Endoscopic mucosal resection of flat and sessile colorectal adenomas: Our experience with long-term follow-ups

Endoskopska mukozna resekcija ravnih i sesilnih kolorektalnih adenoma: naše iskustvo sa dugotrajnim praćenjem

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Abstract

Bacground/Aim. Endoscopic mucosal resection (EMR) or mucosectomy is a removing method of flat or sessile lesions, laterally spreading tumors and carcinoma of the colon or the rectum limited to mucosa or the surface part of the submucosa. The aim of the study was to estimate the efficacy and safety of EMR in removing flat and sessile colorectal adenomas. **Methods.** This prospective study involved 140 patients during the period of 8 years. A total of 187 colorectal adenomas were removed using the EMR method "inject and cut with snare". **Results.** The approximate size of mucosectomised adenomas was 13.6 mm (from 8 mm to 60 mm). There was a total of 48 (25.7%) flat adenomas and 139 (74.3%) sessile adenomas, ($p < 0.01$). Using "en bloc" and "piecemeal" resection, 173 (92.5%) and 14 (7.5%) of colorectal adenomas were re-moved, respectively. In all the cases, a complete removal of colorectal adenomas was achieved. Two (1.4%) patients had adenoma removal with intramucosal carcinoma each. In the average follow-up period of 21.2 ± 17.8 months, 2 (1.4%) patients had adenoma relapse after EMR. Considering complications, there was bleeding in 1 (0.7%) patient with a big rectum adenoma removed with EMR. Furthermore, one (0.7%) patient had a postcoagulation syndrome after cecal adenoma was removed by EMR. **Conclusion.** EMR is an efficient, safe and minimally invasive technique of removing flat and sessile adenomas in the colon and the rectum, with a very low percentage of adenoma recurrence over a long period of monitoring.

Key words:
adenoma; colorectal neoplasms; endoscopy, digestive system; treatment outcome.

Apstrakt

Uvod/Cilj. Endoskopska mukozna resekcija (EMR) ili mukozektomija je metoda uklanjanja ravnih i sesilnih lezija, tumora sa lateralnim širenjem i karcinoma kolona i rektuma ograničenih na mukozu i površni nivo submukoze. Cilj rada bio je da se izvrši procena efikasnosti i bezbednosti EMR u uklanjanju ravnih i sesilnih adenoma kolona i rektuma. **Metode.** Tokom perioda od 8 godina prospektivnom studijom obuhvaćeno je 140 bolesnika kod kojih je tehnikom „ubrizgaj i seci sa omčom" metode EMR uklonjeno 187 kolorektalnih adenoma. **Rezultati.** Prosečna veličina mukozektomiranih adenoma iznosila je 13,6 mm (od 8 mm do 60 mm). Ukupno je bilo 48 ravnih (25,7%) i 139 sesilnih adenoma (74,3%) ($p < 0,01$). „En bloc" resekcijom uklonjeno je 173 (92,5%) kolorektalnih adenoma, dok je resekcijom deo po deo uklonjeno 14 (7,5%) adenoma. Kod svih bolesnika postignuto je potpuno uklanjanje kolorektalnih adenoma. Kod dva (1.4%) bolesnika uklonjen je po jedan adenom sa intramukoznim karcinomom. U prosečnom periodu praćenja od $21,2 \pm 17,8$ meseci, kod dva bolesnika (1,4%) je nakon EMR došlo do recidiva adenoma. Od komplikacija, krvarenje nakon EMR bilo je kod jednog bolesnika sa velikim adenomom rektuma (0,7%). Takođe, kod jednog (0.7%) bolesnika, nakon EMR adenoma cekuma došlo je do nastanka postkoagulacionog sindroma. **Zaključak.** Mukozektomija je efikasna, bezbedna i minimalno invazivna metoda uklanjanja ravnih i sesilnih adenoma kolona i rektuma, sa vrlo niskim procentom recidiva adenoma tokom dugotrajnog perioda praćenja.

Ključne reči:
adenom; kolorektalne neoplazme; endoskopija, gastrointestinalna; lečenje, ishod.

