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/872.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.872

INTRODUCTION

Both endoscopic assessment and histological evidence of gastrointestinal malignancies are necessary to decide the best treatment strategy. Notably, image-enhanced endoscopic technologies have been developed to provide real-time information on malignant hallmarks. In this review, we focused on the development of optical coherence tomography (OCT), the only technology that can depict real-time cross-sectional images of biological tissue at a near-microscopic level without contrast agents[1].

OCT IMAGING

Mechanism of OCT imaging and its advantage

OCT images by near infrared light in the wavelength range of 700-1500 nm are similar to the B-mode images of ultrasonography. To construct an image, optical interferometry measures the delay between the emission of an invisible beam and the detection of its reflection to determine the distance from the emitter to the site. Its axial resolution is determined by coherence length of the light source. Most of the OCT devices reported in previous studies were first-generation probe-types [Light Lab Imaging (Boston, United States)] that used a super-luminescent diode light source with a center wavelength of 1300 nm, a bandwidth of 50 nm, and power output of 10 mW[2-7]. They had 10-20 μm of axial resolution, 5-25 times higher than that of high-frequency endosonography, which was another cross-sectional imaging device. Although its image acquisition rate was gradually improved from 1 frame/s to 9.8 frames/s with a lower signal-to-noise ratio, 4.0 frames/s could be used for the easy interpretation of images (Table 1)[8-10]. As a result, detailed OCT images can be constructed in gray-scale.

These mechanical characteristics provides several advantages to OCT in comparison with other advanced endoscopic technologies, as follows. First, it provides high-resolution cross-sectional images in real-time. OCT shows tissue structures in the mucosal/sub-mucosal layers at a microscopic scale, such as "pit and gland" morphology, revealing crypts/villi/vessels[4,6,7,11,12], as well as intracellular strictures, such as nuclei and other organelles, based on their different intensity of signal scattering[13]. Second, OCT does not always need tissue contact or coupling, although a biocompatible chemical agent was reported to possibly enhance its signal penetration depth[14]. Actually, we used a probe-type OCT [HOYA (Tokyo, Japan)] to depict detailed structures of the esophageal wall components, regardless of the location, while EUS-based imaging required acoustic coupling with a water preparation or a water-filled balloon, resulting in some difficulty in avoiding artifacts[2]. Third, a prototype OCT has a through-the-endoscope design, which may be easier to handle during endoscopic examination. In the next section, we will describe the technique for acquiring high-quality images using the OCT.

Best technique and indication for OCT imaging

Nowadays, two types of OCT probe-devices, such as a radial-probe/linear-probe, and one balloon-type device are available but only for research[10,11,13]. While linear scanning is able to sample only a small area, radial scanning creates an image similar to that of radial EUS with the potential for assessing larger areas, due to its easier identification of the scanning orientation compared with the linear scanning. Therefore, radial-type probes have been applied in most of the previous studies.

The OCT devices are inserted through the accessory channel of an endoscope and maneuvered under direct endoscopic observation so that the imaging plane is perpendicular to the gastrointestinal wall. Its position when scanning across the tissue surface is monitored using visible light. A series of tomograms are obtained, while its spot diameter is selected for maintaining the appropriate depth of focus, while the distance above the surface is controlled by endoscopic maneuvers. In fact, the distance between the device and the site may affect the penetration depth of its signal. While mucosal structures were well-focused when the probe was held about 1 mm above the surface, the structures in the deeper submucosa (SM) could be revealed when the wall was compressed or collapsed around the probe. Using such a technique, the penetration depth of the OCT signal and consequent image quality in the stomach, duodenum, and colon were reported to be inadequate compared with those in the esophagus, suggesting that the OCT device was most suitable for the esophagus[11].

Previous studies demonstrated close correspondences between the clear, five-layered morphologies in the OCT images and those of a normal esophageal wall in the histological findings[4,15]. It was shown that the first relatively less reflective layer corresponded to stratified squamous epithelium (EP); the second more reflective layer to the lamina propria mucosa (LPM); the third less reflective layer to the muscularis mucosa (MM); fourth more reflective layer to the SM; and fifth less reflective layer to the muscularis propria (MP) with deeper structures of the esophageal wall. Subsequent studies based on such findings promoted the development of OCT devices for the management of Barrett's-associated neoplasia and esophageal squamous cell carcinoma (ESCC). Originally, the studies aimed to improve the quality of "optical biopsies" of OCT devices for Barrett's-associated neoplasia and remarkable advances were achieved in the West from the first-generation conventional probe-type OCT to the second-generation OCT (Table 1). In the East, we demonstrated the usefulness of the first-

Table 1 Specification of optical coherence tomography devices

Manuscript	OCT device			Diameter (mm)	Image acquisition rate (frame/s)
	Type	Resolution			
		Axial (μm)	Transverse (μm)		
4	Probe	10	25		4
5	Probe	10	25	2.4	-
6, 7	Probe	10	-	2.5	2
2	Probe	11	30	1.5	4
3					
33	Probe	5	-	1.8	4
34	Probe	Approximately 2	5.6	-	-
39	Probe	5	14	-	60
41	Probe-3D	5	15	-	60
10	Balloon (OFDI)	7	30	18	4
46	Balloon (VLE)	7	-	20	10

OCT: Optical coherence tomography; OFDI: Optical frequency-domain imaging; VLE: Volumetric laser endomicrography.

generation OCT in the preoperative staging of superficial ESCCs (SESCCs) (Table 1). Therefore, we review these achievements, and propose future roles for OCT in the management of esophageal disease.

OCT-BASED DIAGNOSIS OF BARRETT'S-ASSOCIATED NEOPLASM

Significance of OCT in Barrett's esophagus

Barrett's esophagus (BE) is a precursor lesion with a 30-40-fold increased risk of cancer occurrence, *i.e.*, from specialized intestinal metaplasia (SIM) to low grade dysplasia (LGD) and high grade dysplasia (HGD) and, finally, to adenocarcinoma[16]. Based on knowledge of the multi-step transformation, a surveillance program with regular endoscopic examination is recommended, but the prognosis for adenocarcinoma remains poor, with an overall 5-year survival of less than 20%[17]. Previous studies suggested that some dysplasia and intramucosal adenocarcinoma might be overlooked until the advanced stage in the current clinical setting[18]. Most of them were shown to be minute with a patchy distribution in a wide-ranging BE, and subsquamous SIM (SSIM) was found in 71.4% of pre-treatment dysplastic BE when 0.4-6.8 mm of oral extension was observed, although the sampling area and depth by random biopsy were limited[18-22]. Therefore, there still remain controversies about sampling errors and costs/time of endoscopic biopsies in the current surveillance system[18,20,21]. Moreover, several studies have pointed out the low inter- or intra-observer agreement of their histological diagnoses[23-29]. Likewise, cutting-edge endoscopic technologies have difficulties in reaching a consensus on the recognition or interpretation of abnormal patterns, which can limit their clinical usefulness[30]. However, real-time visualization of high-resolution cross-sectional architectural information, even in the SM, analogous to the loupe image, is an important advantage of the OCT imaging. In this section, we list previous achievements by OCT devices employed for endoscopic "optical biopsies" of Barrett's-associated neoplasm.

First-generation of probe-type OCT

Previous studies demonstrated that *in vivo* or *ex vivo* use of probe-type OCT devices could provide characteristic images of normal human esophagus, gastric mucosa, BE, dysplastic BE and adenocarcinoma, although subsequent studies showed that the differences in OCT images between non-dysplastic BE and dysplastic BE were subtle. Bouma *et al*[13] first reported the ability of *in vivo* OCT to provide detailed images of structures in Barrett's-associated neoplasia by investigating biopsy-correlated OCT images, and proposed OCT-based grading criteria for characterizing dysplastic BE, as follows: (1) normal squamous epithelium: homogenous layered structures; (2) BE: absence of the layered-structure of normal esophagus in addition to abnormal/disorganized glandular structure of low reflectance within/under the mucosa; (3) dysplastic BE: highly reflective intensity of the background correlated with increased architectural disorder and heterogeneity; and (4) Barrett's adenocarcinoma: abnormal configuration of neoplastic epithelium containing large pockets and surrounded by cellular stroma.

In 2001, using 288 biopsy-correlated OCT images of 121 patients, Poneros *et al*[4] demonstrated that *in vivo* OCT had sensitivity of 97% and specificities of 92% for the diagnosis of BE. In 2005, Isenberg *et al*[5] conducted a prospective study to evaluate diagnostic accuracy of *in vivo* OCT for dysplastic/non-dysplastic BE in comparison with the histological diagnosis of jumbo biopsy specimens. They used a 2.4 mm-diameter probe under a two-channel endoscope fitted with a cap attachment, which might stabilize the OCT device on the mucosal surface during the procedure. Using a total of 314 biopsy-correlated OCT images of 33 patients, they reported sensitivity of 68%, specificity of 82%, and positive predictive value of 53%, negative predictive value of 89%, and diagnostic accuracy of 78% for the

diagnosis of BE. When the analysis was restricted to the diagnosis of HGD/ adenocarcinoma based on findings, such as: (1) lack of epithelial surface maturation; (2) gland architecture disarray; and (3) cytologic atypia[31,32], its sensitivity and specificity was 54% and 72%, respectively. Although such a negative predictive value may be advantageous for directing the examiners' attention to malignant areas for the biopsy target, there remained limitations, such as large variability in the endoscopists' accuracy rates, 56%-98%. Therefore, more refined criteria for differentiating dysplastic BE from non-dysplastic BE were required. In 2006, in a prospective study, Evans *et al*[6] investigated the relationship between a new scoring system, a "dysplasia index", based on both the OCT findings of surface maturation and gland architecture, and biopsy-proven histology of HGD/adenocarcinoma in BE subjects. Using a total of 177 biopsy-correlated OCT images, the threshold of > 2 in the scoring system had sensitivity of 83% and specificity of 75% for the diagnosis of HGD/adenocarcinoma. Accordingly, these studies demonstrated that discrimination between non-dysplastic BE and dysplastic BE using OCT devices with standard resolution still remained a challenging issue.

Then, Chen *et al*[33] developed an ultra-high resolution OCT (UHR-OCT) with 5-μm axial resolution and compared its image quality and diagnostic accuracy with those of a standard OCT with 12-μm axial resolution. Using a total of 233 biopsy-correlated OCT images of 50 patients, the accuracy of UHR-OCT for making a diagnosis of normal squamous epithelium, non-dysplastic BE, HGD and adenocarcinoma was 100%, 98.1%, 83.3% and 100%, respectively. Actually, UHR-OCT depicted smaller/finer structures and sharper layered structures, resulting in improved discrimination and more detailed features of dysplastic BE. In 2010, Cobb *et al*[34] reported that UHR-OCT detected clearly SSIM as well as abnormal structures of non-dysplastic BE/HGD/adenocarcinoma in 14 post-surgical specimens. Accordingly, these studies suggested that higher-resolution OCT with the developed criteria might be more useful for targeting biopsies to differentiate between BE and normal esophagus, or between dysplastic/cancerous BE and non-dysplastic BE. However, some studies pointed out that the point-sampling nature of a probe-type OCT, similar to those of biopsy, might miss dysplastic lesions in large surface areas of BE[10].

Second generation of OCT

These drawbacks of the probe-type OCT might have been mainly caused by the relatively slow image-acquisition rate, while recent improvements in OCT technology have enabled dramatic increases in imaging speed[35-38]. As a result, three-dimensional balloon-type OCT, referred to optical frequency-domain imaging (OFDI) and three-dimensional probe-type OCT (Light-Lab Imaging, Massachusetts, United States), could be developed with a combination of high-resolution at a near-microscopic level, large field of view, and rapid data acquisition[10].

Three-dimensional probe-type OCT: Volumetric data of a 10-mm circumference and 20-mm length could be acquired in 20 s by the helical scan of a prototype three-dimensional OCT, and each of data set provided comprehensive imaging of the glandular structure over a sampling area of 200 mm^2, which was 30-60 times as large as those of approximately 6 mm^2 by jumbo biopsy forceps and those of approximately 2.5 mm^2 by conventional biopsy forceps[39]. Additionally, the imaging depths of 3D-OCT and biopsy were 1.5-mm and < 1 mm, respectively. Using data of biopsy-correlated OCT images of 3 patients, Adler *et al*[39] demonstrated the usefulness of a three-dimensional OCT system for the detection of large areas of a normal esophagus, non-dysplastic BE and post-ablative BE. The increase in the data volume of three-dimensional OCT improved the clear detection of SSIM at 300-500 μm depth beneath neosquamous epithelium, and they therefore proposed its use to guide decisions concerning additional treatment sessions or biopsy points with a reduction of sampling error[39]. Subsequent studies demonstrated that the pre-treatment thickness of Barrett's mucosa and the presence of residual glandular structures immediately after focal radiofrequency ablation (RFA) in the three-dimensional OCT images were correlated with the treatment response determined by surveillance endoscopy with biopsy 6-8 wk after the latest session[40,41]. Accordingly, the three-dimensional OCT findings might be used as a promising real-time predictor of successful ablative therapy for BE.

Use of OFDI/volumetric laser endomicrography: OFDI can provide more than 100-fold faster imaging, compared with the conventional probe-type OCT[42]. The optical components in the inner sheath, positioned at the center of a 1.8 mm-diameter balloon catheter, are rotated helically, and cross-sectional images of the esophageal wall are revealed when the balloon is in contact with the mucosal surface, whose demonstrable area in the circumferential lumen might be affected by the degree of contact. All raw data are simultaneously stored and displayed in real-time. The OFDI/volumetric laser endomicrography (VLE) image with balloon-compression has four advantage, as follows: (1) the acquirement of microstructural data over large areas; (2) increased contrast of anatomical architecture; (3) increased signal penetration depth; and (4) reduced artifacts during imaging process.

Originally, volumetric OFDI images of the mucosa extended to the outer layer of the MP, with clear delineation of each layer, obtained for 4.5-cm-long segments in less than 6 min. In 2008, in a single-center study, complete acquisition of the OFDI data was successfully performed in 8 of 12 patients, and their images were consistent with the histological findings obtained by target/random biopsy specimens[10]. The loss of

an appropriate image due to inadequate contact of the balloon was observed in 0.37% ± 0.79% of the total tubular esophageal surface area/patient. More recently, the Nvision Volumetric laser endomicrography Imaging System (Nine Point Medical, Cambridge, MA) was developed as a commercially available device. It is derived from OFDI and provides real-time three-dimensional images of mucosa/SM over a 6-cm length of the esophagus in 90 s. Baron *et al*[43] demonstrated that *in vivo* use of VLE clearly depicted SSIM proven by random endoscopic biopsy in 3 post-RFA BE patients, and Leggett *et al*[44] revealed that *ex vivo* use of VLE clearly detected subsquamous adenocarcinoma of endoscopic mucosal resection specimens, which could not be seen by conventional endoscopy or confocal laser endomicroscopy (CLE). In a multicenter prospective feasibility study, 4 lesions of HGD/adenocarcinoma were detected by VLE in 74 BE patients[45].

However, there still remain two drawbacks. First, previous studies pointed out that inadequate contact of the balloon, due to the interference of blood/mucus, existing motion artifacts, or excessive compression of the balloon on the mucosal surface, might still reduce the image quality. Especially, in some parts of the esophagus, such as in large hiatal hernias, tissue contact with the balloon surface was not maintained throughout the imaging window. Second, it is impossible to make one-to-one correlations between OFDI/VLE images and the histological evidence, because the balloon-centering system is not suitable for the subsequent biopsy procedure, nor is the technology to localize the region of interest in the three-dimensional data. Unfortunately, unreliable correlations between them may make it difficult to determine whether the possible discrepancies are caused by either a sampling error or misdiagnosis of the images, so we cannot assess abnormal findings detected in only one session of OFDI/VLE. Actually, the true biological significance of SSIM has not been clarified by the current OFDI/VLE system without histological evidence. To overcome this issue, a biopsy guidance platform that provides endoscopically visible laser markings at VLE-determined sites was developed, and its feasibility was demonstrated in a pilot study[46]. During the examination of VLE, the marks were made in 2 s at 410 mW of electric current, with the thermal-damage predominantly limited to the mucosa[47]. The accuracies of endoscopy, VLE intent-to-biopsy, and corrected VLE post-marking images for diagnosing tissue between the marks were 67%, 93%, and 100%, respectively. The transverse and longitudinal targeting error was 1.2 ± 1.3 mm and 0.5 ± 0.9 mm, respectively, while there were no longitudinal targeting errors in 21 of 30 cases. Henceforth, larger trials by VLE-guided biopsy can be expected to evaluate its practical usefulness.

Doppler OCT: Doppler OCT can directly visualize the intensity of the blood-flow data derived from moving erythrocytes, and its velocity resolution was reported to be 10-100-times as high as that of Doppler EUS[48]. Previous studies demonstrated that it could depict dramatic alterations in the functional microvascular network, which might provide additional clues for improved identification of the layer structure, during the sequential development of Barrett's carcinogenesis[42,49]: (1) Normal esophagus: Distinct layers with small vessels in the LPM and medium vessels in the SM; (2) BE: Absence of the distinct layers with diffuse/small vessels and glandular structure; and (3) Esophageal Adenocarcinoma: Absence of distinct layers with diffuse/small vessels.

Recently, Tsai *et al*[50] developed OCT-angiography with an ultrahigh-speed (more than 10 times than that of conventional systems) and minimal motion artifacts, enabling imaging of the finer/denser microvascular architecture in BE. With an image acquisition of 400 frames/s, the total area of its image acquisition was improved to > 100 mm^2 in 8 s. Because of these technological advances, the OCT-angiography could reveal more detailed structural/functional changes in the subsurface vasculature/glandular structure for early identification of Barrett's carcinogenesis.

OCT-BASED TUMOR STAGING OF SUPERFICIAL ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Significance of OCT-based staging

In the East, ESCC is the most predominant type of esophageal carcinoma, and its mortality rate remains still high. With the development of endoscopic technologies, the indication for endoscopic treatment for SESCCs has been expanded, since it is a minimally invasive procedure with few complications and after-effects. According to the esophageal cancer treatment guidelines of the Japanese Society of Esophageal Diseases, the definitive indication for endoscopic resection (ER) is limited to carcinoma *in situ* and tumors invading the LPM, regardless of tumor size[51]. Although more precise preoperative staging has been required for curative treatment, the accuracy of EUS has not yet been satisfactory, due to its limited visualization[52,53].

Establishment of staging criteria of SESCCs

Second, we established the criteria of OCT-based staging for SESCCs in a phase I study. We used a probe-type OCT system under endoscopic observation in order to detect every part of a key finding for tumor staging[2]. After we investigated correlation the between OCT-based staging and histological staging of *en bloc* ESD specimens, the criteria of OCT-based staging for SESCCs were established. The criteria were classified into 3 categories based on the treatment guidelines: clinical EP/LPM, clinical MM, and clinical SM: (1) Clinical EP/LPM: the thick or normal layer Ⅰ with regular interfacial signal of layer Ⅱ or involvement of the tumor signal

into layer Ⅱ without involvement of layer Ⅲ; (2) Clinical MM: involvement of the tumor signal into layer Ⅲ with regular interfacial signal of layer Ⅳ; and (3) Clinical SM: Destruction of layers Ⅰ to Ⅲ and irregular interfacial signal of layer Ⅳ or loss of layer Ⅴ architecture by high backscattering.

