Role of endoscopic submucosal dissection in treatment of rectal gastroenteropancreatic neuroendocrine neoplasms

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Abstract

Introduction: A significant rise in incidence of rectal gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) has been observed in the last decade. Most detected gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are well differentiated and less than 2 cm in diameter. Endoscopic submucosal dissection (ESD) is a new method for endoscopic treatment of such tumors, difficult to resect by conventional endoscopic techniques and thus subject to surgical treatment.

Aim: To present the results of the endoscopic treatment of GEP NET tumors in the rectum using ESD in single academic center.

Material and methods: From June 2013 to April 2014, 4 cases of GEP-NET in the rectum were treated by ESD in our center. Effectiveness of dissection, complications and tumor recurrence after 3 months of treatment were then retrospectively investigated.

Results: The group contained 2 patients with primary rectal GEP-NET (1 male, 1 female; age range: 48–60 years) and 2 with scars after incomplete polypectomy of rectal GEP-NET (1 male, 1 female; 61–65 years). Primary rectal GEP-NET diameters were 0.6 cm and 1.5 cm. Scar resection specimen diameters were 0.7 cm and 1 cm. Mean resection time was 28 min. The en bloc resection rate was 100% (2 of 2) and the histologically complete resection was confirmed in both cases. No foci of neuroendocrine neoplasia were reported in dissected scars. No complications were observed. After 3 months, 3 patients underwent follow-up colonoscopy – no local recurrence was reported.

Conclusions: Endoscopic submucosal dissection of rectal GEP-NET should be recommended as a treatment of choice when dealing with lesions over 1 cm in diameter without invasion of the muscle layer. Due to technical difficulties, performing this procedure should be reserved for centers with appropriately trained endoscopic staff.

Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), previously called gastroenteropancreatic neuroendocrine tumors (GEP-NETs), are relatively rare lesions that are derived from the diffuse endocrine system (DES) within the gastrointestinal tract [1]. The detection of this type of cancer has significantly increased in recent years. In 2004 the incidence of NET reached the level of 5.25 per 100 000 persons per year. The Surveillance, Epidemiology, and End Results (SEER) program in the United States and the Norwegian Registry of Cancer (NRC) observed an increase in incidence of gastric and colorectal GEP-NEN, with the most common site being the small intestine (37.4%), in contrast to the previously reported appendix. The GEP-NENs comprise over 50% of all NENs and in the US are mostly related to patients of Afro-Caribbean origin. In Caucasians NEN is currently the most frequently diagnosed in the lungs (30% of new NEN diagnoses) [2]. There is slightly higher incidence in men (5.35 per 100, 000 per year) compared to women (4.76 per 100 000 per year) [3, 4]. Within the last 30 years, the age-related incidence of small intestine and digestive tract NENs has increased by 460% and 720% respectively. This is due to greater detectability of these lesions by improved availability of high-resolution endoscopy and diagnostic imaging. Previously, GEP-NENs were found accidentally during abdominal surgery or diagnosed in the presence of symptoms and signs specific to the substances they produce, e.g. with the well-known carcinoid syndrome, which is associated with midgut GEP-NEN after it has metastasized to the

liver [5]. The NENs producing hormonal substances that cause the characteristic symptoms are called functioning. Others – called non-functioning – produce hormonal substances in quantities insufficient to observe the symptoms unless due to local effects of the primary tumor. In 2010 the WHO introduced a new classification, which divided gastroenteropancreatic (GEP) NENs into three groups, based on their pathological grading i.e.: neuroendocrine tumors (NETs, equivalent to carcinoids) that are well differentiated and graded according to their proliferative activity into G1 or G2, and neuroendocrine carcinomas (NECs) that are poorly differentiated and graded as G3. Well-differentiated NETs of the gastrointestinal tract comprise 50% of all GEP-NENs. Due to the character of these tumors, a systematic multidisciplinary approach is essential in order to properly diagnose and manage patients with GEP-NENs.