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Introduction

Colorectal cancer is the most frequent form of digestive system cancer. In most cases, it is caused by malignant transformation of adenoma (adenoma-carcinoma sequence). The evolution of the normal mucosa through adenoma into cancer is estimated to take from 5 to 20 years. Endoscopic removal of adenomatous polyps can reduce 80% of the colorectal cancer incidence [1–3].

Since about 80–90% of adenomatous lesions are smaller than 10 mm and in polypoid shape, the conventional snare polypectomy has been used for over three decades as an acceptable endoscopic method of lesion removal. However, sessile and flat lesions (their Paris classification being type 0-Is and 0-II) require a special skill as well as the experience of the endoscopist to use endoscopic mucosal resection (EMR) or mucosectomy [3]. EMR was first described by Deyhle et al. [4] in 1973, as an endoscopic technique of sessile colonic polyp resection. This technique proved efficient in removing flat colonic lesions or sessile that are bigger than 10 mm, as well as the laterally-spreading tumors of granular type [5, 6]. Non-granular laterally-spreading tumors have a greater malignant potential and can be removed only "en bloc", using the endoscopic submucosal dissection (ESD), the most developed in Japan [7]. With colorectal cancer spreading over the mucosa and surface level of the submucosa (sm1) there is a very low risk for metastasis in lymphic nodes, which absolutely indicates to EMR or ESD [8, 9].

There are various suction and non-suction techniques of EMR. The non-suction technique "inject and cut with snare" is most frequently used in the colon, and it represents submucosal injection of different solutions to elevate the lesion, which is then snared and electroresected. The elevation of a lesion makes easier putting it into the snare and prevents deeper layers of the colon from getting damaged during the electroresection. Lesions smaller than 20 mm are removed in one go ("one piece" resection), while those bigger than 20 mm get removed step by step ("piecemeal" resection) [10].

The aim of this prospective nonrandomized study was to estimate the efficiency and the safety of EMR in removing flat and sessile adenomas of the colon and rectum, as well as assessment of adenoma recurrence over a long period of monitoring.

Methods

In General Hospital Lekovac, Department of Gastroenterology and Hepatology, in the period of 8 years (2004–2011), a total of 187 colorectal adenomas were removed by EMR in 140 patients (98 men and 42 women), whose average age was 62.4 ± 10.12 years (from 42 to 80 years).

Criteria excluding patients from the study were the presence of nonadenomatous histological structure of mucosectomised lesion, synchronous cancer and significant comorbidity of the patients.

All the patients were asked to give their consent to colonoscopy and endoscopic removal of adenomas. Colonoscopic examinations were carried out with video colonoscopes of the Pentax and Olympus brand. The EMR method "Inject and cut" technique was used for the removal of a sessile (according to the Paris clasiffication of type 0–Is) and flat neoplastic lesions (type 0–IIa and 0–IIb). The standard 23 gauge and 4 mm long needle was used for submucosal application of the dilute saline solution of epinephrine (1:100,000). In some cases, we used indigo carmine (0.04%), or a few drops of methylene blue (0.5%) in a dilute solution of epinephrine, which contributed to a better demarcation of the elevated lesion. The total volume of the dilute epinephrine amounted from 4 mL to 20 mL. Submucosal injection was first applied underneath the proximal foreign lesion, then underneath the distal side, until the submucosal "pillow" was formed and lesion elevated. Then we placed an oval or hexagonal polypectomy snare, which got the elevated lesion snared and electroresected by the help of the electrosurgical unit. Resection was performed by cutting combined with electrocoagulation of the lesion (Figures 1–4). The size of adenoma was estimated by the familiar estimate on the basis of the scope of the open biopsy scissors. When adenomas were up to 20 mm in size "en bloc" resection was performed, whereas with adenomas larger than 20 mm we performed "piecemeal" resection. In the case of „piecemeal" resection, before getting each lesion snared a new quantity of the dilute solution of epinephrine was applied submucosally, so as to elevate the lesion.