Thereafter, in a prospective phase Ⅱ study, we investigated the accuracy based on the criteria in 62 consecutive patients[2]. The overall accuracy was 92.7%, and the accuracy of EP/LPM, MM, and SM cancer was 94.7%, 85.0%, and 90.9%, respectively. Although the staging accuracy was not significantly different among tumor locations (P = 0.79), the 0.46 (range 0.10-1.5) mm thickness of the lesion in the images without deep attenuation was significantly thinner than the 2.5 (1.2-5.0) mm images with deep attenuation. Conversely, this study uncovered the following limitations of this modality: (1) the limited depth of OCT signal penetration; (2) the inability to distinguish between cancer cell invasion and inflammatory cell infiltration; and (3) the inability to distinguish between intraepithelial cancer and normal tissue. Still, this phase-Ⅱ study suggested that the criteria might be applicable for clinical use with high accuracy of tumor staging for SESCCs.

Comparison of tumor staging accuracy between OCT and EUS

Finally, we investigated the clinical usefulness of OCT-based staging of SESCCs in a single-center prospective study by comparing the staging accuracy of OCT with that of 20-MHz probe-type EUS (UM-3R; Olympus, Tokyo) without a water-filled balloon for a total of 131 SESCCs in 123 consecutive patients[3]. The histological staging was confirmed by specimens obtained by *en bloc* ESD or surgical resection. As the primary endpoint, the accuracy for EP/LPM, a definitive indication for ER, by OCT was significantly higher than that by EUS (94.6% *vs* 80.6%, respectively, $P < 0.05$). The overall accuracy of OCT and EUS was 90.1% and 77.1%, respectively (P = 0.0046). Although there were no significant differences in the accuracy of OCT among tumor locations, the accuracy of EUS in the distal esophagus was significantly lower than that in the middle esophagus (P = 0.023). Further, due to the inferiority of EUS in image resolution, we found that the accuracy rate in 33.6% of the cases, which had less than 9-layer visualization in the EUS finding, was significantly lower than that in the remaining cases, which showed a clear discrimination of the 9-layer structure (P = 0.015). This study demonstrated that, because of mechanical advantage of OCT compared to EUS, the accuracy of OCT was significantly superior to that of EUS for the preoperative staging of EP/LPM in the clinical management of SESCCs. However, we noted 3 drawbacks of OCT: (1) a limitation in the penetration depth; (2) the limited width of the depiction area (limited to 4 mm); and (3) the inability to distinguish between cancer invasion and inflammatory cell infiltration. Accordingly, since the first-generation OCT-device still had limited usefulness in the management of SESCCs, further development of the OCT devices will be needed.

PERSPECTIVE

From the point of view that OCT may have advantages in the real-time visualization of the mucosal/submucosal architecture with/without functional alterations, we review promising research data on OCT-devices for providing "optical biopsies" for early detection of neoplastic changes during Barrett's carcinogenesis or for accurate staging of SESCCs to improve treatment curability. However, to apply this technology in the clinical setting, the following issues will needed to be addressed, *i.e.*: (1) easy interpretation with low inter-observer variability; (2) real-time image acquisition for large-areas; and (3) cost effectiveness.

As for the first issue, more refined criteria for easy interpretation with less variability are needed for effective and stable stratification during surveillance. Although accurate interpretation is necessary for both well-trained endoscopists and well-trained pathologists, Qi *et al*[54] demonstrated 82% sensitivity, and 74% specificity in a computer-aided algorithm for the diagnosis of dysplastic BE based on the current criteria. Hence, future computer-aided algorithms can be realized by easy-to-identify criteria.

For the next two issues, OFDI/VLE may provide great cues toward real-time imaging of structural/functional alterations in the 6 cm-length circumferential esophageal mucosa during cancer development and the after-effects of endotherapies. Although no study has demonstrated a close correspondence between the OFDI/VLE imaging and histological evidence, a monitoring system for occult lesions, such as SSIM and tiny dysplastic Barrett's mucosa, with a laser marking platform at VLE-determined sites for biopsy-guidance might unmask their true malignant potential during surveillance. Actually, there has been no study of them using conventional endoscopic imaging, CLE or the first-generation OCT, due to the limited sampling width/depth[55]. Instead, recent studies have proposed that OCT devices might be used to guide the biopsy target for enhanced detection of malignant Barrett's mucosa or to assist in predicting the treatment effect[39,40,49]. Future monitoring by biopsy-correlated OFDI/VLE imaging might yield more effective management strategy with a risk-stratification, which could have the greatest impact on cost-effectiveness and clinical risk-management.

Regarding this point, we also emphasize that the second-generation OCT-devices with marking equipment may have a great impact on the development of new management strategies for SESCCs. In fact, there remain two difficulties in the current strategy for SESCCs. First, accurate staging for large-sized SESCCs by the detection of tiny abnormalities of superficial microvascular structure in the magnifying endoscopic findings with point-sampling characteristics is more difficult than that for small-sized SESCCs[56]. Second, another well-known

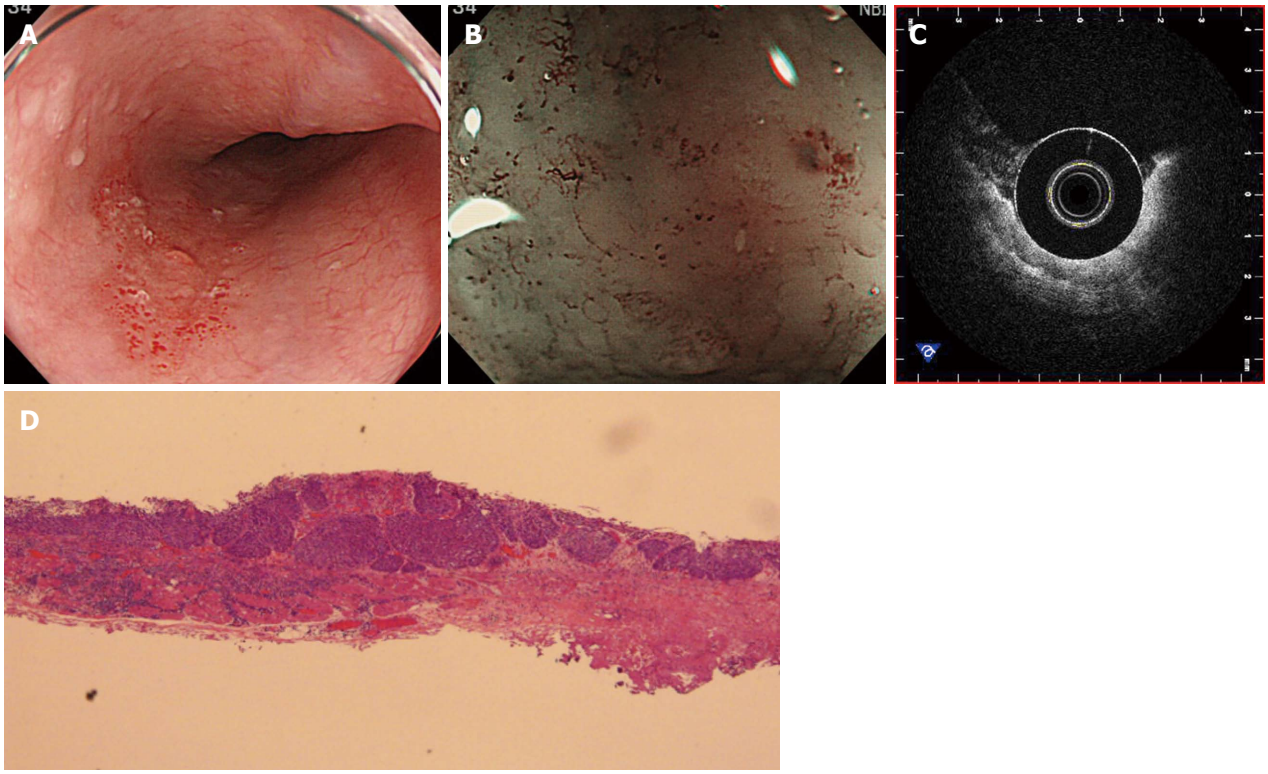

Figure 1 Representative images of superficial esophageal squamous cell carcinoma (0-IIc) with the recurrence after chemo-radiation therapy. A 71-year-old patient suffered from the recurrence of esophageal squamous cell carcinoma after chemo-radiation therapy. A: Irregular reddish lesion in the middle-esophagus in a non-magnifying white light endoscopic finding; B: Avascular area with irregular microvessels was observed in narrow-band imaging magnifying endoscopic finding; C: The involvement of the tumor signal into layer II without involvement of layer III in the OCT-imaging; D: A representative photo of *en bloc* ESD specimen demonstrated pT1a-LPM of histological diagnosis (× 10). OCT: Optical coherence tomography; LPM: Lamina propria mucosa.

difficulty is achieving early detection of the subepithelial recurrence of SESCCs after chemo-radiation therapy (Figure 1). However, the newly advanced OCT-devices can help with early detection by revealing tiny and invasive spots in large lesions and small subepithelial lesions[57]. Accordingly, real-time inspection with the OCT devices, after further technologic innovation, may play a central role in the histological diagnosis and choice of management strategies for esophageal malignancies.

CONCLUSION

In this review, we described previous achievements by which endoscopic OCT enhanced the visualization of structural/functional alterations in mucosal/submucosal tissue of the esophagus, and suggested that it might be useful for guiding/monitoring the area to be targeted for biopsy and treatment as well as to predict the treatment effect. Basically, it is important that the examiner/reviewer have familiarity and expertise in both histopathology and OCT imaging in order to achieve high accuracy in the diagnostic process. However, if reliable criteria of OCT imaging can be developed with computer-aid algorisms, the general use of OCT-related devices may provide "optical biopsies" or "optical staging" of Barrett's-associated neoplasia and SESCCs. Therefore, further development of OCT technology is required for the future progress of management strategies of the esophageal malignancies.

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ORIGINAL ARTICLE

Retrospective Study

For "difficult" benign colorectal lesions referred to surgical resection a second opinion by an experienced endoscopist is mandatory: A single centre experience

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Author contributions: Luigiano C and Iabichino G designed research and wrote the text; Luigiano C performed the endoscopic resection; Iabichino G, Miraglia S and Judica A managed the medical record and extracted all the results from the endoscopy and surgical database for analysis; Pagano N and Eusebi LH were involved in editing the manuscript and literature research; Alibrandi A performed data analysis; Virgilio C reviewed the paper for important intellectual content.

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Abstract

AIM: To assess how many patients with benign "difficult" colorectal lesions (DCRLs) referred to surgical resection, may be treated with endoscopic resection (ER) rather than surgical resection.

METHODS: The prospectively collected colonoscopy database of our Endoscopic Unit was reviewed to identify all consecutive patients who, between July 2011 and August 2013, underwent an endoscopic re-evaluation before surgical resection due to the presence of DCRLs with a histological confirmation of benignancy on forceps biopsy. ER was attempted when the lesion

did not have definite features of deeply invasive cancer. The "nonlifting sign" excluded ER only in naive lesions without a prior attempted resection. Lesions were classified, using the Kyoto-Paris classification for mucosal neoplasia. For sessile and non-polypoid lesions the "inject and cut" resection technique was used. Pedunculated and semi-pedunculated lesions were transected at the stalk just below the polyps head and before or after resection, metal clips or a loop were applied on the stalk to prevent bleeding. The lesions were histologically classified according to the Vienna criteria and for the pedunculated lesions the Haggitt classification was used.

RESULTS: Eighty-two patients (42 females, mean age 62 years) with 82 lesions (mean size 37 mm) were included in the study. Sixty-nine (84%) lesions were endoscopically resected, while 13 underwent surgical resection since ER was deemed unsuitable. On histology, cancer was found in 21/69 lesions (14 intra-mucosal, 7 sub-mucosal) and was associated with the size ($P < 0.001$) and with type 0-Ⅱa + Ⅰs ($P = 0.011$) and 0-Ⅱa + Ⅱc ($P < 0.001$) lesions. All patients with sub-mucosal cancer, underwent surgical resection. Complications occurred in 11/69 patients (7 bleedings, 2 transmural burn syndromes, 2 perforations), all managed endoscopically or conservatively, and were associated with presence of invasive cancer ($P = 0.021$). During follow-up recurrence/residual tissue was found in 14/51 sessile or non-polypoid lesions (13 treated endoscopically, 1 underwent surgical resection) and was associated with type 0-Ⅱa + Ⅰs lesions ($P = 0.001$), piecemeal resections ($P = 0.01$) and with lesion size ($P = 0.004$). Overall, 74% of patients avoided surgery. Surgical resection was significantly associated with type 0-Ⅱa + Ⅰs ($P = 0.01$) and 0-Ⅱa + Ⅱc ($P = 0.001$) lesions, with sub-mucosal invasion on histology ($P < 0.001$), with presence of the "nonlifting sign" ($P < 0.001$), and related to the dimension of the lesions ($P = 0.001$). In the logistic regression analysis, the only independent predictor for surgical resection was the dimension of the lesions ($P = 0.002$).

CONCLUSION: Before submitting patients to surgical resection for a benign DCRL, a second opinion by an experienced endoscopist is mandatory to avoid unnecessary surgery.

Key words: Difficult colorectal lesion; Complications; Endoscopic resection; Non-polypoid lesions; Polypoid lesions; Recurrence

Core tip: A "difficult" colorectal lesion (DCRL) is defined as any lesion that due to its size, shape and location or due to fibrosis as a consequence of previous attempts of endoscopic resection (ER), makes it difficult to remove. Patients with DCRLs are often referred to surgeons for surgical colorectal resection. In our institution, for all patients referred for colorectal surgical resection for DCRLs, the surgeons request an endoscopic re-evaluation and if possible an ER of the lesions. The purpose of this study was to review our results with this approach.

Luigiano C, Iabichino G, Pagano N, Eusebi LH, Miraglia S, Judica A, Alibrandi A, Virgilio C. For "difficult" benign colorectal lesions referred to surgical resection a second opinion by an experienced endoscopist is mandatory: A single centre experience. *World J Gastrointest Endosc* 2015; 7(9): 881-888 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/881.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.881

INTRODUCTION

A "difficult" colorectal lesion (DCRL) is defined as any lesion who's endoscopic resection (ER) is technically challenging due to the size, the shape or the location, or due to the presence of fibrosis as a consequence of previous attempts of ER[1].

For these reasons, patients with DCRLs are often referred to surgeons for colorectal surgical resection[2,3].

However, surgery is associated with significant morbidity and mortality, especially in older patients with comorbid illnesses, as well as higher costs of the procedures[4-6].

In our institution, patients referred for surgical colorectal resection of DCRLs, with a histological confirmation of benignancy on forceps biopsy, are advised by surgeons to undergo an endoscopic re-evaluation and, if possible, an ER of the lesions.

The aims of this study were to estimate how many patients referred to our unit with DCRLs really needed surgical resection, and to evaluate the outcomes of ER of the lesions in whom it was possible.

MATERIALS AND METHODS

Patients

The prospectively collected colonoscopy database of our Endoscopic Unit was reviewed to identify all consecutive patients who, between July 2011 and August 2013, underwent an endoscopic re-evaluation before surgical resection due to the presence of DCRLs with a histological confirmation of benignancy on forceps biopsy.

All patients underwent a colonoscopy to confirm the presence and location of the lesions, to exclude synchronous lesions, and if possible to endoscopically resect the lesion.

ER was attempted when the lesion did not have definite features of deeply invasive cancer, such as surface ulceration, converging folds, firm consistency with a surface pit pattern suggestive of invasion.

The "nonlifting sign" excluded ER only in naive lesions without a prior attempted resection, whereas it was

not considered an exclusion criteria in case of recurrent lesions or that had undergone a previous partial resection.

Lesion classification

Lesions were classified, using the Kyoto-Paris classification for mucosal neoplasia[7,8]. Polypoid types rise > 2.5 mm above the surrounding mucosa, including lesions with a clear stalk, pedunculated (0-Ip) and semi-pedunculated (0-Isp) types, and lesions without clear stalk, defined as sessile (0-Is) type. Non-polypoid types rise < 2.5 mm above the surrounding mucosa and include elevated (0-Ⅱa), barely perceptible elevated or flat (0-Ⅱb) and slightly depressed (0–Ⅱc) types. Mixed types are lesions with mixed pattern of both a polypoid sessile and a non-polypoid morphology in distinct sectors and include 0-Ⅱa + Is and 0-Ⅱa + Ⅱc types.

ER procedure

All endoscopic procedures were performed by one expert interventional endoscopist (Carmelo Luigiano)[9-12].

For sessile and non-polypoid lesions the "inject and cut" resection technique was used; *en bloc* resection was attempted for lesions ⩽ 30 mm, while for lesions > 30 mm piecemeal resection was performed, taking care to include 1-3 mm of normal tissue in the lateral margins of the resection[9,10].

Pedunculated and semi-pedunculated lesions were transected at the stalk just below the polyps head, complete ensnarement of the head portion with a single application of the snare was first attempted; if this failed, the lesion was trimmed with piecemeal technique until the snare could be placed around the lesion. Before or after resection, metal clips or a loop were applied on the stalk to prevent bleeding[11,12].

Patients were prepared with a fiber- and residue-free diet within 72 h and 4000 mL of a polyethylene glycol electrolytic lavage solution 18 h before colonoscopy.

The procedures were performed with a high-definition colonoscope (Pentax EC-3490L: Pentax, Hamburg, Germany), with a paediatric colonoscope or with an operative or diagnostic video gastroscope (Pentax, Hamburg, Germany), with a high-definition processor (Pentax EPK-i HD).

Submucosal injections were performed with variceal injection needles (Olympus). The injection solution contained only saline, saline with epinephrine (1:10000) or saline and epinephrine with methylene blue mixture (1:10000). The snares used were standard, jumbo or stiff (US Endoscopy, Mentor, Ohio).

Electrosurgery was performed using a combination of cutting (120 W) and coagulation current (60 W), using an ERBE-ICC 200 (Erbe Elektromedizin GmbH, Tübingen, Germany). For sessile or non-polypoid lesions argon plasma coagulation (APC) at a power of 40-60 W and gas flow of 2 L/min using an ERBE APC 300 (Erbe Elektromedizin) was used to ablate any residual tissue at the edge of the resection area.

If localization of the ER site during colonoscopic follow-up was likely to be difficult, the site was marked with a submucosal injection of sterile carbon particle suspension (Spot, GI Supply, Camp Hill, Penn) in the adjacent normal mucosa.

ER procedures were performed on outpatients in the morning. After ER, patients remained in a second-stage recovery area for 4 to 6 h until medically cleared for discharge by the endoscopist. If the case of clinical concerns, the patient was admitted for observation. On discharge, dietary instructions, written contact information and instructions regarding symptoms and potential problems were provided to patients.