Treatment modalities

Surgery plays a major role in both primary treatment for localized tumors as well as a part of medical treatment of advanced disease. Surgical treatment varies according to the site and size of the tumor, and single or multifocal character of disease, and can be divided into:
– Curative resections;
– Cytoreductive procedures – aimed at optimally achieving 90% reduction in tumor mass, which might help to improve systemic treatment. In the case of liver metastasis, cytoreduction is recommended if more than 70% of the tumor load is thought resectable;
– Palliative treatment – to diminish symptoms and improve quality of life in unresectable disease (surgical procedures, endoscopic radiofrequency ablation, embolization, drainage).

Rectal gastroenteropancreatic neuroendocrine tumors

During the last decade, the highest rise in incidence of GEP-NET has been observed in the rectum. Many of the observed tumors are less than 1 cm in diameter and remain asymptomatic. Accordingly, the nature of the treatment is usually determined by the size of the tumor. Until recently, endoscopic treatment of rectal NET was limited to tumors with a diameter of less than 1 cm and in selected cases to tumors with a diameter up to 2 cm, i.e. those not invading the muscle layer, without the presence of enlarged lymph nodes or ulceration of the mucosal layer over the tumor. Rectal NET with a diameter greater than 2 cm was usually treated according to the standards applicable to adenocarcinoma of the rectum (rectal resection with mesorectal excision). Currently, the rapid development of new endoscopic techniques and the introduction of such procedures

as endoscopic ultrasonography (EUS) and endoscopic submucosal dissection (ESD) enable an accurate assessment of NET local progression as well as precise radical excision of the tumor. This leads to increased use of endoscopic methods as the treatment of choice in dealing with GEP-NET tumors located in the rectum, which is a preferred alternative to surgical treatment.

Aim

In this paper we aim to present the results of our experience with endoscopic treatment of GEP-NET tumors in the rectum using ESD.

Material and methods
Patients

The colorectal ESD service was commenced in the Department of General and Colorectal Surgery, Medical University of Lodz in June 2013. It was preceded by training of one surgeon in an endoscopic center of excellence in Japan – Showa Digestive Disease Center, Yokohama. Patients were referred to ESD from the departmental Outpatient Clinic and Colonoscopy Service. By June 2014, 4 ESDs of rectal neuroendocrine tumors had been performed in our institution.

Endoscopic submucosal dissection procedure

Patients were admitted to the hospital on the day of the procedure. The day before ESD patients had bowel preparation using 4 l polyethylene glycol (PEG). If there were additional comorbidities, especially diabetes, patients were admitted on the day before the procedure and had bowel preparation in the hospital. The following laboratory parameters were routinely determined: full blood count (FBC), serum electrolytes, blood group, activated partial thromboplastin time (APTT), and international normalized ratio (INR). In some high-risk patients, tumor markers (CEA and Ca 19-9) were additionally determined. Antiplatelet agents and anticoagulants were discontinued for 5 days before and 1 week after ESD. Analgesia was not administered routinely. Fentanyl was administered in the event of severe pain during the procedure. Endoscopic submucosal dissection was performed in the endoscopic room, outside the operating theater. Endoscopic submucosal dissection was principally carried out by using a single-channel endoscope (Olympus EVIS Exer II CF-Q180AL/I) with a disposable distal attachment (D-201-14304, Olympus), mounted onto the tip of the endoscope. ERBE VIO 200D was used for pure dissection. The dissection was performed with an Olympus Dual Knife (KD-650L). All procedures were documented using Endobase Olympus. Dissection

started from topical administration of 0.4% indigo carmine using a catheter-type spray Olympus (PW-250V) to delineate the lesions. Then, after an assessment of tumor boundaries, the lesion was elevated by injecting into the submucosa the hyaluronate sodium solution outside the tumor margin. Hemostatic forceps (Coagrasper, FD-411UR, Olympus) were used to stop more severe bleeding or to prevent hemorrhage before vessel cutting. After completion of the dissection, mucosal edges were carefully investigated to minimize the risk of leaving a residual tumor lesion. Procedural time was determined from the insertion of the camera into the rectum to complete recovery of dissected material.

Histopathological assessment

Resected specimens were immersed in 10% formalin and sectioned serially at 2 mm intervals. Then, they underwent histological evaluation in accordance with the Vienna classification. If the tumor was removed en bloc, particular attention was paid to the lateral margins of dissection and the depth of the possible infiltration of submucosa (sm1-sm3). Curative resection was defined as tumor-free vertical or lateral margins of the lesion. En bloc resection was defined as resection in one piece of tissue. In the case of NETs, immunoperoxidase stains (chromogranin A, synaptophysin) were performed and the Ki-67 index was reported.