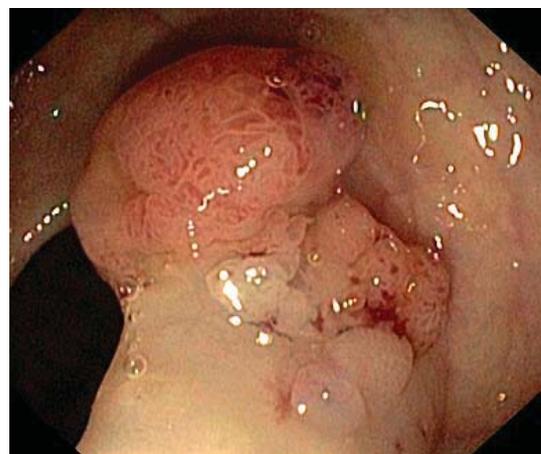**Fig. 1 – Lagre sessile adenoma of the colon.**

Fig. 2 – Adenoma elevation with submucosal injection of diluted epinephrine.

Fig. 3 – Adenoma electroresection with snare.

Fig. 4 – Lager ulceration after a complete adenoma resection.

Patients with synchronous polyps had the polyps removed with common polypectomy techniques, such as "cold forceps" polypectomy, "hot forceps" polypectomy, "cold snare" polypectomy and the common electrosection of polyps with a snare.

After EMR, endoscopic estimate was made to see if the adenoma was completely eliminated. The remaining adenoma tissue was removed by a new electroresection with a snare, and in case it was smaller than 5 mm, by "hot biopsy forceps". The material was sent to the Pathology Department, where the standard histology protocols of staining with hematoxylin and eosine were performed.

After having colorectal adenomas removed with endoscopy, patients subsided one or two days on a liquid diet, and the following day the intake of food was normal. After the endoscopic intervention, they were checked colonoscopically, for the residue or recedive estimate, once in three or six months, depending on the histologic findings about the removed adenoma. The next three years, colonoscopy examination was done once a year, and then at a longer interval of time. The average follow up was 21.2 ± 17.8 months (3 to 72 months).

For statistical analysis we used measures of central tendency (average value, $\bar{x}$) and measures of dispersion [standard deviation (SD)]. The method used to assess the significance of difference was Pearson's χ^2 test with Yates's correction. The existence of statistically significant differences between individual characteristics was considered at values of $p < 0.01$.

Results

Most frequently, there was one mucosectomy per a colonoscopic examination, in 103 (73.5%) of the patients, whereas the largest number of performed mucosectomies per patient, in a course of a single colonoscopy, was 5. Nine mucosectomies were performed on a patient in the course of 4 colonoscopic examinations. "En bloc" resection was used to remove 173 (92.5%) of colorectal adenomas, whereas "piecemeal" resection 14 (7.5%) were removed adenomas. In all the cases mentioned, colorectal adenomas were completely removed.

In 40/140 (28.5%) patients submitted to EMR using colonoscopy, 60 synchronous polyps were discovered, and endoscopycally removed.

The approximate size of the mucosectomised adenomas was 13.6 mm (from 8 mm to 60 mm). All mucosectomised sessile colonic adenomas were greater than 10 mm.

Regarding their endoscopic shape, there was a total of 48 (25.7%) flat and 139 (74.3%) sessile adenomas, which represents a statistically important difference ($p < 0.01$). Considering of their location, there was a statistically significant higher incidence of sessile adenomas in the rectum and the sigmoid part of the colon ($p < 0.01$), while in the other segments of the colon there was no statistically significant difference in endoscopic shape of adenomas ($p > 0.01$) (Table 1).

Table 1

Endoscopic shape of mucosectomised adenomas depending on their location

Endoscopic shape	Rectum n = 51	Sigma n = 77	Descendens n = 6	Transfersum n = 28	Ascendens n = 18	Caecum n = 7	Total n = 187
Flat, n (%)	11 (21.6)	16 (20.7)	1 (16.6)	11 (39.2)	7 (38.8)	2 (28.5)	48 (25.7)
Sessile, n (%)	40 (78.4)*	61 (79.2)*	5 (83.3)	17 (60.7)	11 (61.1)	5 (71.4)	139 (74.3)*

*$p < 0.01$ compared to other groups *vs* flat adenomas (χ^2 test)

Histologically, the largest number of removed adenomas were of tubular structure (128, 68.4%), then of tubulovillous structure (57, 30.5%), and the least frequent among them were villous (2, 1%), which was a statistically significant difference ($p < 0.01$). Regarding their location, it was statistically significant that tubular structure of adenoma occured more frequently in the rectum, the sigmoid section of the colon, the colon transversum and ascendens ($p < 0.01$), while only in the descendens and the caecum the difference

was not statistically significant in histologic structure of adenoma ($p > 0.01$) (Table 2).