Assessment of lesions size and histopathology

The size of the lesions was estimated by comparison with open biopsy forceps and, when possible, also after retrieval. All removed tissue was retrieved using a basket or through the suction channel. All specimens were stained with hematoxylin and eosin for histopathological assessment, and two experienced pathologists examined the resected material. Based on the histological configuration of the crypts, adenomas were classified into tubular, villous, and tubulo-villous. The lesions were histologically classified according to the Vienna criteria and for the pedunculated lesions the Haggitt classification was used[13,14].

Complications

ER induced bleeding was defined as procedural (occurring during resection), early (within 24 h) or delayed (after 24 h). The diagnosis of early and delayed bleeding was based on the presence of rectorrhagia or melena. Transmural burn syndrome, caused by thermal injury, with resultant serosal inflammation, was characterized by localized abdominal pain, leucocytosis and, occasionally, fever. Perforation was diagnosed either by endoscopy during the resection or by the presence of free air on plain abdominal film or abdominal computed tomography scan.

Clinical and endoscopic follow-up

Clinical follow-up was performed after 3 wk from the ER, when the histological results were communicated to the referring specialists and patients.

In patients with pedunculated and semi-pedunculated lesions, surveillance colonoscopy was performed at 12 and 24 mo for lesions with high and low-grade dysplasia, respectively, while for lesions harbouring cancer at 6 and 12 mo, and annually thereafter.

In patients with sessile, non-polypoid and mixed type lesions surveillance colonoscopy was performed after 3, 6 and 12 mo, and then annually after the initial ER.

In patients with sessile, non-polypoid and mixed types lesions, recurrence was defined as the presence of tissue on a follow-up endoscopy. If visible tissue was seen on follow-up examinations, it was snare resected when

Table 1 Characteristics of patients and colorectal lesions recruited

No. of patients	82
Age (mm ± SD) (range)	62 ± 10 (38-81)
Sex (M/F)	40/42
Associated extra-intestinal diseases (%)	
Hypertension	6 (7.5)
Cardiac diseases	3 (3.5)
Chronic renal failure	1 (1.5)
Neoplasms	1 (1.5)
Diabetes mellitus	1 (1.5)
Associated intestinal diseases (%)	
Diverticula	15 (18)
Others colorectal lesions	10 (12)
Left hemicolectomy	3 (3.5)
Number of lesions	82
Size (mm ± SD) (range)	37 ± 18 (20-100)
Indication for surgical resection (%)	
Location	36 (44)
Size	32 (39)
Shape	10 (12)
Recurrence	4 (5)
Shape (%)	
0-Ip	11 (13)
0-Isp	1 (1.5)
0-Is	17 (21)
0-Ⅱa	19 (23)
0-Ⅱa + Is	18 (22)
0-Ⅱa + Ⅱc	12 (14.5)
0-Ⅱb	4 (5)
Location (%)	
Anorectal junction	4 (5)
Rectal	7 (8.5)
Rectosigmoid junction	14 (17)
Sigmoid	16 (19)
Descending colon	3 (4)
Splenic flexure	4 (5)
Transverse	3 (3.5)
Hepatic flexure	10 (12)
Ascending colon	8 (10)
Caecum only	9 (11)
Cecum with ileocecal valve involvement	3 (3.5)
Cecum with appendix orifice involved	1 (1.5)
Biopsy results at the first colonoscopy (%)	
Low-grade dysplasia	18 (22)
High-grade dysplasia	64 (78)
Successful endoscopic resection (%)	69 (84)
Aborted endoscopic resection (%)	13 (16)
Non-lifting sign	6
Frankly malignant lesions	3
Difficult position	2
Very large lesions with difficult position	2

mm: Millimeters; M: Male; F: Female; 0-Ip: Pedunculated lesions; 0-Isp: Semi-pedunculated lesions; 0-Is: Sessile lesions; 0-Ⅱa: Elevated non-polypoid lesions; 0-Ⅱb: Barely perceptible elevated non-polypoid lesions; 0-Ⅱc: Slightly depressed non-polypoid lesions.

feasible and submitted for histopathological examination. The edges of the resection site were typically cauterized with the argon plasma coagulator. Lesions that were too small for snare resection were removed with forceps and then fulgurated with an argon plasma coagulator. During the endoscopic follow-up, any alterations of the mucosa in the area of the previous resection (ulceration, scarring, retraction of mucosa, *etc.*) underwent biopsies.

Outcomes of the study

The parameters evaluated in the study were: age, sex, associated intestinal or extra-intestinal diseases, lesions size, shape and location, reason for surgical resection, successful of ER, reason of aborted ER, technique of ER, complications, technique of treatment of complications, histology, grade of dysplasia and cancer, and recurrence.

Statistical analysis

Continuous data are described by mean, standard deviation and range, according to distribution. Categorical data are presented as numbers and percentages. Relationships between numerical variables were examined by the Spearman correlation coefficient, between categorical and numerical variables by the Biserial correlation, and between categorical variables by the Log-likelihood Ratio test. Results were analyzed in relation to lesion size (divided in two groups: group A lesions < 35 mm and group B lesions ⩾ 35 mm) and were also compared for the technique of resection used (*en bloc vs* piecemeal; APC *vs* no APC). Logistic regression was used to assess the independent predictors of outcomes. A *P*-value of less than 0.05 was considered statistically significant. The software packages applied were SPSS for Windows 11.0. Data analysis of the study was performed by a biomedical statistician (Angela Alibrandi).

RESULTS

During the study period, 82 patients (42 female; mean age 62 years) underwent an endoscopic re-evaluation before surgical resection of a DCRLs with a histological confirmation of benignancy on forceps biopsy. Demographic and clinical data of the included patients are summarised in Table 1.

The reason for referral was the location of the lesion in 36 cases, the size in 32 cases, the type in 10 and recurrence in 4 cases.

The mean (± SD) lesion size was 37 ± 18 mm (range 20-100 mm). The most frequent type was the mixed types in 30 cases (18 type Ⅱa + Is and 12 type Ⅱa + Ⅱc) and the most frequent location was the sigmoid colon in 16 cases.

Among the included lesions, 44 (54%) were < 35 mm, while 38 (46%) were ⩾ 35 mm in diameter.

Of the 82 lesions, 69 (84%) were successfully resected endoscopically, while 13 cases were referred for surgical resection since ER was considered unsuitable due to the following reasons: presence of the "nonlifting sign" in 6 patients, endoscopic appearance of invasive cancer in 3 cases, very large size with difficult location in 2 cases (one patient with a sessile lesion occupying more than 60% of the lumen in the rectosigmoid junction and one patient with a type Ⅱa lesion involving more than half of the cecum and more than half of the circumference of the proximal ascending colon) and in 2 cases due to difficult location (1 with ileocecal valve and 1 with appendiceal orifice involvement).

Table 2 Characteristics of colorectal lesions resected

No. of lesions	69
Size (mm ± SD) (range)	33 ± 12 (20-80)
Shape (%)	
0-Ip	11 (16)
0-Isp	1 (1.5)
0-Is	15 (22)
0-Ⅱa	16 (23)
0-Ⅱa + Is	15 (22)
0-Ⅱa + Ⅱc	8 (11.5)
0-Ⅱb	3 (4)
Location (%)	
Anorectal junction	4 (6)
Rectal	6 (8.5)
Rectosigmoid junction	13 (19)
Sigmoid	15 (22)
Descending colon	2 (3)
Splenic flexure	3 (4)
Transverse	1 (1.5)
Hepatic flexure	9 (13)
Ascending colon	6 (8.5)
Caecum only	8 (11.5)
Cecum with ileocecal valve involvement	2 (3)
Technique of endoscopic resection for the 57 sessile and non-polypoid lesions	
En-bloc endoscopic mucosal resection	23
Piecemeal endoscopic mucosal resection	34
Resection with argon plasma coaugulation	15
Technique of endoscopic resection for the 12 pedunculated and semipedunculated lesions	
Clips	9
Endoloop	3
Complications (%)	11 (16)
Bleeding	7
Perforation	2
Transmural burn syndrome	2
Histology (%)	
Tubular adenoma	13 (19)
Villous adenoma	22 (32)
Tubulovillous adenoma	33 (47.5)
Serrated adenoma	1 (1.5)
Low-grade dysplasia	3 (4)
High-grade dysplasia	45 (65.5)
Intramucosal cancer	14 (20.5)
Invasive cancer	7 (10)

mm: Millimeters; 0-Ip: Pedunculated lesions; 0-Isp: Semi-pedunculated lesions; 0-Is: Sessile lesions; 0-Ⅱa: Elevated non-polypoid lesions; 0-Ⅱb: Barely perceptible elevated non-polypoid lesions; 0-Ⅱc: Slightly depressed non-polypoid lesions.

The characteristics of the 69 resected lesions are presented in Table 2. All lesions were resected in a single session and the resection was evaluated as endoscopically complete in all procedures.

Of the resected lesions, 42 (61%) were < 35 mm, while 27 (39%) were ⩾ 35 mm in diameter. In 12 pedunculated and semi-pedunculated lesions, bleeding prophylaxis was performed with the application of clips to the stalk in 9 cases and with endoloop in the 3 remaining cases.

In the 57 sessile and non-polypoid lesions, *en-bloc* resection was performed in 23 cases while piecemeal resection was used in the other 34 cases. Argon plasma coagulation was applied to the margins of the lesions in 15 of the 57 lesions (all piecemeal resections).

Histological diagnosis of the resected lesions showed 47.5% tubulo-villous, 32% villous, 19% tubular and 1.5% serrated adenomas. Carcinoma was found in 30% of patients (21 cases), out of which 14 showed intra-mucosal and 7 sub-mucosal invasion. All patients with lesions showing sub-mucosal invasion on histology underwent surgery.

Of the 7 invasive lesions, one was located at the rectum, one at the rectosigmoid junction and the remaining 5 lesions in the colon.

The presence of cancer on histology was significantly associated with type 0-Ⅱa + Is (P = 0.011) and 0-Ⅱa + Ⅱc (P < 0.001), and was also related to the size (P < 0.001) of the lesions.

Procedural bleeding occurred in 5/69 (7%) resected lesions; one early (within 10 h) and one delayed (after 72 h) bleeding occurred, both requiring blood units transfusion. The procedural bleeding was always managed endoscopically by applying clips.

Transmural burn syndrome occurred in 2 patients (3%) and was successfully managed conservatively.

Two patients had a perforation that occurred during the final resection of a 40 mm 0-Ⅱa lesion of the ascending colon and during a resection of a 30 mm 0-Is recurred lesion of the rectum. In both patients, successful closure of the perforation with clips was achieved and no further intervention was required.

Endoscopic complications were significantly associated with the presence of invasive cancer on histology (P = 0.021), and in the logistic regression analysis, the only independent predictor of a complication was the dimension of the lesions (P = 0.002).

Among the 69 cases of successful ER, 62 (90%) patients have undergone colonoscopy follow-up for a mean (± SD) time of 16 ± 6 mo (range 6-24).

Among the sessile and non-polypoid lesions (51 cases), during the endoscopic follow-up residual/recurrence tissue was found in 14 (27%) cases; 13 were successfully treated endoscopically, while one patient underwent surgical resection due to 2 recurrence during the endoscopic follow-ups.

Recurrence of the lesion after ER was significantly associated to type 0-Ⅱa + Is (P = 0.001) lesions, to piecemeal resection (P = 0.01) and to the dimension (P = 0.004) of the lesions.

Overall, 74% of patients avoided surgery. Surgical resection was significantly associated with type 0-Ⅱa + Is (P = 0.01) and 0-Ⅱa + Ⅱc (P = 0.001) lesions, with sub-mucosal invasion on histology (P < 0.001), with presence of the "nonlifting sign" (P < 0.001), and related to the dimension (P = 0.001) of the lesions.

In the logistic regression analysis, the only independent predictor for surgical resection was the dimension of the lesions (P = 0.002).

DISCUSSION

This report describes a single-center experience in the endoscopic treatment of a cohort of patients with

DCRLs, showing that three quarters of the patients referred for surgical resection were successfully treated endoscopically.

Data of an European regional FOBT-based colorectal cancer screening program, suggest that up to 10% of patients with benign adenomas detected by screening colonoscopy after a positive fecal occult blood test will be treated surgically[15].

Indeed, a proportion of colorectal lesions, due to their location, size, or shape are considered technically more challenging to be removed endoscopically or are associated with an increased risk of complications (such as bleeding or perforation). Thus, these lesions are not routinely endoscopically resected and are often referred to surgeons for surgical resection[1-3].

Our study confirms these findings since, in our series, failure of ER was associated with the large size and the type of the lesions, as well as the lack of the lifting sign.

However, considering all the patients evaluated, 69 (84%) of them were successfully treated endoscopically, and 61 (74%) have so far avoided an unnecessary surgical procedure.

Our results are in agreement with other studies in whom, in referral centers surgical resection was avoided in the majority of patients with DCRLs (range 58%-90%)[2,16-18].

Therefore, it is possible that endoscopists who are inexperienced or are not used to treat technically challenging lesions, choose to refer patients for surgical resection.

Compared to the 20.1% morbidity and 1.3% mortality rates for surgery of colorectal tumors, general data on ER show much lower morbidity rates (0.7% to 3.7% for perforation and 0.4% to 3.8% for bleeding) and no mortality[19].

The Munich Polypectomy Study showed a correlation between large size, non-pedunculated shape and right-sided location of colorectal lesions and the occurrence of post-procedural complications[20].

Considering only the studies on DCRLs resection, these findings were evident, indeed the mean morbidity rate was 18% (the majority treated endoscopically), however without mortality[2,16-18,21,22].

In accordance with previous studies[2,16-18,21,22], also in our series, ER for DCRLs was performed without mortality and with an acceptable rate of morbidity (16%); moreover, all the complications that occurred were successfully managed endoscopically or conservatively. Procedural bleedings were controlled endoscopically in all cases and all the perforations were detected during the procedure and closed endoscopically with good clinical outcomes.

Furthermore, the complications of ER seem to depend on the lesions characteristics as well as on the experience and skills of the endoscopist.

The present study confirms that ER of DCRLs can be performed with satisfactory safety and that high-risk ERs should be performed by experts at a high-volume center.

Residual/recurrent disease can occur after ER of non-pedunculated colorectal lesions, with a mean rate of 15%[23].

For DCRLs, the mean rate of residual/recurrence is doubled, approximately 30%[2,16-18,21,22]. In our study the local residual/recurrence was detected in 27% of cases in accordance with the results of previous studies on the ER of DCRLs. Moreover, our results confirmed that the piecemeal technique is associated with a higher rate of residual/recurrent neoplasia, as stated by the Italian Colorectal ER Study Group in a recent published paper[24], and was similar despite the use or not of APC after resection.

Our results show also a correlation with the size of the lesions, in accordance with a recent systematic review[23]. The review also confirmed that the pooled estimate risk of recurrence was significantly higher for piecemeal (20%; 95%CI: 16%-25%) than for en bloc resections (3%; 95%CI: 2%-5%; Cochran's Q test $P < 0.0001$)[23].

To reduce residual/recurrence rates, endoscopic submucosal dissection (ESD) has been proposed as a superior technique compared to the "inject and cut" piecemeal ER, since it allows an *en bloc* excision of large colorectal neoplastic tissue, thus allowing a more accurate pathological diagnosis[19].

However, ESD in the colon is technically demanding, with a long learning curve and increased procedures duration; moreover, it requires the use of specialized accessories, increasing the costs of the procedures and has a high perforation rate, making it unlikely to be adopted into therapeutic colonoscopy practice in western countries[19].

Hypothetically, applying ESD to our series, at the best of the performance of the technique, we would have achieved an *en-bloc* resection rate of 80% (45 out of 57 patients). This could have allowed a better evaluation of the submucosal invasion in the 7 patients in which it was found to be present, virtually avoiding surgery to 2 or 3 more patients. The lower recurrence rate (about 1%-2%) could allow a reduction of the number of treatments needed to achieve complete clearance of the lesion, but the higher costs of the procedures counterbalance the reduction of the number of sessions. Moreover, ESD has higher complication rates, requiring the mandatory admission of the patient to be treated. About 1% to 2% of these complications need surgical intervention, reducing the beneficial effect of the better *en-bloc* resection rate.

Furthermore, if the piecemeal ER is performed acquiring as bigger and fewer pieces as possible, including at least 1-3 mm of normal tissue surrounding the lesions, and all fragments of the lesion are retrieved, the risk of missing neoplastic invasion seems negligible, and the recurrence rate is acceptable.

Our results also show that the endoscopic treatment of residual/recurrent tissue was easy and effective (successful in 93%), in accordance with the systematic review by Belderbos *et al*[23], in which after a mean of 1.2 endoscopic re-treatments, successful eradication was

achieved in 91.4% of recurrences.

The main limitations of our study are the relatively small number of reported lesions and the non-prospective, randomized design of the study. Thus, the superiority of ER over surgical treatment cannot be proven, however, such a trial would probably be unethical to perform.

In conclusion, before submitting patients to surgical resection of a benign colorectal lesion, a second opinion by an examiner who is experienced in ER of such lesions is worthwhile and mandatory to avoid unnecessary surgery.

COMMENTS

Background

A "difficult" colorectal lesion (DCRL) is defined as any lesion who's endoscopic resection (ER) is technically challenging. In less experienced endoscopic centres, benign DCRLs are often referred to surgical resection.

Research frontiers

This study aimed to assess how many patients with benign DCRLs referred to surgical resection, may be treated with ER rather than surgical resection.

Innovations and breakthroughs

In these research results, 74% of patients with DCRLs referred to surgeons for colorectal resection, after an endoscopic re-evaluation were successfully treated with ER and avoided surgery.

Applications

Before submitting patients to surgical resection for a benign DCRL, a second opinion by an experienced endoscopist is mandatory to avoid unnecessary surgery.

Terminology

A DCRL is defined as any lesion who's ER is technically challenging due to the size, the shape or the location, or due to the presence of fibrosis as a consequence of previous attempts of ER.

Peer-review

It is an good article.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of endoscopic stenting for malignant biliary obstruction: A single-center study

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Abstract

AIM: To evaluate the efficacy and safety of single-step endoscopic placement of self-expandable metallic stents (SEMS) for treatment of obstructive jaundice.

METHODS: A retrospective study was performed among 90 patients who underwent transpapillary biliary metallic stent placement for malignant biliary obstruction (MBO) between April 2005 and October 2012. The diagnosis of primary disease and MBO was based on abdominal ultrasound, computed tomography, magnetic resonance imaging, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography with brush cytology, biopsy, and/or a combination of these modalities. The type of SEMS (covered or non-covered, 8 mm or 10 mm in diameter) was determined by the endoscopist. Ninety patients were divided into two groups: group 1 (49 patients) who underwent a single-step SEMS placement and group 2 (41 patients) who underwent a two-step SEMS placement. The technical success rate, complication rate, stent patency, and patient survival rate were compared between the groups. In addition, to identify the clinical prognostic factors associated with patient survival, the following variables were evaluated in Cox-regression analysis: gender, age, etiology of MBO (pancreatic cancer or non-pancreatic cancer), clinical stage (Ⅳb; with distant

metastases or Ⅳa >; without distant metastases), chemotherapy (with or without), patency of the stent, and the use of single-step or two-step SEMS.