Post-procedural hospitalization and follow-up

The ESD was performed after admission to hospital. On the day of the procedure, the patient remained on an empty stomach and received 2,000 ml of crystalloids intravenously. In the absence of significant bleeding during the procedure, the patient received low molecular weight heparin at a prophylactic dose in the evening hours. Antibiotic therapy was not administered on a routine basis. Also abdominal X-ray after ESD was not routinely performed. In the absence of intraprocedural complications and an uncomplicated course on the first day after the procedure (POD 1), on POD 2 a clear liquid diet was introduced instead of intravenous fluids and the patient was discharged from hospital with the recommendation of remaining on a liquid diet for another 2–3 days. In the event of complications (bleeding, perforation), the treatment was modified individually. The first follow-up visit with the doctor was usually carried out 3 weeks after dissection. During the visit the pathological report of the dissected specimen and any complications which occurred after discharge were discussed. When presence of invasive cancer was excluded in the report, the patient was scheduled for follow-up colonoscopy 3 months after ESD.

Results

Seventy-two endoscopic submucosal dissections of colorectal tumors were performed in the reviewed period. In 4 cases, the indication for the procedure was a neuroendocrine tumor of the rectum. In 2 cases the dissection involved the primary tumor (1 male aged 60 years, 1 female aged 48 years). In the other 2, the aim of ESD was to dissect the scar remaining after incomplete resection of the NET during snare polypectomy (1 male aged 61 years, 1 female aged 65 years). The mean size of the removed tumor was 1.05 cm (respectively 0.6 and 1.5 cm). In the case of dissecting scars after incomplete polypectomy a broader margin of healthy tissue was achieved – the mean size of the dissected tissue was 3 cm. The mean operating time was 28 min. In the analyzed group of patients, there were no early or late complications.

Histological results were as follows:
– in 2 cases of dissected tumor: neuroendocrine tumor NET-G1, Ki-67 index < 1%, chromogranin A negative, synaptophysin positive – WHO 1.
– in 2 cases of dissected scars: normal mucosa without neuroendocrine tumor foci.

Three patients underwent follow-up colonoscopy after 3 months – there was no recurrence reported.

Discussion

The recommendations of the Polish Network of Neuroendocrine Tumors published in 2013 clearly stated that the standard polypectomy is not recommended in treating neuroendocrine tumors [5, 6]. The same conclusions arise from our experience. In 2 of the analyzed cases, we dissected scars after incomplete excisions of neuroendocrine tumors during standard polypectomy performed in other centers. This is an uncomfortable situation, both for patients and healthcare providers. Patients are exposed to great stress arising from the following factors. They are aware that the administered treatment of neoplastic disease was ineffective and further intervention is necessary. Patients have to wait for another procedure and afterwards for results of histopathological examinations, which may take up to two months. Incomplete polypectomy and secondary endoscopy or surgery creates unnecessary costs for the healthcare system. Such a scenario is also not easy for the endoscopist, who is forced to perform the secondary procedure in difficult conditions. The dissection has to be made in the area of the scar with disarranged layers of the rectal wall, which often translates into a longer procedural time and increases the risk of complications. In our material, both dissected specimens with scars show no foci of neuroendocrine tumor. This may result from coagulating the base of the lesion during the initial colonoscopy.

Heo *et al.* came to such a conclusion after analyzing the results of rectal NET treatment by ESD and endoscopic mucosal resection (EMR) in his own department. In 7 cases R0 resection was not achieved and in only 1 case local recurrence after 10 months was observed [7].

Endoscopic submucosal dissection is likely to become the method of choice in treatment of rectal GEP-NET without submucosal invasion. Endoscopic submucosal dissection has proved to be an effective treatment modality with high rates of complete resection and minor risk of local recurrence [5, 6]. However, ESD is a long and technically difficult procedure, which carries high risk of complications. The two most frequent and important ones are perforation and bleeding from the dissection site. These observations are based on the results reported by Korean and Japanese centers, where ESD is the most developed and widely used [8–10]. In a study summarizing experiences with colorectal ESD of 18 Japanese endoscopic centers of excellence performing 816 dissections in the years 2007–2010, en-bloc and R0 resections were achieved in 94.5% and 90.5% respectively. Only 7.6% of patients required additional surgical resection, whereas the rate of complications (perforation and bleeding) was about 2% [11].