advantage over the traditional surgical methods for malignantly alterated colorectal adenoma and cancer, because of a

Table 2

Histological structure of mucosectomised adenomas depending on their location

Histologic structure	Rectum N = 51	Sigma n = 77	Descendens n = 6	Transfersum n = 28	Ascendens n = 18	Caecum n = 7	Total n = 187
Tubular adenoma, n (%)	29 (56.8)	55 (71.4)	5 (83.3)	22 (78.5)	13 (72.2)	4 (57.1)	128 (68.4)
Tubulovillous adenoma, n (%)	21 (41.2)	21 (27.2)	1 (16.7)	6 (21.4)	5 (27.8)	3 (42.8)	57 (30.5)
Villous adenoma, n (%)	1 (1.9)	1 (1.3)	0	0	0	0	2 (1)

*$p < 0.01$ vs other groups (χ^2 test)

All the removed adenomas were mainly of the second-degree dysplasia (97, 51.9%), then third-degree (59, 31.5%), and, least frequently, first-degree (31, 16.6%), which was statistically significant, $\chi^2 = 34.16 > [\chi^2$ (2 and 0.01) = 9.21, $p < 0.01$]. In 2 (1.4%) patients with adenoma removed each, severe dysplasia with intramucosal cancer focus was detected histologically.

In the average follow-up period of 21.2 ± 17.8 months in 2 (1.4%) patients after EMR occurred adenoma recurrence (Table 3). In 1 patient, after 18 months occured relapse of a big sessile adenoma on the hepatic flexure of the colon. Recurrent adenoma had tubulovillous structure with third-degree dysplasia, which was a finding identical to the one of the initial adenoma. Recurrent adenoma was then endoscopically removed, and twelve months after the removal there was no relapse. In the other patient with large sessile adenoma in the rectum, about 50 mm in diameter, 12 months after the "piecemeal resection", there was a recurrence which was completely removed endoscopically. Histologic findings of the removed relapse were identical to the ones of the original tumor – tubular adenoma with a third-degree dysplasia.

Table 3

Endoscopic mucosal resection outcomes

Outcome	Patients n (%)
Adenoma relapse	2 (1.4)
Complications	
bleeding	1 (1.7)
post coagulation syndrome	1 (0.7)

As far as complications are concerned (Table 3), there was bleeding after mucosectomy in 1 (0.7%) of the patients with a big sessile adenoma in the rectum, which had been removed with a "piecemeal" resection. The bleeding was stopped by placing 6 clips. After mucosectomy of a flat adenoma in the caecum, with one (0.7%) patient there occured the postcoagulation syndrome with abdominal pain and pericaecal infiltration. The patient was operated on, but later the existent liver and kidney insuficiency worsened, leading to lethal outcome.

Discussion

Today, EMR represents a rutinary procedure of removing flat, larger sessile lesions, as well as laterally spreading tumors in the colon and the rectum. EMR has an

lower rate of procedural morbidity and mortality [11]. This method can remove cancer spreading over mucosa and the surface level of the submucosa, deep to 1,000 μm (sm1 invasion level), on condition that the cancer has been well histologically differentiated, and there is no lymphatic or venous invasion. This is particularly important with elderly patients with significant comorbidity, where the risks of surgical interventions are high [7, 12, 13].

There are various suction and non-suction techniques of EMR. Suction techniques run a higher risk of affecting the muscular layer, especially in the colon and the rectum, so the submucosal application of a larger amount of different solutions and a controlled power of suction are recommended [14]. Safer for the colon and the rectum are the non-suction EMR techniques. The non-suction technique "inject, lift and cut", where lesion gets elevated by forceps before resection, requires a double-channel endoscope [15]. Still, "inject and cut with snare" is the most frequently used technique for the colon and the rectum, and we used it for our patients, too. The essence of this technique is to use an injection of different solutions submucosally, underneath the proximal and then the dystal part of the lesion, in order to elevate it, which enables its snaring and electroresection. Elevation of the lesion thickens the colon wall and the refore prevents the deeper layers of the wall from getting damaged during electroresection [16].