RESULTS: Immediate technical success was achieved in 93.9% (46/49) in group 1 and in 95.1% (39/41) in group 2, with no significant difference (P = 1.0). Similarly, there was no difference in the complication rates between the groups (group 1, 4.1% and group 2, 4.9%; P = 0.62). Stent failure was observed in 10 cases in group 1 (20.4%) and in 16 cases in group 2 (39.0%). The patency of stent and patient survival revealed no difference between the two groups with Kaplan-Meier analysis, with a mean patency of 111 ± 17 d in group 1 and 137 ± 19 d in group 2 (P = 0.91), and a mean survival of 178 ± 35 d in group 1 and 222 ± 23 d in group 2 (P = 0.57). On the contrary, the number of days of hospitalization associated with first-time SEMS placement in group 1 was shorter when compared with that number in group 2 (28 *vs* 39 d; P < 0.05). Multivariate analysis revealed that a clinical stage of Ⅳa > (P = 0.0055), chemotherapy (P = 0.0048), and no patency of the stent (P = 0.011) were independent prognostic factors associated with patient survival.

CONCLUSION: Our results showed that single-step endoscopic metal stent placement was safe and effective for treating obstructive jaundice secondary to various inoperable malignancies.

Key words: Endoscopic stenting; Single-step; Malignant biliary obstruction; Self-expandable metallic stents; Two-step

Core tip: Single-step placement of expandable metallic stents for treating malignant biliary obstruction is useful for shortening hospitalization. To maximize symptomatic relief and cost benefits, stent placement should not be delayed after deciding on metal stent palliation.

Yamamoto R, Takahashi M, Osafune Y, Chinen K, Kato S, Nagoshi S, Yakabi K. Comparison of endoscopic stenting for malignant biliary obstruction: A single-center study. *World J Gastrointest Endosc* 2015; 7(9): 889-894 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/889.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.889

INTRODUCTION

Because of improvements in operative procedures and diagnostic techniques, both the incidence of biliary pancreatic malignancies and resection rates have increased. Nevertheless, partly due to the high incidence obstructive jaundice in affected patients, some cases remain inoperable with a poor prognosis. Presently, the preferred treatment for jaundice due to malignant biliary pancreatic obstruction is biliary stent placement. Such stenting was initially performed using polyethylene plastic stents; however, expanding metal stents have been available for several years[1,2]. These expandable metallic stents have several advantages over plastic stents: (1) they can be introduced by a smaller delivery catheter; (2) they have a large inner diameter; and (3) they can remain fixed in position after release[3-6]. In this study, we assessed the safety and efficacy of single-step endoscopic placement for self-expandable metallic stents (SEMS) for treating obstructive jaundice secondary to various inoperable malignancies.

MATERIALS AND METHODS

This study included 90 patients who underwent transpapillary biliary metallic stent placement for malignant biliary obstruction (MBO) between April 2005 and October 2012 at the Saitama Medical Center of Saitama Medical University. For these 90 patients (72 men and 18 women), the diagnoses of primary disease and MBO were based on abdominal ultrasound, computed tomography, magnetic resonance imaging, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography with brush cytology, biopsy, and/or a combination of these modalities. Before cholangiography, all patients were diagnosed with obstructive jaundice caused by an unresectable malignancy because of either very advanced carcinoma or old age. The type of SEMS (covered or noncovered, 8 mm or 10 mm in diameter) was determined by the endoscopist. Ninety patients were divided into two groups: group 1 (49 patients) who underwent a single-step SEMS placement and group 2 (41 patients) who underwent a two-step SEMS placement, depending on the severity of cholangitis. The flowchart for the single-step and two-step SEMS placements for distal MBO is shown in Figure 1.

The technical success rate, complication rate, length of hospital stay, stent patency, and patient survival rate were compared between the groups. Techinical success was defined as successful endoscopic deployment of the stent at the appropriate position resulting in a smooth drainage of the stented bile ducts. Complication rate was defined as the pancreatitis, bleeding and cholangitis arising from stent placement for malignant bile duct obstruction. And, length of hospital stay was defined as the period between hospital admission and discharge. In addition, to identify the clinical prognostic factors associated with patient survival, the following variables were evaluated with a Cox-regression analysis: gender, age, etiology of MBO (pancreatic cancer or nonpancreatic cancer), clinical stage (Ⅳb with distant metastasis or Ⅳa > without distant metastasis), chemotherapy (with or without), patency of the stent, and the use of single-step SEMS or two-step SEMS. This study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained from the patients and/or their families.

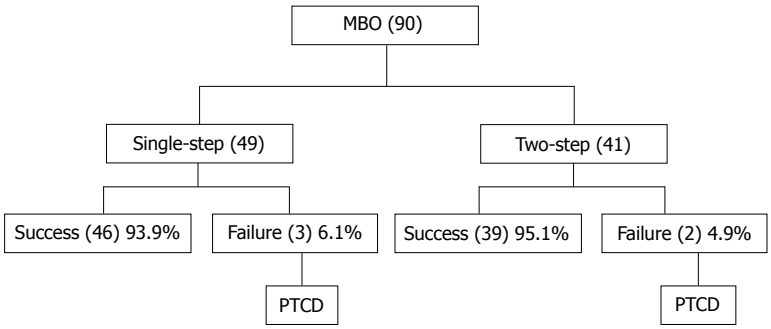

Figure 1 Flowchart showing one-step and two-step self-expandable metal stent placement for distal malignant biliary obstruction. MBO: Malignant biliary obstruction; PTCD: Percutaneous transhepatic cholangiodrainage.

Table 1 Patients characteristics in the two groups

Variable	Single-step (n = 49)	Two-step (n = 41)	P
Mean age (yr)	70.1 ± 12.6	74.3 ± 9.9	NS
Gender (n)			
Male	49	23	< 0.01
Female	0	18	
Etiology of MBO: pancratic cancer (%)	59.2	31.7	0.016
MPD tumor involvement present (%)	36.7	24.4	NS
Spincterotomy (%)	2.0	22.0	0.003
Hilar biliary obstruction (%)	22.4	46.3	0.03
Clinical stage			
Ⅳa > (%)	40.8	61	NS
Ⅳb (%)	59.2	39	NS
Bilateral drainage (%)	4.1	12.2	NS
Technical success rate (%)	93.9	95.1	NS
Complication rate (%)	4.1	4.8	NS
Chemotherapy (%)	55.1	51.2	NS
Length of hospital stay (d)	28.1 ± 28.6	39.6 ± 25.7	< 0.05

MBO: Malignant biliary obstruction; MPD: Main pancreatic duct.

Statistical analysis

We reviewed medical records and radiological images of all patients undergoing stent placement. We then assessed the following variables using univariate analyses (χ^2 test or Fisher's exact test) to identify patient survival: sex, age, etiology of MBO (pancreatic cancer or nonpancreatic cancer), clinical stage (Ⅳb with distant metastasis or > Ⅳa without distant metastasis), chemotherapy (with or without), stent patency, and the use of single-step SEMS or two-step SEMS. We estimated survival times with the Kaplan–Meier method and compared them using the log-rank test. We also calculated odds ratios with 95%CIs for all variables. These statistical tests were two-sided, and statistical significance was set at P value < 0.05 for all analyses. The statistical evaluation was performed using SPSS (IBM, JAPAN) 21.0 for Windows.

RESULTS

The clinical characteristics of the study participants are summarized in Table 1. The single-step group (group 1) included only 49 men (percentage of men = 100%) with a mean age of 70.1 years. The two-step group (group 2) included 23 men (56.1%, P < 0.01) and 18 women (43.9%) with a mean age of 74.3 years. The incidence of pancreatic cancer was higher in group 1 than in group 2 (59.2% *vs* 31.7%, P = 0.016) (Table 1). The information concerning stricture location and endoscopic sphincterotomy (EST) performance before stenting is shown in Table 1. The number of ESTs performed before stenting was statistically significantly higher in group 1 than in group 2 (2.0% *vs* 22%, P < 0.01). The patient characteristics in the two groups categorized by treatment are summarized in Table 1. Although hilar obstruction was significantly less frequent in group 1 than in group 2 (22.4% *vs* 46.3%, P = 0.03), there was no difference in bilateral drainage rate between the two groups (group 1, 4.1% and group 2, 12.2%; P = 0.24). Immediate technical success was achieved in 93.9% (46/49) patients in group 1 and 95.1% (39/41) patients in group 2; there was no significant difference (P = 1.0). Serum total bilirubin levels were within normal limits within two weeks after placement of the stent in all patients who underwent successful procedures. Likewise, there was no difference in the occurrence of complication between the groups (group 1, 4.1% and group 2, 4.9%; P = 0.62).

We observed stent failure in 10 cases in group 1 (20.4%) and 16 cases in group 2 (39.0%). The stent was patent in all 26 cases. There was no difference in the stent patency or patient survival between both groups using the Kaplan–Meier analysis, with a mean patency of 111 ± 17 d in group 1 and 137 ± 19 d in group 2 (P = 0.91, Figure 2), and a mean survival of 178 ± 35 d in group 1 and 222 ± 23 d in group 2 (P = 0.57, Figure 3). In contrast, the number of hospitalization days associated with first-time SEMS placement in group 1 was shorter than in group 2 (28 *vs* 39 d; P < 0.05). Multivariate analysis found that a clinical stage of Ⅳa > (P = 0.0055), chemotherapy (P = 0.0048), and no patency of the stent (P = 0.011) were independently associated prognostic factors for patient survival (Table 2).

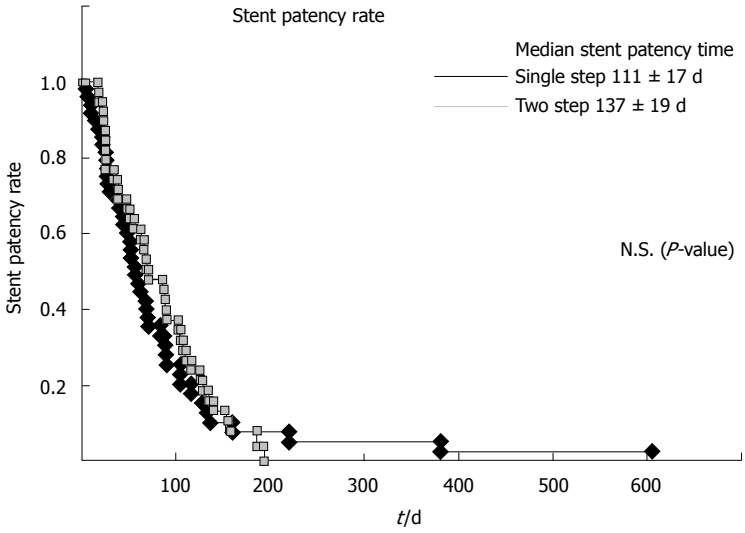

Figure 2 Kaplan-Meier curves showing the patency time of the stent in the single-step and two-step groups.

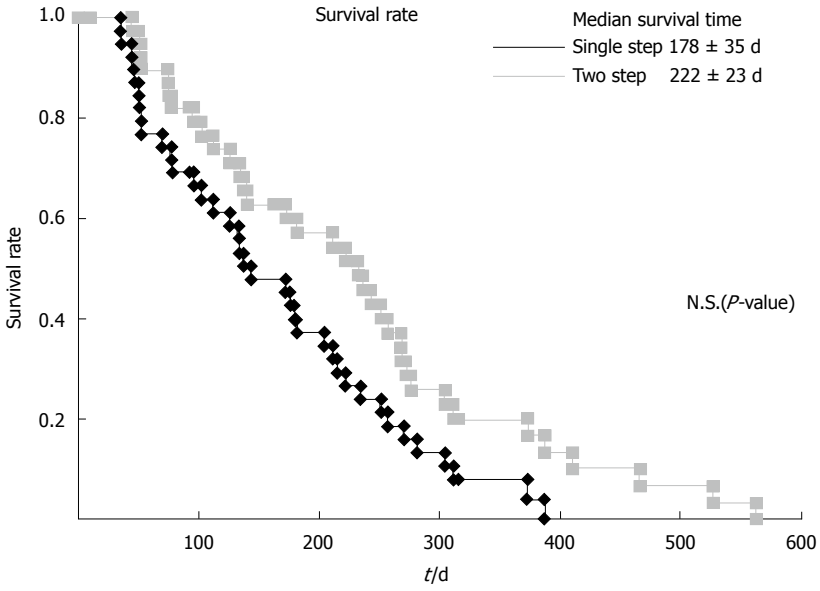

Figure 3 Kaplan-Meier curves showing the survival time of the patient in the single-step and two-step groups.

DISCUSSION

Patients with malignant bile duct obstruction have poor long-term survival and are not candidates for surgical resection. The goals of palliation using a biliary stent placement are symptomatic relief of obstructive jaundice, prevention of cholangitis, and prolongation of survival. Stenting has also been found to improve quality of life of these patients. To maximize the symptomatic relief and cost benefits, the stent should be placed as soon as the decision for metal stent palliation has been made. However, a recent study[7,8] that compared the single-step and two-step procedures found that procedure-related complication rate improved with single-step procedures with no increase in early complications. However, Hamada *et al*[8] reported that single-step SEMS placement for distal MBO was associated with a shorter time to dysfunction and a higher rate of stent migration than two-step SEMS placement. In addition, single-step procedure caused minimal patient discomfort, and avoided both the second intervention and drainage catheter dislocation risk before the deployment of the stent. The single-step placement procedure has two goals: (1) reducing the number of interventions and hence the procedural expenses; and (2) eliminating the need for bile-collecting bags or bottles, thus resulting in an improvement in quality of life as well as reduction in hospitalizations.

In this study, we evaluated the efficacy and safety of the single-step endoscopic placement of SEMS for treating obstructive jaundice that can be caused by various inoperable malignancies. There was no difference in stent patency and patient survival between the two groups in the Kaplan–Meier analysis. In contrast, the

Table 2 Multivariate analysis to identify the clinical prognostic factors for patient survival

Variables	OR	95%CI	*P*
Step (single *vs* two)	0.81	0.49-1.36	0.42
Gender (male *vs* female)	1.05	0.66-1.67	0.83
Age (69 ≥ *vs* 70 <)	1.02	0.59-1.76	0.96
Pancratic cancer (yes *vs* no)	1.01	0.21-1.61	0.98
Clinical stage (ⅣA ≥ *vs* ⅣB)	2.03	1.23-3.34	0.006
Chemotherapy (with *vs* without)	2.18	1.27-3.76	0.005
Patency of the stent (no *vs* yes)	2.21	1.20-4.07	0.011

number of hospitalization days associated with first-time SEMS placement in group 1 was lower than in group 2 (28 *vs* 39 d, $P < 0.05$). The multivariate analysis revealed that a clinical stage of ⅣA > ($P = 0.0055$), chemotherapy ($P = 0.0048$), and no patency of the stent ($P = 0.011$) were independently associated prognostic factors of patient survival. Patients with inoperable malignant strictures generally receive only palliative radiotherapy or chemotherapy and have a limited life expectancy. One possible reason for poor outcomes may be the delay between the diagnostic cholangiography and the placement of the metallic stent[9]. McDougall *et al*[9] determined that 25 (78%) patients had a plastic stent placed before placement of the metallic stent, leading to a mean delay of 123 d, and that 7 (22%) patients had > 1 metallic stent placed. This clearly suggests that if a metallic stent is placed earlier in the course of the disease, the stent patency can be prolonged.

The strategies for self-expandable metal stent placement can depend on the primary cancer types because of the differences in their biological behavior. However, the survival times were not significantly different between patients with pancreatic cancer and those with other primary cancers in our study population. Therefore, this factor may not have any effects on the results of the analyses.

The limitations of our study were as follows. Firstly, our study population was not large enough for a meaningful analysis regarding the efficacy of single-step endoscopic metal stent placement. Secondly, because this was not a prospective study, selection biases regarding the type of SEMS and the procedure adopted for cannulation of the ampulla were present. We propose the implementation of initial stenting for partial drainage of malignant hilar bile duct strictures, rendering contralateral drainage as a last resort for cases with severe cholangitis or insufficient reduction of jaundice.

To conclude, single-step placement of expandable metallic stents for MBO cases that are inoperable is a useful method to shorten hospitalization. Once the decision about metal stent palliation has been made, the stent should be placed as soon as possible to maximize symptomatic relief and cost benefits.

In conclusion, our results showed that single-step endoscopic metal stent placement was safe and effective for treating obstructive jaundice secondary to various inoperable malignancies.

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COMMENTS

Background

Although self-expandable metal stent (SEMS) placement has been widely performed for treating malignant biliary obstruction (MBO), few studies have compared single-step SEMS (direct placement without a prior plastic stent) and two-step SEMS (stent placement at second session following temporary plastic stent placement).

Research frontiers

The objective of this study was the evaluation of the safety and efficacy of single-step endoscopic placement of SEMS for treating obstructive jaundice caused by various inoperable malignancies.

Innovations and breakthroughs

This was a retrospective single-center study of 90 consecutive patients who had undergone endoscopic retrograde cholangiopancreatography-guided transpapillary biliary metallic stent placement for MBO during a 7.5-year-period. The patients of this study were divided into two groups: a single-step SEMS placement group ($n = 49$) and a two-step SEMS placement group ($n = 41$). MBO etiologies were similar between both groups, with pancreatic cancer accounting for 46.7% cases. No significant differences in the patency rate of stents and patient survival were observed between the single-and two-step groups. In contrast, the number of hospitalization days associated with first-time SEMS placement in the single-step group was lower compared with that in the other group (28 *vs* 39 d). Multivariate analysis identified that ⅣA > clinical stage ($P = 0.0055$), chemotherapy ($P = 0.0048$), and no patency of the stent ($P = 0.011$) were independently associated prognostic factors for patient survival.

Applications

These findings will be particularly interesting to the readership of World Journal of Gastrointestinal Endoscopy as they demonstrate that single-step endoscopic metal stent placement is effective and safe for treating obstructive jaundice caused by various inoperable malignancies.

Peer-review

This is a manuscript about an interesting issue that has not been published extensively. It is written in fluent, simple English, easy to comprehend.

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Review on sedation for gastrointestinal tract endoscopy in children by non-anesthesiologists

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Abstract

AIM: To present evidence and formulate recommendations for sedation in pediatric gastrointestinal (GI) endoscopy by non-anesthesiologists.

METHODS: The databases MEDLINE, Cochrane and EMBASE were searched for the following keywords "endoscopy, GI", "endoscopy, digestive system" AND "sedation", "conscious sedation", "moderate sedation", "deep sedation" and "hypnotics and sedatives" for publications in English restricted to the pediatric age. We searched additional information published between

January 2011 and January 2014. Searches for (upper) GI endoscopy sedation in pediatrics and sedation guidelines by non-anesthesiologists for the adult population were performed.

RESULTS: From the available studies three sedation protocols are highlighted. Propofol, which seems to offer the best balance between efficacy and safety is rarely used by non-anesthesiologists mainly because of legal restrictions. Ketamine and a combination of a benzodiazepine and an opioid are more frequently used. Data regarding other sedatives, anesthetics and adjuvant medications used for pediatric GI endoscopy are also presented.