In the case of endoscopic treatment of NET in the rectum, the risk of complications is relatively low. This is due to the retroperitoneal location of the lower third part of the rectum. Hence even full thickness damage of the rectal wall does not lead to peritonitis. Retroperitoneal perforation is most often asymptomatic. In addition, the majority of rectal NETs suitable for endoscopic treatment are less than 2 cm in diameter and easy to dissect. This is reflected in the duration of the procedure, which in our material was markedly shorter when compared with dissection for other rectal tumors, i.e. 28 min vs. 95 min respectively. Moreover, no complications were observed in our series. Beside the reported results, neuroendocrine tumor ESD cannot be perceived as simple. To achieve en-bloc resection, the operator must dissect in the lowest layer of the submucosa, just above the muscularis propria layer, which demands vast experience. Mastering this technique in the Far East countries is relatively simple because of the prevalence and approved role of ESD as a treatment option and the availability of dedicated training programs. The learning curve starts with tumors located in the antrum of the stomach, and the first 50 procedures are performed under the strict supervision of an expert. After performing at least 70 ESDs in the upper GI tract, the trainee is allowed to start performing colorectal ESD [12]. The concern is how to efficiently implement such programs in European settings, where the number of centers performing ESD on a large scale is small. What

is more, in Western Europe detection of gastric carcinoma in the microcarcinoma stage, suitable for ESD, is too low to meet the demands of the program. As a result, endoscopists in Europe and the United States are forced to start performing ESD on the colon and rectum. The European Society of Gastrointestinal Endoscopy (ESGE) has published guidelines describing suggested ways of mastering this technique in Europe [13]. According to them, each endoscopist should undergo training in one Asian center of excellence and attend several courses on animal models to further improve their skills before commencing ESD. In our center, the aforementioned recommendations were fully applied. The endoscopist selected for performing ESD (MS) took a training course in one of the leading centers in Japan and participated in courses on animal models conducted in Europe. This allowed effective implementation of this method in the Polish environment and allowed good results to be achieved with endoscopic treatment of selected colorectal tumors, including GEP-NET, at our center. Still, this method is in the early phase of implementation in Poland and knowledge about potential applications of ESD is not evident among surgeons and gastroenterologists. There are only a few papers, originating from Poland, which present the results of ESD in treating colorectal tumors [14–16]. In the case of GEP-NENs such papers have not been published yet. Worldwide, due to the character of the disease, reports of ESD application in treatment of GEP-NEN usually do not exceed 30 cases [17–19]. In this study ESD achieved a higher complete resection rate than EMR and comparable to TEM, confirming that small neuroendocrine colorectal tumors can be managed reliably with endoscopic resection [20]. The same situation refers to GEP-NENs in the upper part of the gastrointestinal tract, where ESD is considered as an initial treatment in this type of tumor [21]. This is so far the first report from Poland, though preliminary, which shows the feasibility of ESD in treatment of GEP-NENs in the colon and rectum. Moreover, it gives the readers evidence that such treatment is available in Poland and is a valuable alternative to the surgical approach. It also emphasizes the necessity of referring patients to centers of excellence, where advanced endoscopic methods are performed with negligible risk of recurrence and low complication rates. Because there are now official recommendations or guidelines concerning the role of ESD in treatment of rectal tumors, including GEP-NENs, in Poland, this study presents comprehensive information about which tumors can be successfully treated with ESD, how the procedure is performed and what the potential complications are. This information may help the gastroenterologist refer patients, including those with rectal tumors of etiology

other than GEP-NENs, for endoscopic treatment, thus avoiding operations and limiting the treatment costs.

Conclusions

Endoscopic submucosal dissection is the treatment of choice for rectal GEP-NET. Endoscopic submucosal dissection is technically difficult and fraught with significant risk of serious complications. Performing this procedure should be reserved for centers with appropriately trained endoscopic staff.

Conflict of interest

The authors declare no conflict of interest.

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