CONCLUSION: General anesthesia by a multidisciplinary team led by an anesthesiologist is preferred. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Key words: Gastro-intestinal endoscopy; Gastroscopy; Colonoscopy; Sedatives; Pediatric ages; Anesthetics; Analgesics

Core tip: Sedation for pediatric gastro-intestinal endoscopy is preferably performed by pediatric anesthesiologists, as part of a multidisciplinary team. However, in many hospitals pediatric anesthesiology is insufficiently developed. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an effective and safe alternative. These teams should be in line with national legislation and institutional regulations. This paper will help non-anesthesiologists to provide as good-as-possible sedation for children undergoing endoscopy. Practical protocols were developed providing up-to-date information on the most effective and most safe options.

Orel R, Brecelj J, Dias JA, Romano C, Barros F, Thomson M, Vandenplas Y. Review on sedation for gastrointestinal tract endoscopy in children by non-anesthesiologists. *World J Gastrointest Endosc* 2015; 7(9): 895-911 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/895.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.895

INTRODUCTION

Esophago-gastro-duodenoscopy in children needs almost always to be performed under anesthesia or deep sedation. Procedural analgesia and sedation for procedures performed in ambulatory care are changing. The authors reviewed the literature on sedation and for endoscopy by non-anesthesiologists and to propose practical algorithms.

In order to obtain the greatest yield from a pediatric gastrointestinal (GI) endoscopic procedure and to perform these with the highest quality and with the maximum level of safety, some prerequisites must be fulfilled. A pediatric gastroenterologist or dedicated pediatrician must have judged the necessity of the procedure to optimize patient management. The procedure must be performed by a skilled endoscopic team with appropriate equipment in a suitable environment. The patient and parents or guardians must be informed as much and good as possible.

General anesthesia is only possible in a limited number of centers because of shortness of anesthesiologists. The aim of this review is to present and discuss different sedation protocols for non-anesthesiologists for pediatric GI endoscopies. Several protocols for procedural sedation by non-anesthesiologists have been produced by different professional bodies and organizations. However, practical algorithms for these procedures have not been published[1].

MATERIALS AND METHODS

The search for studies on pediatric sedation for GI endoscopy was an update of van Beek and Leroy[2]'s search strategy for the period between January 2011 (when their search was finished) and January 2014 and utilized the following databases: MEDLINE, Cochrane, and EMBASE[2]. These were searched for the keywords "endoscopy, GI", "endoscopy, digestive system" and "sedation", "conscious sedation", "moderate sedation", "deep sedation", and "hypnotics and sedatives" for publications in English restricted to the pediatric age group, which was defined as 0 to 18 years. Subsequently a search for pediatric GI endoscopy sedation guidelines for the same keywords as above for the last 20 years with the same limits (publications in English, pediatric population) was undertaken. The search was expanded to include guidelines for GI endoscopy sedation by non-anesthesiologists for the adult population for the last 10 years. Furthermore a search for guidelines for pediatric procedural sedation published in the last 10 years was made.

RESULTS

The first search revealed 12 studies of which 8 are listed in Table 1[3-10]. Four of them were not relevant: Liu *et al*[11] analyzed anesthesia for outpatient gastroscopies and colonoscopies in adults only, Yen *et al*[12] studied sex differences in sedation with midazolam and alfentanil for gastroscopy only in adults, too[3,4]. The aim of the study of Vadlamudi *et al*[13] was evaluation of ileoscopy *via* stoma and not a sedation[13]. And finally, Siwiec *et al*[14] tested transnasal gastroscopy with ultrathin endoscope in non-sedated healthy volunteers or patients with the signs or symptoms of gastro-esophageal reflux disease.

We found one guideline for pediatric GI endoscopy in

Table 1 Publications from the first search ("endoscopy, gastrointestinal", "endoscopy, digestive system" AND "sedation", "conscious sedation", "moderate sedation", "deep sedation", and "hypnotics and sedatives"; limits: publications in English, paediatric population

Ref.	Methodology	Results	Limitations	Conclusions
Bedirli *et al*[3]	Study type: prospective, randomised, double-blinded Patients: *N* = 80; 1–16 yr; ASA Ⅰ, Ⅱ Procedure: upper GI endoscopy Drugs: baseline: propofol (1 mg/kg; additional 0.5–1 mg/kg as needed); intervention: fentanyl (2 μg/kg) *vs* tramadol (2 mg/kg) Intended sedation level: deep sedation Additional interventions: spray of lidocaine 10%; infusion of 10 lactated Ringer's solution (10 mL/kg per hour); supplemental oxygen 3–4 L/min) Administered by: anesthesiologist Outcome measures: Adverse events: HR (change for 20% from the baseline), BP (change for 20% from the baseline), SpO2 (< 90% for more than 15 s), respiratory rate, agitation score Effectiveness: Ramsey sedation score, duration of endoscopy, Steward recovery score, endoscopist's rating of ease of procedure, total propofol consumption	Adverse events: self-limited bradycardia and transient desaturation in age group 0–2 yr, more in the fentanyl group Effectiveness: lower sedation scores in tramadol group; no difference of gastroenterologist rating	Only one dosage of drugs instead of titrating them	Propofol with tramadol or propofol provided efficient sedation; significantly less adverse effects in the tramadol group
Brecelj *et al*[4]	Study type: randomized, controlled, single-blinded Patients: *N* = 201; 1–18 yr Procedure: gastroscopy, colonoscopy Drugs: ketamine (0.75 mg/kg with additions of 0.25 mg/kg up max. to 1.5 mg/kg; repeated after 10–15 min at 0.5 mg/kg as needed) Intervention: midazolam (0.1 mg/kg; max 2.5 mg; repeated after 30–60 min at 0.05 mg/kg as needed) *vs* no premedication Intended sedation level: deep sedation Additional interventions: none Administered by: dedicated nurse under supervision of endoscopist Outcome measures: Adverse events: respiration rate, HR, BP, SaO2 (any drop below 92%), adverse reactions Effectiveness: ease of procedure, total ketamine consumption	Adverse events: mild self-limited laryngospasm in 3%, high rate of desaturations (approx. in 40%), vomiting in 17%, regardless of study group; more emergence reactions in ketamine group during recovery (10 *vs* 2) Effectiveness: high rate of sedation adequacy	Study was not double-blinded	Ketamine starting dose should be at least 1 mg/kg; more emergence reactions without midazolam premedication; same frequency of other adverse reactions
Miqdady *et al*[5]	Study type: retrospective cohort study Patients: *N* = 301; 1 (more than 10 kg) –18 yr; ASA Ⅰ, Ⅱ Procedure: upper, lower or combined GI endoscopy Drugs: atropine (0.01–0.02 mg/kg per minute. 0.1 mg, max. 0.4 mg); midazolam (0.05–0.2 mg/kg); ketamine (0.5–1 mg/kg) Intended sedation level: deep sedation Additional interventions: none Administered by: endoscopist Outcome measures: Adverse events: respiration rate, HR, BP, SaO2 (any drop below 94%), side effects Effectiveness: the adequacy of sedation	Adverse events: desaturation in 12.3%, in 1.2% disruption of examination due to persistent desaturation; in 1.2% respiratory distress after examination Effectiveness: effective and uneventful sedation in 79.4%	Retrospective study	Midazolam and ketamine sedation is safe and effective for diagnostic GI endoscopies in children older than 1 yr weighting more than 10 kg without comorbidities

Motamed *et al*[6]	Study type: prospective, randomised, double-blinded Patients: *N* = 150; 1–18 yr; ASA Ⅰ, Ⅱ Procedure: upper GI endoscopy Drugs: main sedative: midazolam (0.1 mg/kg; if needed repeated doses up to 5 mg or 0.3 mg/kg); premedication 45 min before the procedure with oral placebo (normal saline), oral ketamin (5 mg/kg), or oral fentanyl (2 μg/kg) Additional interventions: spray of lidocaine 10%; additional oxygen trough nasal cannula at 2 L/min Administered by: registered nurse supervised by anaesthesiologist Outcome measures: Adverse events: respiration rate, HR (decrease by 30% from baseline), BP (decrease or increase by 20%), SaO2 (any drop below 90%) Effectiveness: total midazolam dose, modified Ramsey sedation score, procedure time, discharge time, ease of *iv* catheter placement, separation from parents agitation, the adequacy of sedation	Adverse events: in total in 26% of patients (hypoxia in 7.3%, hypotension in 6.7%, dizziness in 20%, nausea in 10%, vomiting in 17.6%); mild, easily managed Effectiveness: the total recovery and procedure duration time was shorter in the ketamine-midazolam group, inadequate sedation in 10.2% in placebo-midazolam and in 8% in fentanyl-midazolam *vs* in 3.9% in ketamine-midazolam group; the mean administered dose of midazolam was the lowest in ketamine-midazolam group; the *iv* line placement and separation from parents was easier in ketamine-midazolam group; only 27.4% of patients did not remember the procedure		Sedation with oral ketamine-iv midazolam is better than placebo-midazolam or oral fentanyl-iv midazolam
Chiaretti *et al*[7]	Study type: retrospective (12 yr), multicentric Patients: N = 36516; 1 to > 10 yr; ASA Ⅰ, Ⅱ, Ⅲ Procedure: different painful procedures Drugs: main sedative: propofol 2 mg/kg in children from 1 to 8 yr of age and 1 mg/kg in older children and in children younger than 1 yr; further doses of 0.5–1.0 mg/kg in the case of agitation or complain; premedication: atropine 0.010–0.015 mg/kg, ketamine (0.5 mg/kg) to avoid infusion pain in 2 centres (not in gastroscopy); additional oxygen trough nasal cannula at 6 L/min Intended sedation level: deep sedation Administered by: paediatrician (anaesthesiologist available in case of need) Outcome measures: mean arterial pressure, heart rate and SatO2, incidence, type and timing of adverse events (major and minor) and number of calls to the emergency team Effectiveness: total dosage of the sedative agents, level of sedation (Ramsay scale)	Adverse events: in 6 patients (0.02%) emergency team intervention (prolonged laryngospasm in 3 patients, bleeding in 1, intestinal perforation in 1, and 1 during lumbar puncture); milder adverse events: hypotension in 19 patients (0.05%), ventilation by face mask and additional oxygen in 128 patients (0.4%), laryngospasm in 78 patients (0.2%), bronchospasm in 15 patients (0.04%); minor complications more often in children who underwent gastroscopy; none of the children experienced severe side effects or prolonged hospitalisation.	Retrospective study	Propofol is safe and effective for paediatrician-administered procedural sedation in children; appropriate training for paediatricians is important
Gül *et al*[8]	Study type: randomized, controlled, double-blinded Patients: *N* = 64; 3-14 yr; ASA I Procedure: esophagogastroduodenoscopy Drugs: main sedative: propofol 2 mg/kg; analgesic: group R: remifentanil 0.25 μg/kg, group F: fentanyl 0.5 μg/kg; additional oxygen trough nasal cannula at 4 L/min Intended sedation level: deep sedation Administered by: anesthesiologist Outcome measures: MAP, HR, RR, and SpO_2 Effectiveness: ease of gastroscopy, patient's movements during procedure, additional doses of drugs; level of sedation (Ramsay scale); duration of PACU stay	Adverse events: prolonged apnoea in 14 (43.8%) children in group R and in 11 (33.3%) children in group F; none required endotracheal intubation; Effectiveness intraoperative respiratory rate, time to eye opening, opioid consumption, and duration of recovery were significantly shorter in group R duration of PACU stay were significantly shorter in group R than in group F		Remifentanil (combined with propofol) is an efficient and as safe as fentanyl propofol combination for esophagogastroduodenoscopy in children
Long *et al*[9]	Study type: retrospective analysis of prospectively collected data Patients: *N* = 4904; 15-90 yr; ASA Ⅰ-Ⅳ Procedure: esophagogastroduodenoscopy Drugs propofol 1-100 mg and/or midazolam 1-3 mg^2 mg/kg Administered by: endoscopist Outcome measures: influence of pre-existing disease and ASA score on oxygen desaturation (SpO_2) < 90%	Adverse events: hypoxemia in 245 patients (5%); risk factors: high BMI (30 kg/m^2), hypertension, diabetes, gastrointestinal disease, heart disease ASA score was not predictive for hypoxemia	Retrospective study	Independent risk factors for hypoxemia were high BMI, hypertension, diabetes, gastrointestinal and heart diseases and combined gastro and colonoscopy

Agostoni *et al*[10]	Study type: retrospective analysis of prospectively collected data Patients: *N* = 17999 (17524 in older than 12 yr, 457 in < 12 yr); 4-74 yr; ASA I-IV Procedure: esophagogastroduodenoscopy and in some cases different procedures (mucosectomy, hemostatic clip, percutaneous endoscopic gastrostomy, …) Drugs: propofol induction (in children 1-2 mg/kg BW) then in continous infusion Intended sedation level: deep sedation Administered by: anesthesiologist Outcome measures: adverse events (hypotension, desaturation, bradycardia, hypertension, arrhythmia, aspiration, respiratory depression, vomiting, cardiac arrest, respiratory arrest, angina, hypoglycemia, and/or allergic reaction)	Adverse events: rare in children (2.6%) and in adults (4.5%), in children were more often only bradycardia (2.1%) and hypotension (0.44%) 3 adult patients died; no death case in children	Retrospective analysis, single centre data	Deep sedation with intravenous propofol for endoscopic procedures is safe in children and adults

ASA: American Society for Anesthesiology; BP: Blood pressure; GI: Gastrointestinal; HR: Heart rate; SpO2: Oxygen saturation; BMI: Body mass index; RR: Respiratory rate.

English which addressed different aspects including sedation[15].

We expanded the search to guidelines for sedation for GI endoscopy performed by non-anesthesiologists in adult patients during the last 10 years. The search revealed 9 publications which are listed in Table 2[16-24].

The search for guidelines for pediatric procedural sedation published in English during the last 10 years revealed 10 publications. Two are general guidelines for sedation in children[25,26]. Another one, followed by an update published 7 years later, addresses specifically ketamine sedation for emergency departments[27,28]. Others are specifically developed for sedation for dental procedures in children. They are listed in Table 3[15,25,26,28-33].

Pre-requisites for safe and effective sedation by non-anesthesiologists

GI endoscopy must be discussed with the child if emotionally and intellectually competent enough and parent(s)/guardian(s). The pre-sedation assessment is listed in Table 4. Patients should be classified by physical status assessment as developed by the American Society for Anesthesiology (ASA) (Table 5). If the child's ASA classification conforms to class Ⅰ or Ⅱ, sedation can be performed safely. If the child fits in ASA class Ⅲ classification, the benefits of sedation must be carefully weighed against the risks and in the vast majority of cases anesthesiology will be preferable. Patients in ASA class Ⅳ and Ⅴ must be anesthetized by anesthesiologists[28,34].

The depth of sedation is influenced by the procedure. If analgesia is needed together with sedation, as in the case of endoscopic-therapeutic procedures, the patient has to be anesthetized. The same is valid for emergency GI endoscopies such as removal of a foreign body from the upper GI tract and GI bleeding. Sedation necessitates that a team member assigned for observing the vital signs of the patient, since monitoring of pulse oximetry, heart rate and preferably also capnography are insufficient[8,12].

Equipment for resuscitation must be present in the endoscopy room. The team has to be trained in pediatric advanced live support techniques and has to be familiar with measures needed in any scenario of complications[1].

Sedatives and their combinations

Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country. Therefore, limitations caused by local legislation should be carefully checked. In most countries, the administration of inhalation anesthetics is only authorized by anesthesiologists.

Premedication

Premedication with midazolam (oral or intra-nasal) lessens the stress for an intravenous (*iv*) catheter placement and other preparations for GI endoscopy before sedation or anesthesia. This procedure is effective and safe although intranasal administration may cause local discomfort. In order to decrease the stress and pain caused by a venepuncture, an eutectic mixture of the topical anesthetics lidocaine and prilocaine provides local anesthesia when applied with an occlusive dressing 30-60 min before venipuncture[35].

An *iv* catheter provides the most effective way of delivering agents needed for sedation and analgesia. Inhalation, intramuscular or other sedation regimens are less well

Table 2 Gastrointestinal endoscopy sedation guidelines for adults

Organisation Ref.	Title	Year of publication
American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates Vargo *et al*[16]	Multisociety sedation curriculum for GI endoscopy	2012
Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Dumonceau *et al*[17]	Guideline: Non-anesthesiologist administration of propofol for GI endoscopy	2010
Society of American Gastrointestinal Endoscopic Surgeons Heneghan *et al*[18]	Surgeons. Society of American Gastrointestinal Endoscopic Surgeons guidelines for office endoscopic services	2009
Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy Lichtenstein *et al*[19]	Sedation and anesthesia in GI endoscopy	2008
Training Committee of the American Society for Gastrointestinal Endoscopy Vargo *et al*[20]	Training in patient monitoring and sedation and analgesia	2007
Working Group on Endoscopy, Austrian Society of Gastroenterology and Hepatology (OGGH) Schreiber[21]	Austrian Society of Gastroenterology and Hepatology (OGGH)-guidelines on sedation and monitoring during GI endoscopy	2007
Training Committee American Society for Gastrointestinal Endoscopy[22]	Training guideline for use of propofol in gastrointestinal endoscopy	2004
American Society for Gastrointestinal Endoscopy, Standards of Practice Committee Waring *et al*[23]	Guidelines for conscious sedation and monitoring during GI endoscopy	2003
Standards Practice Committe American Society for Gastrointestinal Endoscopy Faigel *et al*[24]	Guidelines for the use of deep sedation and anesthesia for GI endoscopy	2002

GI: Gastrointestinal.

Table 3 Paediatric procedural sedation guidelines

Organisation Ref.	Title	Year of publication
Green *et al*[28]	Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update	2011
National Clinical Guideline Centre (United Kingdom)[26]	Sedation in children and young people: Sedation for diagnostic and therapeutic procedures in children and young people	2010
American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs[29]	Guideline on use of anesthesia personnel in the administration of office-based sedation/general anesthesia to the pediatric dental patient	2009
American Academy on Pediatrics; American Academy on Pediatric Dentistry[30]	Guideline for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures	2009
American Academy of Pediatrics; American Academy of Pediatric Dentistry Coté *et al*[25]	Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update	2006
American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs[31]	Guideline on use of anesthesia care providers in the administration of in-office deep sedation/general anesthesia to the pediatric dental patient	2005
American Academy of Pediatric Dentistry American Academy of Pediatric Dentistry Committee on Sedation and Anesthesia[15]	Guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients	2005
American Academy of Pediatric Dentistry[32]	Clinical guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients	2004
Green *et al*[27,28]	Clinical practice guideline for emergency department ketamine dissociative sedation in children	2004
UK National Clinical Guidelines in Pediatric Dentistry Hosey[33]	UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry	2002

Table 4 Preparation of a child for sedation for gastrointestinal endoscopy

	Preparation of the patient	Comments
Planning of the investigation /procedure	Understanding of the investigation	Explanation of the examination:
		Aims of investigation
		Possible risks
	Informed consent	Signed by parents and/or the child (depending on the age and legislation)
	Presedation assessment	Co-morbidity
		ASA score (Table 5)
		Medicines
		Bleeding tendency
		Previous undesirable effects of sedation/anesthesia
		Specific contraindications for the planned sedation
		Previous complications of investigations
		Allergies
		The need for antibiotic prophylaxis
		Laboratory investigation/consultation before the investigation/procedure (*e.g.*, tests of hemostasis in case of bleeding tendency)
		Additional important data
Preparation	Exact instructions (fasting time, colon cleansing *etc.*)	
On the day of examination	Focused history:	
	Current health state	
	Infectious diseases	
	Epidemiologic situation	
	Fasting	
	Allergy	
	Specific contraindications for the planned sedation	
	Physical examination	Complete physical examination with the focus on respiratory and cardiovascular system
	Measurement of vital signs	Arterial blood pressure
		Heart rate
		Arterial oxygen saturation
	Laboratory investigations	If needed

ASA: American Society for Anesthesiology.

Table 5 American Society of Anesthesiologists physical status classification[24]

Class	Description	Suitability for sedation
Class Ⅰ	A normally healthy patient	Excellent
Class Ⅱ	A patient with mild systemic disease (*e.g.*, controlled asthma)	Generally good
Class Ⅲ	A patient with severe systemic disease (*e.g.*, a child who is actively wheezing)	Intermediate to poor
Class Ⅳ	A patient with severe systemic disease that is a constant threat to life (*e.g.*, a child with status asthmaticus)	Poor
Class Ⅴ	A moribund patient who is not expected to survive without the operation (*e.g.*, a patient with severe cardiomyopathy requiring heart transplantation	Extremely poor

documented. An *iv* catheter is also important for emergency access in the case of adverse events occurring during sedation or the endoscopic procedure[25,36,37].

Mechanisms of action and the main undesirable effects of sedatives and adjuvant medicines are listed in Table 6[8,38-49]. Usual dosage regimens and the main contraindications are listed in Table 7.

Propofol

Propofol is a rapid onset and short acting anesthetic without analgesic properties and with a narrow therapeutic range. Its sedative properties result from agonistic action on gamma-aminobutyric acid (GABA) receptors. Propofol is contraindicated in infants younger than 1 mo bacasue of missing data on safety according to a Cochrane review[50]. The main undesirable effects include pain on injection, respiratory depression, bradycardia and hypotension[38,46].

van Beek and Leroy[2] reported failure to conduct a procedure due to incomplete sedation in only 0.0%–0.4% of cases, despite the fact that the sedation was performed in 88.1% by non-anesthesiologists[2]. The recovery time after propofol administration was shorter than after midazolam/meperidine[2]. Major respiratory complications occurred in 11/3883 propofol sedations (0.3%), but no I intubation and no sequelae were reported. The incidence of undesirable effects (*e.g.*, temporary desaturation due to hypoventilation, laryngospasm) was comparable to other protocols and was more frequent in younger children, especially infants[2].

A randomized study in 90 adults undergoing colonoscopy showed that the satisfaction of patients was greater

Table 6 Sedatives and adjuvant medicines for paediatric gastrointestinal endoscopy sedation

Generic name	Mechanism(s) of action	Main undesirable effects	Comments	Ref.
Sedatives				
Fentanyl	Opioid receptors agonist; analgesia and sedation	Respiratory depression, hypotension	Due to analgesic effect only it should be combined with benzodiazepine; antagonist naloxone	[38-40]
Ketamine	Binds to the Nmethyl-Daspartate (NMDA) receptors; anesthesia, analgesia, amnesia, sedation, immobilisation	Laryngospasm, hypertension, tachycardia, hypersalivation, vomiting, random movements, increase in intraocular pressure, emergence phenomena (floating sensations, vivid dreams, blurred vision, hallucinations, and delirium)	Beneficial respiratory properties and analgesic potency S(+) isomer has less adverse effects	[40-42]
Meperidine	Opioid receptors agonist; analgesia and sedation	Respiratory depression, pruritus, vomiting	Interaction with monoamine oxidase inhibitors	[38,43,44]
Midazolam	GABA receptor agonist; anterograde amnesia, anxiolysis, sedation, hypnosis	Respiratory depression, hypotension, paradoxical agitation	Without analgesic effect; should be combined with analgesic (usually opioids) Concomitant use with opioid increases the risk of respiratory depression antagonist flumazenil	[38-40]
Nitrous oxide	Inhalation anaesthetic	Vomiting, dizziness, voice change, euphoria, laughter	The need of scavenging system Use mostly limited to anaesthesiologists	[38,40,45]
Propofol	GABA receptor agonist; sedation, hypnosis, amnesia	Respiratory depression, apnoea, hypotension, painful injection		[38,40,46]
Sevoflurane	Inhalation anaesthetic	Recovery agitation, bradycardia, hypotension, cough, vomiting, seizures	The need of scavenging system Use limited to anaesthesiologists	[47-49]
Antagonists				
Flumazenil	Benzodiazepine antagonist	Nausea, vomiting	Contraindicated in benzodiazepine dependence, seizure disorder, cyclic antidepressant overdose, elevated intracranial pressure in patients, and in patients taking medicines known to lower the seizure threshold	[40]
Naloxone	Opioid antagonist	Nausea, vomiting, tachycardia		[40]

and there were less undesirable effects when they were sedated by an endoscopist than by an anesthesiologist[51]. A Scandinavian study tested a 6-wk educational program for registered nurses with excellent safety results[52].

The largest multicenter prospective study of propofol sedation for different pediatric procedures outside an operating theatre was published by the international (United States and Canada) Pediatric Sedation Research Consortium. They analysed the data of 49836 propofol sedation episodes and showed that propofol-based sedation is amongst the safest sedation practice for children[53]. Cardio-respiratory resuscitation was necessary in two cases. Pulmonary aspiration of gastric fluid secondary to vomiting during sedation occurred in four patients. Less serious respiratory adverse events were: desaturation in 154/10000 procedures; central apnea or upper airway obstruction in 124/10000; stridor in 10/10000; laryngospasm in 20/10000; excessive salivation in 73/10000; and vomiting in 10/10000 cases. The authors of this report estimate propofol sedation safe in children. Interestingly there were no differences in adverse effects between anesthesiologists and non-anesthesiologist. However, it should be pointed out that this report did not focus on upper GI endoscopy specifically, in which a shared airway is an important consideration, especially as attempting esophageal intubation may have the potential for induction of laryngospasm. However, it is stressed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Endoscopy Working Group that the advice of the Pediatric Sedation Research Consortium, including institutions with highly motivated and well organized sedation/anesthesia teams, is only to be considered when anesthetic teams are not available, and that priority should go to actions to obtain these anesthetic teams.

Chiaretti *et al*[7] published a retrospective study on pediatric procedural sedation with propofol over a 12-year period in three Italian hospitals[7]. They analyzed 36516 procedural sedations for different painful procedures. Deep sedation was achieved in all patients. None of the children experienced severe side effects or needed a prolonged hospitalization. In six patients (0.02%) emergency team had to intervene (prolonged laryngospasm in three patients, bleeding in one, intestinal perforation in one, and one during lumbar puncture). But milder adverse events were more often: hypotension in 19 patients (0.05%), ventilation by face mask and additional oxygen in 128 patients (0.4%), laryngospasm in 78 patients (0.2%), bronchospasm in 15 patients (0.04%). Minor complications were more often in children who underwent gastroscopy.

The usual loading dose of propofol is 2 mg/kg in infants and young children (younger than 3 years) and 1 mg/kg in older children and teenagers. Subsequent

Table 7 The list of sedatives/analgesic, adjuvant medicines and antagonists with usual dosage regimens, and main contraindications

Medicine generic name	Route	Dose	Time to start sedation/ analgesia (after *iv* application)	Sedation/ analgesia duration	Repeating time and dose	Contraindications	Comments	Ref.
Sedative/ analgesic								
Fentanyl	*iv*	1–2 μg/kg (up to 50 μg)	0.5 s	20–40 min (30–60 min)	3 min 1–1.25 μg/kg		Due to higher clearance younger children need frequent dosing	[38,40]
Ketamine	*iv* slowly over 1 min; other routes have less predictive effects and different dosing – see the discussion	1–1.5 mg/kg	1–5 min	15 min	10 min 0.5 mg/kg	Severe cardiovascular disease, malignant hypertension, CSF obstructive states (controversial), intraocular pressure pathology; previous psychotic illness, hyperthyroidism or thyroid medicine use; porphyria	A single enantiomer S(+); the anesthetic management of seriously ill hypovolemic patients, it may be the agent of choice for managing children and burned patients; low cost	[8,40-42]
Meperidine	*iv* slowly over 1–2 min	0.3–2 mg/kg	3–6 min	60–180 min		Simultaneous treatment with monoamine oxidase inhibitors		[38,43,44]
Midazolam	*iv* slowly over 2–3 min; other routes have less predictive effects and different dosing	0.05–0.1 mg/kg in < 5 yr (max. 0.6 mg/kg); in 6–12 yr 0.025–0.05 mg/kg (max.0.4 mg/kg); in older than 12 yr 2–2.5 mg (in total not per kg BW)	2–3 min	45–60 min	Repeating doses every 2–5 min until desired effect; in children 6 mo–5 yr total dose up to 0.6 mg/kg or max. 6 mg; in 6–12 yr total dose up to 0.4 mg/kg or max. 10 mg; in older than 12 yr additional boluses of 1 mg until desired sedation	Respiratory depression, hypotension	Rarely used as a sole sedative; might be used to sedate the frightened child before iv catheter placement; mostly combined with opioids; paradoxical irritation in 1%–5% of patients	[38-40]
Nitrous oxide	Inhalation	Mostly the mixture of nitrous oxide (50%) and oxygen	0.5–1 min	5 min	Continuously or "on demand"	Pneumothorax, bowel obstruction, head injury, pregnancy	Its use limited to anaesthesiologists	[38,40,45]
Propofol	*iv*	2 mg/kg in infants and young children (younger than 3 yr); 1 mg/kg in children older than 3 yr	1–2 min	5–15 min	1 mg/kg (infants and children up to 3 yr); 0.5 mg/kg (children older than 3 yr) to reach the desired sedation; may be continuously infused at 100 μg/kg per min and increasing the speed of infusion by 50 μg/kg per min for prolonged procedures	Egg or soy allergy	For additional medication to alleviate infusion pain see text; alfentanil but not fentanyl increases propofol blood level; in many countries the use is limited to anaesthesiologists	[38,40,46]
Sevoflurane	Inhalation	Different concentrations according to the age				Duchenne's muscular dystrophy, moderate to severe liver disease of unknown aetiology, history of malignant hyperthermia	Its use limited to anaesthesiologists	[47-49]
Antagonists								
Flumazenil	*iv*	0.02 mg/kg (max. 1 mg)	1–3 min	30 min	1 min; same dose	Chronic benzodiazepine use; ingestion of drugs that increase the risk for seizures development (*e.g.*, cyclic antidepressants, cyclosporine, and others)	Due to its shorter duration of action than most of benzodiazepines (*e.g.*, midazolam) repeated doses may be needed	[38,40]
Naloxone	*iv* or *i.m.*	0.1 mg/kg (max. 2 mg)	2 min	20–40 min	2 min; same dose	Hypersensitivity only	Due to its shorter duration of action than most of opioids (*e.g.*, fentanyl) repeated doses may be needed	[38,40]

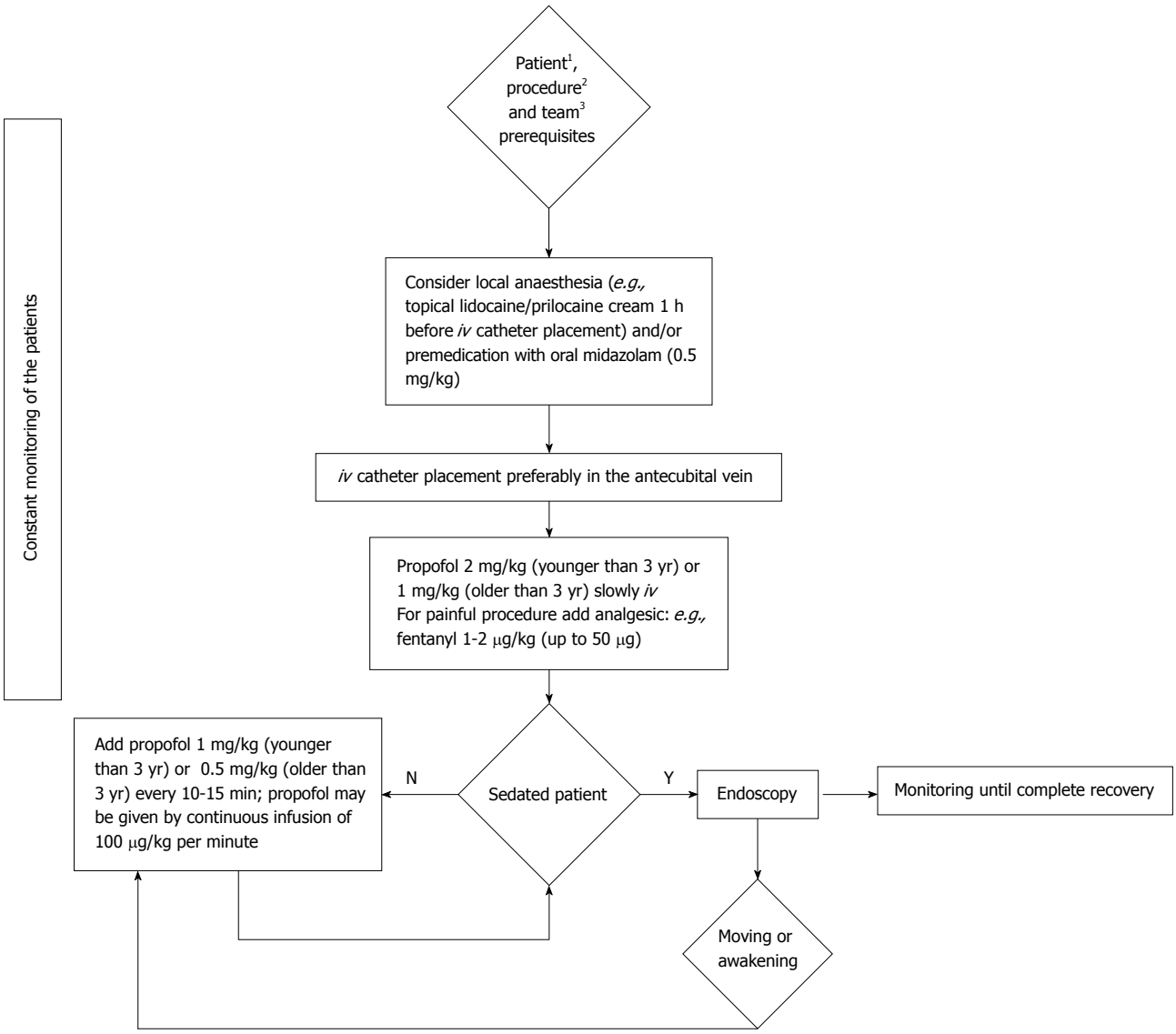

Figure 1 Flow chart of propofol sedation protocol for paediatric gastrointestinal endoscopy. [1]Older than 1 mo, without contraindications (egg or soy allergy); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

boluses of 1 mg/kg for younger, or 0.5 mg/kg for older children, may be added to ensure the appropriate level of sedation. For longer procedures propofol may be administered in a continuous infusion[38].

For painful procedures an analgesic must be added as propofol has no analgesic properties[38]. Bedirli *et al*[3] showed that the addition of tramadol or fentanyl to propofol provided efficient sedation, with less adverse events in the tramadol group (less desaturation, hypotension, and bradycardia; but more vomiting in fentanyl group)[3]. According to Gül *et al*[8] there was no difference in safety and efficacy between remifentanil and fentanyl co-administration with propofol.

The pain of propofol injection can be reduced by choosing a larger vein such as the antecubital site, or alternatively the injection of lidocaine[54]. A possible flow chart of propofol sedation for pediatric GI endoscopy is presented in Figure 1.

Generally, one cannot extrapolate data from adult practice to children. However, four different European Societies (of Gastrointestinal Endoscopy, of Gastroenterology, of Endoscopy Nurses and Associates, and of Anesthesiology) jointly issued guidelines for propofol sedation of adults for GI endoscopy by non-anaesthesiologists[16]. It is interesting that although the Board of Directors of the European Society of Anesthesiology (ESA) decided unanimously to endorse these guidelines, a majority of the national societies of the ESA did not support them. Consequently ESA retracted the endorsement[55]. The Danish training program for nurses includes training on how to administer propofol for GI endoscopic procedures in adults[52].

Ketamine

Ketamine is a dissociative anesthetic and analgesic. It is an N-methyl-D-aspartate channel antagonist and

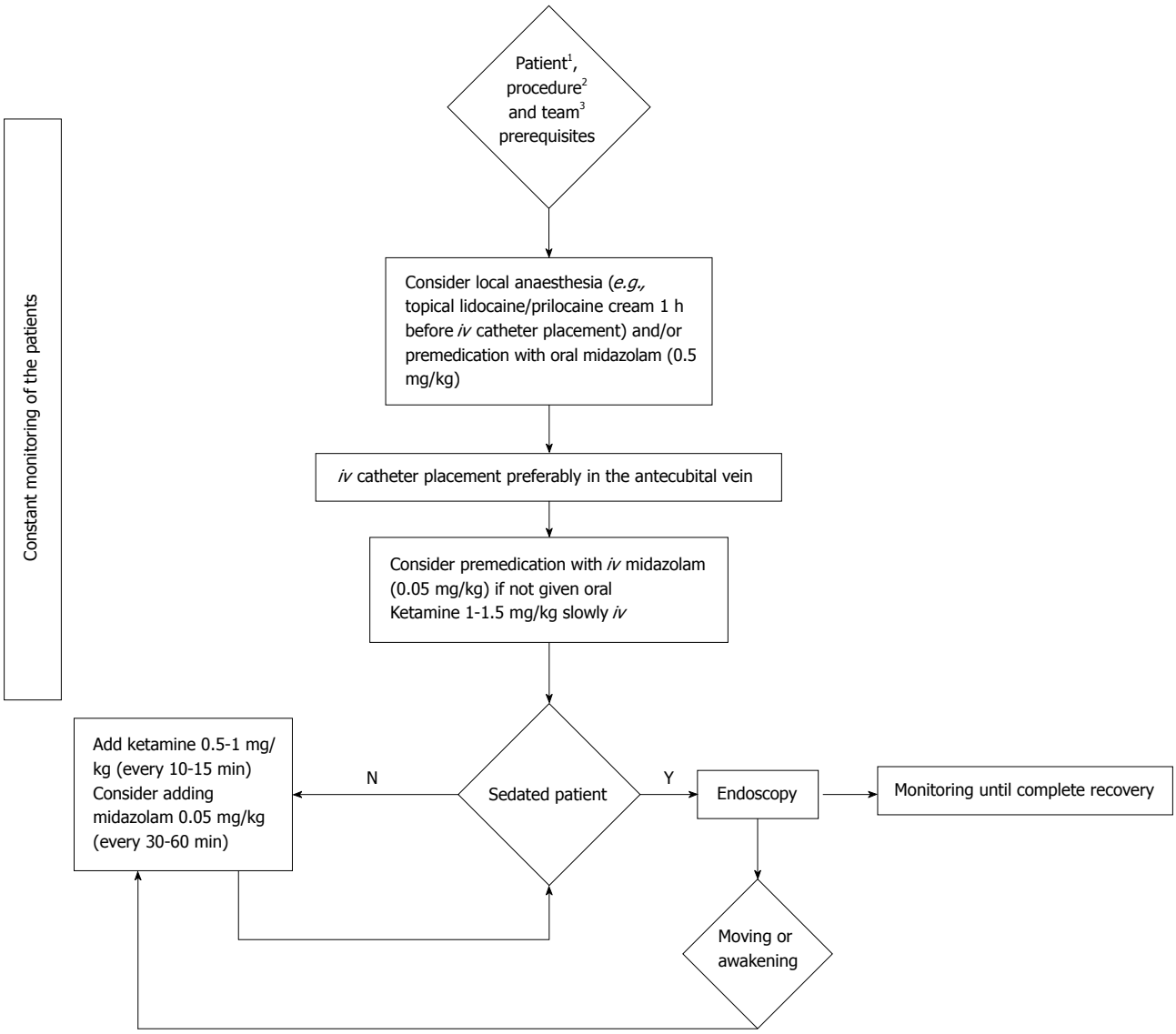

Figure 2 Flow chart of ketamine sedation protocol for paediatric gastrointestinal endoscopy. [1]Older than 3 mo, without contraindications (severe cardiovascular disease, malignant hypertension, CSF obstructive states, intraocular pressure pathology, psychotic illness, hyperthyroidism or thyroid medicines use, and porphyria); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

depresses sensory association areas of the cortex, limbic system and thalamus. It has been used for a long time for sedation and analgesia in emergency pediatrics due to its association with a preserve gag reflex and lack of respiration depression and hypotension[41]. Despite its good safety profile, the significant association with laryngospasm (especially with gastroscopy), emergence phenomena such as hallucinations, excitation, nightmares, delirium, recurrent illusions or "flashbacks", vomiting, and hypersalivation limit ketamine's broader use[27,38,41].

When used as a sedative, ketamine must be administered by slow *iv* injection at a dosage of 1-2 mg/kg initially. The sedative effect lasts 10-15 min. Repeated doses of 0.5 mg/kg prolong its action (Figure 2)[27,38].

The most frequent undesirable effects are vomiting, hypersalivation, nystagmus, hypertension, tachycardia, skin erythema, and emergence phenomena. Laryngospasm, which is potentially of greatest danger, is uncommon. The use of ketamine is contraindicated in infants younger than 3 mo, patients with psychosis, uncontrollable hypertension or hyperthyroidism, and as it increases intracranial and intraocular pressure. Ketamine should not be used after a head or eye trauma, or surgery, although some data advocate against these precautions[27,38].

The concomitant use of midazolam with ketamine decreases the frequency of emergence phenomena, although this remains controversial[56]. Two randomized double-blind studies performed in pediatric emergency departments did not find sufficient evidence to support the addition of midazolam for this purpose[57,58]. However, a randomized study using midazolam in co-administration with ketamine for pediatric sedation for GI endoscopy

suggests that midazolam does prevent emergence phenomena[4]. Other co-administered medicines might lessen some undesirable effects of ketamine but their use is not supported by sufficient evidence. Anticholinergics may prevent hypersalivation[59], but this has also been contradicted[60]. The anti-emetic ondansetron prevents vomiting in some patients[61].

Benzodiazepines and opioids

Midazolam is a short-acting benzodiazepine which is widely used for sedation but is generally considered to be insufficient as a monotherapy. It has anxiolytic, amnesic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties which result from GABA receptor activation[38,39]. The major undesirable effects are respiratory depression and hypotension, which are avoidable with appropriate dosing and are reversed by the antagonist flumazenil[38]. Other undesirable effects such as paradoxical agitation are reported in up to 15% of children[38].

Midazolam may be administered orally as an anxiolytic before the placement of an *iv* cannula but its effect is less predictive orally than when administered *iv* The usual starting dose is 0.1 mg/kg *iv* as a pre-medication but may be titrated to the desired effect by incremental doses of 0.05 mg/kg[39].

Opioids are potent analgesics which express their activity *via* different opioid receptors. The most suitable for sedation is fentanyl due to its rapid onset and short action. As it has no sedation properties it must be combined with benzodiazepines but the combination increases the risk of respiratory depression[38]. Other undesirable effects are itching, hypotension and vomiting but those are less pronounced than in histamine-releasing opioids such as morphine and meperidine[38]. Naloxone is an opioid receptor antagonist and is administered intravenously at 0.1 mg/kg[38].

Meperidine was the first synthetic opioid agent. It acts mainly as an antagonist of μ and κ receptors and has an analgesic potency ten times greater than that of morphine[62]. Like other opioid drugs, meperidine causes nausea, vomiting, urinary retention and respiratory depression. Its property of acting on nerve fibers, similar to those of local anesthetics, allows its use as an alternative for anesthetic blockade and differentiates it from other opioids. An *iv* route has been used for treating moderate to severe pain, for regional anaesthesia, for pre-medication and for analgesia during anesthesia. The combination of midazolam and meperidine can be used to achieve sedation and analgesia during colonoscopy[63]. There are few studies that have compared the efficacy of midazolam alone to midazolam and meperidine. According to Ozel *et al*[64], there were no significant differences in oxygen saturation/blood pressure but a better patient compliance was observed in the combined sedation group[64]. Cinar *et al*[65] showed that in respect of the recovery and procedure time there were no significant differences between the midazolam and the midazolam/meperidine group[65]. In a randomized trial comparing the efficacy and recovery time of two sedation regimens consisting of midazolam in combination with either meperidine or fentanyl, it was found that the fentanyl combination with midazolam resulted in a significantly faster recovery, without any apparent loss of analgesic effect[66]. Again, these are adult studies, and extrapolation to pediatrics is not necessarily appropriate.

Meperidine is administered intravenously at 1 mg/kg[64]. A possible flow chart of benzodiazepine and opioid sedation for pediatric GI endoscopy is presented in Figure 3.

Fentanyl is usually administered at 1–2 μg/kg. The analgesic effect lasts 20-40 min[38].

van Beek and Leroy[2]'s analysis found opioid and benzodiazepine sedation protocols suboptimal. These protocols were inferior in comparison to general anaesthesia. The comparison of midazolam/fentanyl with propofol sedation by Lightdale *et al*[67] addressed mainly procedure duration and discharge times which were similar for both groups, but the endpoint of this study was not to compare safety or efficacy.

Inhalation anesthetics

In most countries, legislation limits the administration of inhalation anesthetics to anesthesiologists.

Sevoflurane: Sevoflurane is an inhalational anesthetic with a very good safety profile (low incidence of airway hypersecretion, respiratory depression or cardiovascular events)[47]. When used for paediatric sedation for endoscopies it was characterized by a shorter recovery time and earlier discharge. Sevoflurane can only be administered by an anesthesiologist. The insertion of an *iv* catheter may not be needed. The use of inhaled anesthetics requires waste gas scavenging to prevent anesthetic gases being released into the ambient air[47].

There are no recently published studies on sevoflurane sedation for pediatric GI endoscopies.

Nitrous oxide: Nitrous oxide is an inert gas which has analgesic, sedative and amnesic properties of short duration. Michaud *et al*[68] reported a good experience with 50% nitrous oxide for gastroscopies and procto-sigmoidoscopies in children. They did not evaluate it for ileo-colonoscopy nor compare this type of sedation to other protocols[68]. There are no newer studies on nitrous oxide sedation for GI endoscopy in children.

In adults nitrous oxide has been used successfully for proctoscopies and colonoscopies. In a systematic review Welchman *et al*[45] analyzed in a systematic review 11 studies including 623 patients. Continuous nitrous oxide inhalation provided comparable analgesia to *iv* sedation for colonoscopies. There was no difference in procedural pain between on-demand nitrous oxide and no sedation for colonoscopies. The recovery time was shorter in the nitrous oxide groups[45].

Nitrous oxide is often more used as an anxiolytic before *iv* catheter placement if the face mask does not agitate the patient. However, most anesthesiologists

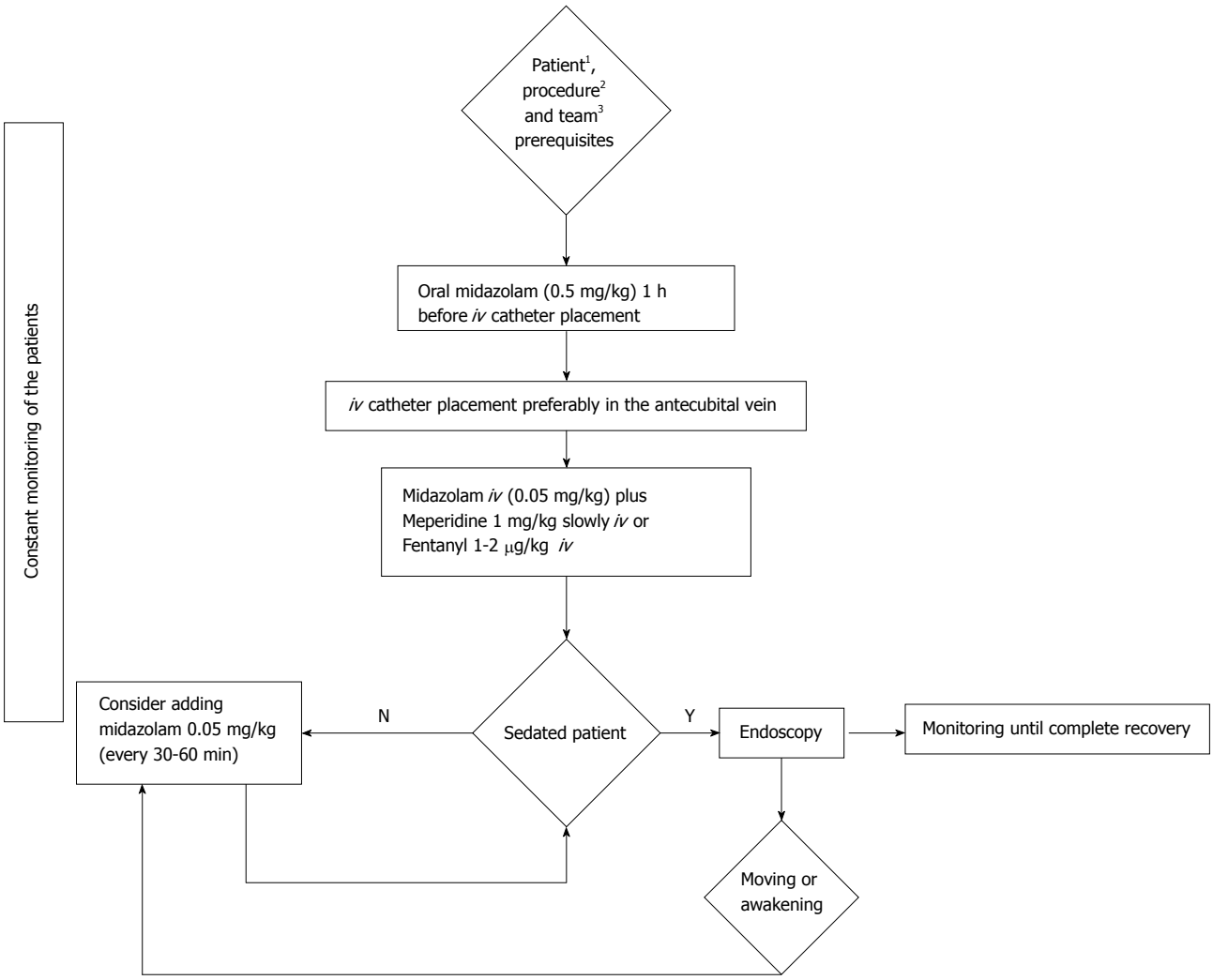

Figure 3 Flow chart of opioid and benzodiazepine sedation protocol for paediatric endoscopy. [1]Patient without contraindications (not being simultaneously treated with monoamine oxidase inhibitors); [2]Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; [3]The team qualified for paediatric sedation for gastrointestinal endoscopy.

would suggest that age-appropriate calming of a patient by engagement would have a similar result. Vomiting occurs in up to 10%. It is contraindicated in bowel obstruction and should not be administered if any of the team members is pregnant[38]. Its routine use in pediatric GI endoscopy is not ratified.

Adjuvant medicines and antagonists

Anti-cholinergics: As discussed in the section on ketamine, anti-cholinergics (*e.g.*, atropine or glycopirolate) decrease the hypersalivatory effect which may influence airway patency[59]. However, importantly, it should be noted that available evidence does not support this practice and anti-cholinergics are no longer routinely recommended[26,60].

Anti-emetics: Many sedative/analgesic agents (*e.g.*, ketamin, fentanyl), with the exception of propofol, provoke vomiting[50]. Ondansetron reduced the incidence of vomiting in a double-blind, randomized, placebo-controlled study in 255 children in an emergency department sedated by ketamine[61].

Flumazenil: Flumazenil is an antagonist used to reverse the undesirable effects of benzodiazepines such as respiratory depression. It is delivered *iv* at 0.1 mg/kg up to a maximum of 2 mg and has a rapid onset of action in 1-3 min. The half-life of flumazenil is shorter than that of other benzodiazepines (*e.g.*, midazolam) making close monitoring essential and reapplication sometimes needed[38,40].

Naloxone: Naloxone reverses opioid effects and results in normal respiration within 1-2 min of application of 0.1 mg/kg (up to 2 mg) *iv* or intramuscular. Its duration of action is around 20-40 min hence repeated doses might be needed as the duration of action of most opioids (*e.g.*, fentanyl) is longer[38,40].

DISCUSSION

Effective and safe sedation for pediatric endoscopic proce-

dures is a non-negotiable pre-requisite and an important factor for lowering patient distress. In principle, total *iv* anesthesia should be performed by anesthesiologists. However, it has to be recognized that in many countries, including a majority of European countries and in parts of the United States, the limited availability of anesthesiology teams and limited organizational considerations represents a medical dilemma. In many European countries anesthesia departments cannot cope with the increasing demands[37]. Therefore, a shortage of anesthetic teams may force pediatric endoscopists to conduct sedation without anesthetic teams applying guidelines adapted according to national regulations and institutional practices[4]. However, this situation is not optimal and requires consequent actions to increase the number of anesthesiologists.

In this situation, the intention of the authors is not to encourage such practice. This paper summarizes the evidence for sedation schemes which could be safely and efficiently performed by non-anesthesiologists. Sedation protocols have to be adapted to international, national and local legislation and institutional practice. The national institutions must organize multidisciplinary teams for education, licensing and supervision of non-anesthesiologists and registered nurses involved in sedation practices as long as there is a shortness of anesthesiologists. An efficient system of quality control is a paramount.

The choice of medicines for procedural sedation is wide, but none has the properties of an ideal sedative, which are: predictable dose dependent level of sedation with rapid onset; broad therapeutic window; anxiolytic effect with anterograde amnesia for the duration of the procedure; absence of respiratory, cardiovascular and other undesirable effects; and a smooth post-procedural recovery without side effects[34]. Another important problem in pediatrics is the off-label use of many medicines, which was recently addressed for medicines prescribed for outpatients in pediatric gastroenterology[69]. The investigators found that in 33.2% of the prescriptions, medicines were used "off-label" and that 47.3% of the patients had at least 1 medicine described as an "off-label" medication. Sedatives and other *iv* medicines were not covered by this study. The legal risk of a prescribing doctor is greater when using "off-label" medicines or indications. Parents should be informed of the "off-label" use. A solution of this problem is to motivate the pharmaceutical companies to register medicines for pediatric use, as has happened in the majority of the EU Countries under the jurisdiction of the European Medical Agency for new medicines.

Propofol is probably the most promising and controversial sedative/anesthetic at present. It is stated that only those trained in anesthesia should use it, a position that anesthesiologists and their societies strongly defend[70]. On the other hand, there are studies of safe and efficient use of propofol for sedation for GI endoscopic investigations in pediatric and adult gastroenterology[2,3,7,8,51,71]. The administration of propofol by non-anesthesiologists is "off-label" in most cases and, therefore, every adverse event might have medico-legal consequences.

Therefore, these data could not be simply extrapolated to every sedation/analgesia practice. According to the review by Havidich *et al*[72] the evidence of the safety of sedation by non-anesthesiologists for procedures outside operating theatres is growing, especially for propofol. Despite the drawbacks listed above, published data justify propofol use in certain circumstances[2].

Ketamine-based sedation is safe and effective in otherwise healthy infants older than 3 mo[27]. Ketamine has dissociative anesthetic and analgesic properties with a wide safety margin and is frequently used in pediatric emergency departments[27,28]. Emergence reactions are observed in adults in up to 28%, but seem less prevalent in paediatric studies and not influenced by the addition of midazolam to ketamine[56-58]. Guidelines advised against routine benzodiazepine pre-medication[27,28]. Data from larger studies are needed as one recent study found less emergence reactions when midazolam was routinely administered as a pre-medication[4]. Another major limitation of ketamine-based sedation for endoscopy is laryngospasm. In general, the laryngospasm resolves without consequences rapidly after removal of the endoscope and administration of oxygen[73]. Another study reports transient laryngospasm manageable with simple measures in 3% of gastroscopies[4]. Therefore, the ketamine-based sedation regime for GI endoscopy is an acceptable option when sedation with propofol is not feasible.

Midazolam is most likely the most widely used drug for sedation in everyday endoscopic work. The duration of action of midazolam is dependent on the duration of its administration. The sedative and amnestic effects of benzodiazepines sometimes do not provide adequate patient comfort during colonoscopic procedures[74]. Opioids are often added and meperidine is commonly used[75]. The value of adding analgesics to sedatives has well evaluated in large number of prospective, randomized and placebo-controlled studies[76]. Sedation with midazolam/meperidine is safely and can be administrated under adequate monitoring[77].

These recommendations review and discuss sedation practices for pediatric GI endoscopy which can be safely and efficiently performed by non-anesthesiologists, but only when the necessary pre-requisites regarding patient assessment, team composition and experience, medicines and equipment are met.

ACKNOWLEDGMENTS

The authors reviewed the literature and made practical recommendations for effective and safe sedation for endoscopic procedures in children. However, the authors decline every legal responsibility for the proposed algorithms. Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country.

Therefore, limitations caused by local legislation should be carefully checked.

COMMENTS

Background

Anesthesia is by preference performed by anesthesiologists.

Research frontiers

The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Innovations and breakthroughs

The intention of this review is to offer effective and safe alternatives for non-anesthesiologists.

Peer-review

The present paper was well organized and well investigated. This paper will give us important information about the anesthesia during endoscopy especially in children.

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CASE REPORT

Carcinoma *in situ* in a 7 mm gallbladder polyp: Time to change current practice?

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Abstract

Detection of polypoid lesions of the gallbladder is increasing in conjunction with better imaging modalities. Accepted management of these lesions depends on their size and symptomatology. Polyps that are symptomatic and/or greater than 10 mm are generally removed, while smaller, asymptomatic polyps simply monitored. Here, a case of carcinoma-*in-situ* is presented in a 7 mm gallbladder polyp. A 25-year-old woman, who had undergone a routine cholecystectomy, was found to have an incidental 7 mm polyp containing carcinoma *in situ*. She had few to no risk factors to alert to her condition. There are few reported cases of cancer transformation in gallbladder polyps smaller than 10 mm reported in the literature. The overwhelming consensus, barring significant risk factors for cancer being present, is that such lesions should be monitored until they become symptomatic or develop signs suspicious for malignancy. In our patient's case this could have led to the possibility of missing a neoplastic lesion, which could then have gone on to develop invasive cancer. As gallbladder carcinoma is an aggressive cancer, this may have led to a tragic outcome.

Key words: Gallbladder; Polyp; Cholecystectomy; Size; Carcinoma

Core tip: Current guidelines for management of gallbladder polyps recommend cholecystectomy for

polyps with size > 10 mm and/or presence of symptoms. Considering some cases of carcinoma in polyps with size less than 10 mm have been seen, consideration of a cholecystectomy for smaller size polyps is warranted.

Kasle D, Rahnemai-Azar AA, Bibi S, Gaduputi V, Gilchrist BF, Farkas DT. Carcinoma *in situ* in a 7 mm gallbladder polyp: Time to change current practice? *World J Gastrointest Endosc* 2015; 7(9): 912-915 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/912.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.912

INTRODUCTION

Detection of polypoid lesions of the gallbladder (PLG) has become increasingly more frequent over the last thirty years primarily due to an increase in the use of ultrasound and other imaging modalities in evaluation of patients with abdominal complaints. In the adult population, 0.03%-9.5% of people are estimated to have PLG[1]. Due to the malignant potential of these lesions their management has been well documented[2,3].

In current practice, symptomatic lesions or polyps greater than 10 mm warrant cholecystectomies, while asymptomatic polyps less than 10 mm are followed with routine ultrasound every 3-6 mo for one to two years[3]. Here, we present a case of a 25-year-old woman who presented with a 7 mm PLG which was found, after cholecystectomy, to contain carcinoma-*in-situ*. Our goal is to add to existing literature of PLG and to caution physicians that delaying polyp removal simply due to lack of a lesion's symptoms or significant size may be harmful.

CASE REPORT

A 25-year-old female presented to the emergency room with right upper quadrant abdominal pain for duration of 2 d. On physical examination she had mild tenderness in right upper quadrant. Laboratory work up revealed: WBC 7500/mL, ALT 148, AST 254, ALP 119, Total Bilirubin 0.5 and direct bilirubin 0.3. Ultrasound examination showed multiple gallstones and a common bile duct (CBD) of 12 mm. She underwent an endoscopic retrograde cholangiopancreaticography at which time her CBD was cleared of stones, and subsequently a laparoscopic cholecystectomy was performed. The postoperative period was uneventful and the patient was discharged home.

The final pathology report revealed acute and chronic cholecystitis with multiple small gallstones. An incidental 7 mm pedunculated tubular adenoma was seen in the fundus of the gallbladder, with a segment of carcinoma *in situ*.

The patient was informed, and an appointment for oncology was arranged, but the patient chose not to go. Current guidelines do not recommend further treatment for T1a tumors, and certainly not for Tis disease[4,5]. Even aggressive surveillance is not recommended according to the National Comprehensive Cancer Network[6]. The patient next presented to our hospital system for an unrelated problem three years later, and was showing no signs of disease.

DISCUSSION

Approximately 4% of the adult population is estimated to have gallbladder polyps, the majority of which are benign cholesterol lesions[1,2]. Adenomas comprise the second most common PLG, 3% to 8% of which are reported to have malignant potential[1,2].There is no correlation between symptomatology and the probability of a malignant lesion. As such, there is no reliable way of differentiating a benign polyp from a malignant one outside of pathologic examination of the polyp[1,3].

The consensus regarding resecting a patient's gallbladder or leaving it in place has been widely documented. A search including PubMed, Embase, and Web of Science was done to locate relevant literature on the subject. Keywords included gallbladder, polyps, carcinoma or neoplasms, and gallbladder neoplasms were used.

Boulton *et al*[7] published the basic algorithm utilized today which differentiates lesions primarily based on size and symptoms but also included "complicating factors," or risks, in ultimately making a decision[8]. These risk factors include age greater than 50 and the presence of gallstones. Cha *et al*[9] include diabetes mellitus as a significant risk, while Myers *et al*[1] include polyp growth and a solitary lesion among these complicating factors, but state that no "consistent profile" exists among patients. Polyps > 10 mm (or some say > 9 mm) are resected regardless of a person's symptoms or risk factors, as are symptomatic PLG[7,10]. All asymptomatic lesions < 10 mm in patients with limited/no risk factors are monitored by ultrasound[7]. The duration of monitoring is inconclusive with some sources quoting every 3-6 mo for 1-2 years, while others state that lesions less than 6 mm do not need monitoring at all[3,7,10,11].

A number of studies have been done in an attempt to ascertain the appropriate size that gallbladder polyps should be removed due to their risk of malignant potential. Corwin *et al*[10] published a study in 2011 describing 346 patients with PLG. Following these patients with cholecystectomy and serial ultrasound, no neoplastic lesions were found in polyps < 6 mm, one neoplastic polyp was noted in polyps 7-9 mm, and two polyps greater than 10 mm were neoplastic[10]. Their conclusion was that PLG's < 6 mm require no follow up, but regarding lesions > 7 mm no conclusion could be made and further studies were recommended[10]. Another study published in 2010 by Matos *et al*[12] followed 93 patients, 91 of whom had benign polyps and two who had malignant ones. Of the two, which were found to be malignant, the average size in diameter was 18.8

mm and they concluded that polyp diameters greater than 10 mm were required to induce surgery, assuming no known risk factors existed[12]. Several other studies of asymptomatic patients with PLG have been reported in the literature, with case series ranging between 161 and 417 patients. These have all come to the conclusion that 10 mm or greater was the appropriate cutoff in asymptomatic patients with no risk factors to require surgery[13-15].

In our patient, a 7 mm polyp was incidentally identified after a cholecystectomy performed due to symptomatic gallstones. Upon pathological examination carcinoma *in situ* was discovered within the lesion. In a less fortunate person with a PLG and no symptomatic gallstones, current management would have resulted in missing a precancerous lesion. Considering that gallbladder carcinoma usually presents late, with a five-year survival from 5%-13%[16], this may have led to a detrimental outcome in our patient. This is a drastic difference in survival outcome compared to gallbladder cancers that are removed early, which has up to a 95% to 99% survival if extracted prior to muscularis and mucosal invasion, respectively[17].

Our patient demonstrates the care that must be taken regarding the management of polyps even smaller than 10 mm. This is especially true considering the significant benefit of avoiding a serious cancer relative to the small risk of surgical complications. Perhaps we should consider removing gallbladders with asymptomatic PLG that are between 5 mm-10 mm in size even in the absence of known risk factors. While this paper adds to the growing literature on these smaller size polyps, larger studies with more cases are necessary before formal recommendations can be made.

COMMENTS

Case characteristics

A 25-year-old woman presented with right upper quadrant abdominal pain for two days.

Clinical diagnosis

There was mild right upper quadrant tenderness on exam, with no jaundice.

Differential diagnosis

Differential diagnosis included acute cholecystitis or biliary colic, with choledocholithiasis less likely at this point.

Laboratory diagnosis

White blood cell count was normal, with elevation of transaminases, minimal elevation of alkaline phosphatase and normal bilirubin.

Imaging diagnosis

Ultrasound showed gallstones and a significantly dilated common bile duct of 12 mm.

Pathological diagnosis

Acute and chronic cholecystitis with gallstones, and an incidental finding of a 7 mm gallbladder polyp with carcinoma *in situ*.

Treatment

Patient underwent endoscopic retrograde cholangiopancreaticography and then laparoscopic cholecystectomy, which is sufficient for her carcinoma *in situ*.

Related reports

Other reports have suggested observation for polypoid lesions of gallbladder less than 10 mm.

Term explanation

Polypoid lesions of the gallbladder refer to lesions seen on imaging that look like a polyp, as opposed to stones which are mobile and layer in the dependent region of the gallbladder.

Experiences and lessons

The important lesson from this case is that malignant degeneration can develop in polyps less than 10 mm in size.

Peer-review

This adds to the literature of polyps less than 10 mm, and can suggest lowering the threshold for recommending cholecystectomy, but more research with larger numbers is necessary.

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CASE REPORT

Unusual complication of amebic liver abscess: Hepatogastric fistula

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Abstract

Amebic liver abscess is a parasitic disease which is often encountered in tropical countries. A hepatogastric fistula secondary to an amebic liver abscess is a rare complication of this disease and there are only a handful of reported cases in literature. Here we present a case of an amebic liver abscess which was complicated with the development of a hepatogastric fistula. The patient presented with the Jaundice, pain and distension of abdomen. The Jaundice and pain improved partially after he had an episode of brownish black colored increase in frequency of stools for 5 to 6 d. Patient also had ascites and anemia. He was a chronic alcohol drinker. Esophagogastroduodenoscopy performed in view of the above findings. It showed a fistulous opening with bilious secretions along the lesser curvature of the stomach. On imaging multiple liver abscesses seen including one in sub capsular location. The patient was managed conservatively with antiamebic medications along with proton pump inhibitors. The pigtail drainage of the sub capsular abscess was done. The patient improved significantly. The repeat endoscopy performed after about two months showed reduction in fistula size. A review of the literature shows that hepatogastric fistulas can be managed conservatively with medications and drainage, endoscopically with biliary stenting or with surgical excision.

Key words: Amebic liver abscess; Hepatogastric fistula; Esophagogastroduodenoscopy; Entaameba histolytica; Ultrasonography; Computed tomography

Core tip: Hepatogastric fistula is a rare complication of the amebic liver abscess. High index of suspicion is required for its diagnosis. The presenting complaints may be brownish black vomitus or stool. It can be managed conservatively, endoscopically or surgically depending on case. Hence in cases of amebic liver abscess developing brownish black stools or vomiting we should always rule out hepatogastric fistula formation especially when it is associated with improvement of symptoms.

Pawar SV, Zanwar VG, Gambhire PA, Mohite AR, Choksey AS, Rathi PM, Asgaonkar DS. Unusual complication of amebic liver abscess: Hepatogastric fistula. *World J Gastrointest Endosc* 2015; 7(9): 916-919 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i9/916.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i9.916

INTRODUCTION

Amebic liver abscess is a parasitic disease which is commonly encountered in tropical countries[1]. A hepatogastric fistula secondary to an amebic liver abscess is a rare complication and only a handful of cases have been reported in literature[2,3]. A patient presenting with an anchovy sauce like vomitus or stool along with a simultaneous decrease in a preexisting pain in the abdomen should alert a clinician to the possibility of a hepatogastric fistula due to an abscess. There are a few other causes of this clinical entity. This condition can be managed conservatively with antibiotics and proton pump inhibitors, failing which surgery is the treatment of choice. Surgery involves excision of the fistulous tract with anastomosis. Here we report a case which presented with an anchovy sauce like stool and was successfully managed conservatively.

CASE REPORT

A 47-year-old male, with a history of regular alcohol intake presented with a history of pain and swelling in right upper abdomen which was mild to moderate in intensity, dull aching in character with occasional throbbing sensation with no radiation to any other site. The pain lasted a month and a half and was followed by generalized distension of the abdomen. This was accompanied with high color urine and jaundice. There was no fever. The patient then developed an increased frequency of stool which was liquid brownish-black and went on for 6 d. This was associated with a marked improvement in the abdominal pain and a decrease in the swelling over right upper abdomen. On examination there was tender hepatomegaly with ascites. The patient's hemoglobin was 9.3 g/dL and leucocyte count was 16700/mcl. There was reversal of albumin and globulin ratio, increase in aspartate transaminase was more than alanine transaminase and increased total and direct bilirubin. Ascitic routine microscopy revealed a high serum ascites albumin gradient. Patient's ultrasonography showed hepatomegaly with multiple heterogeneous solid cystic lesions with thickened walls, the largest measured 13.7 cm × 7.5 cm. In view of a history of daily alcohol intake with recent onset of black stool and a physical finding of ascites an esophagogastroduodenoscopy was performed. The study revealed a 2 cm × 2 cm deep ulcer with bilious discharge just above incisura on lesser curvature of the stomach (Figure 1). There were no varices. On further evaluation computed tomography (CT) suggested multiple large hepatic abscesses in both lobes of liver, the largest measuring 12.8 cm × 8.6 cm × 3.4 cm in the right lobe of liver. One of the abscesses in right lobe was sub capsular. The left lobe of liver had a hepatic abscess in segment 3 which had an exophytic extension and was indenting the lesser curvature of stomach. Air pockets were seen in the abscess cavity suggesting the probability of a fistulous opening within the stomach (Figure 2). His blood antibodies [enzyme linked immunosorbent assay (ELISA)] for entaamoeba histolytica came positive. An ultrasonography guided pigtail catheter was placed in right sub capsular abscess. The abscess content was anchovy sauce like. Pus culture was negative for bacteria. He was started on metronidazole and other supporting medications. He was also started on diloxanide furoate for luminal clearance of cysts. The patient improved clinically and at 4 wk a repeat endoscopy was performed. It showed a significant decrease in the size of the fistulous tract. A surgical option was explained to the patient and his relatives but they opted for medical line of management in view of risk associated Child Pugh C status. He was continued with close monitoring with proton pump inhibitors. The patient has been in regular follow up since the past 6 mo. The patient had American society of anesthesiologists' classification of physical status of 4 on presentation, 3 at the time of discharge and 2 at 6 mo follow up.

DISCUSSION

The prevalence of E. histolytica infections in India has been shown to range from 3.6% to 47.4% in different areas[1]. Amebic liver abscess occurs in less than 1% of entaameba histolytica infested patients[2]. Liver abscess rupturing into the pleural and peritoneal cavities is a relatively common phenomenon[3]. Only a handful of case reports of hepatogastric fistula have been published till now as it is a rare complication[3]. Hepatogastric fistulas have also been reported in cases of hepatocellular carcinoma intruding into stomach and presenting as an upper gastrointestinal bleed[4], post embolization for hepatocellular carcinoma leading to the formation of an abscess[5], as a complication of placing a pig tail in a liver abscess and also in cases of post hepatic surgeries. An iatrogenic hepatogastric fistula can be done for biliary drainage in infants with congenital obstructive jaundice.

The presentations of hepatogastric fistula secondary

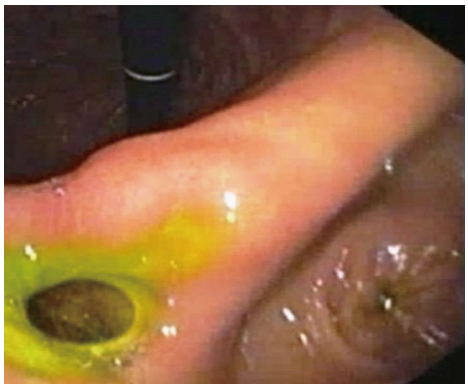

Figure 1 On retroflexon in stomach fistula with bile seen.

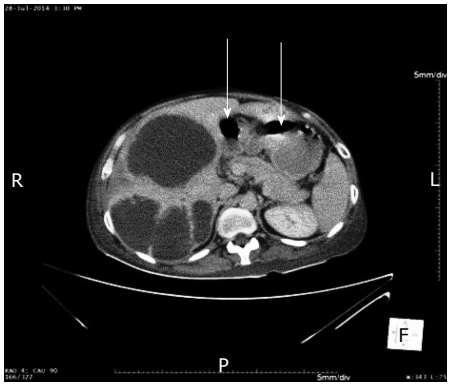

Figure 2 Multiple liver abscess with air pocket seen in the abscess in left lobe. (White arrows).

to amebic liver abscess can be as an anchovy sauce color vomitus or stool, hematemesis or malena[6]. In our patient decompression of the abscess into the stomach probably lead to the anchovy sauce color of stool and subsequent improvement of pain. Diagnosis was made based on the imaging and endoscopic findings. ELISA test for detecting antibodies was done for confirming entaameba histolytica as the causative agent. On the CT scan images the abscess seen with air pocket in continuation with the stomach was also a clue to the presence of the fistula (if it was performed before the endoscopy). On esophagogastroduodenoscopy the fistulous opening was seen as deep ulcer with (as in our case) or without bilious discharge[3]. In our case the diagnosis was confirmed taking into account the serology, CT finding and endoscopic findings. Rupture of an amebic liver abscess into an adjacent structure such as pleural and peritoneal cavity is a life threatening condition but rupture into stomach is not a dreaded complication.

Definitive management is surgical but if the patient's general condition does not permit surgery (as in our case) conservative management has also showed improvement[7]. Conservative treatment includes metronidazole for clearance in extraintestinal site and diloxanide furoate or paromomycin for luminal clearance. In certain cases of impending rupture of sub capsular abscess, pigtail drainage of the liver abscess has to be done to avoid complications. Biliary stenting has been found to hasten the recovery due to selective drainage of bile through common bile duct[8]. Nutrition can be given through per oral, nasojejunal tube, or feeding jejunostomy. Spontaneous closure of fistula can be seen within 5 wk of conservative management which was observed in our case[9]. If no improvement is observed on conservative management or if there is clinical worsening then surgical excision of the fistulous tract with gastric anastomosis is an option. Complications of hepatogastric fistulas include sepsis, debilitation and electrolyte imbalance[10].

In conclusion, hepatogastric fistula is a very unusual complication of liver abscess. One has to have a high index of suspicion for it to be diagnosed early. Management can either be conservative, endoscopic or surgical. We have managed this patient conservatively as patient was Child Pugh C status and high risk for surgery.

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COMMENTS

Case characteristics

A 47-year-old male, chronic alcoholic presented with pain and distention of abdomen along with jaundice followed by brownish black diarrhea for 5 to 6 d.

Clinical diagnosis

Patient was having symptoms of chronic liver disease along with hepatomegaly and pain specifically in right upper quadrant.

Differential diagnosis

This is a case of chronic liver disease with either hepatocellular carcinoma or liver abscess or spontaneous bacterial peritonitis causing decompensation of liver disease.

Laboratory diagnosis

Patient had anemia and high leucocyte count along with inversion of albumin and globulin ratio and presence of antibodies to entaameba suggestive of chronic liver disease along with infection.

Imaging diagnosis

Ultrasonography and computed tomography suggestive of liver abscess with air in left lobe abscess probably fistulous opening which is confirmed on esophagogastroduodenoscopy.

Treatment

Patient was managed conservatively with metronidazole, diloxanide furoate.

Related reports

Very few case reports were published related to hepatogastric fistula due to hepatocellular carcinoma, iatrogenic and abscess.

Term explanation

Hepatogastric fistula is communication of liver with stomach due to various etiologies.

Experiences and lessons

High index of suspicion is required for diagnosis of hepatogastric fistula. Patient had marked improvement in pain and upper right quadrant swelling once he had brownish black stools for 5 to 6 d. Though rare, knowledge of this complication leads to early diagnosis and prompt treatment.

Peer-review

This is a well prepared and detailed case report referring to a rare complication of amebic liver abscess, a hepatogastric fistula. The manuscript is well organized with a comprehensive discussion section.

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