For submucosal injections of the EMR "inject and cut with snare" technique we used a 1 : 100,000 physiological saline solution with epinephrine, which was used most frequently. Epinephrine dilution of 1 : 200,000 is also used. Attenuated epinephrine has no role in preventing delayed bleeding but is useful for creating a bloodless field during EMR. Furthermore, epinephrine limits the submucosal solution dispersion field which contributes to a longer elevation [3]. Some studies have shown the advantage of the usage of other solutions for submucosal injection, such as hyaluronic acid, hydroxypropylmethylcellulose, glycerol and succinylated gelatin, which contribute to a longer elevation. The disadvantage of these solutions is their price and not being available to many endoscopic units [3, 17]. Besides, the use of hydroxypropylmethylcellulose, as well as other solutions like hypertonic sodium chloride (3.75%) and dextrose (20%) may harm the tissue and cause local inflammatory reactions [7].

In some cases, we applied indigo carmine or methylene blue in a diluted solution of epinephrine. The use of biologically inert color of indigo carmine and methylene blue provides good elevated lesion demarcation and well-defined

safety of the resection line. The color does not tie into the muscular layer, so in case this layer gets involved in resection, there can be observed a discontinuum in the uniform blue of submucosis. Furthermore, adenoma tissue, which is red, can clearly be identified. The use of color eliminates the need for thermal marking of the resection margins. A special benefit of the use of color is with lesions which are not clearly separated, such as laterally spreading tumor and sessile serrated adenoma [18].

We applied a total of 4–20 mL diluted solution of epinephrine submucosally. In "piecemeal" resection of adenomas larger than 20 mm, before each snaring we applied a new amount of epinephrine solution submucosally in order to elevate the lesion. According to literature, the total volumen of the applied solution during EMR amounted to 5–50 mL. "Non-lifting sign" signaled that structures deeper in the colon wall were affected by tumor and such patients were sent to laporascopic or open surgical resection [3].

According to the literature, complete removal of colorectal adenomas is achieved in 75–100% cases [6, 8, 19–22]. Sucess of the EMR technique depends on adenoma size and depth of the invasion. Laterally spreading tumors larger than 30 mm are rare and require a special skill for a safe removal. They can hardly be removed "en bloc", usually they are removed "piecemeal". According to a study [19], "en bloc" resection was achieved in 73.1% of tumors smaller than 30 mm, and only 15.4% of tumors larger than 30 mm. A high success (100%) of complete adenoma removal in our patients can be explained by the fact that intramucosal cancer in adenoma was found with only two (1.4%) patients and the fact that the average size of the removed adenoma (13.6 mm) was smaller in comparison to other series [6, 8, 19–22].

Removed adenomas in our patients were significantly more sessile (74.3%) than flat adenomas (25.7%). Regarding their location, sessile structure of adenomas was significantly more likely to be present in the rectum and the sigmoid part of the colon, while in other segments, despite a high occurence of sessile adenomas in comparison to flat adenomas, the difference was not statistically significant. According to the literature, flat adenomas are found in 6.8% to 36% of all adenomas [23–25].

The largest number of adenoma are of tubular structure (80–86%), then tubulovillous (8–16%), and least frequently villous (3–16%) [26]. A similar ratio was there with our series of examinees. According to the literature, adenomas most frequently show mild dysplasia (70–86%), then moderate dysplasia (18–20%), and the least frequent severe dysplasia with carcinoma *in situ* (5–10%) or invasive carcinoma (5–7%) [27]. In our examinees, adenomas most frequently had moderate dysplasia, then severe dysplasia and the least frequent mild dysplasia.

After extensive piecemeal EMR, it is advised that colonoscopic examinations take place from 3 to 6 months, then once a year over the next 3 years, and then at longer intervals [3]. Our patients underwent similar examinations. Adenoma relapse after EMR ranges from 0–46%, depending on adenoma size and follow-up period. A higher risk for relapse was observed in adenomas larger than 35 mm. In case of visible adenoma residue after EMR, use of argon plasma coagulation reduces the frequence of relapsing adenoma for 50% [28]. In order to provide a long term monitoring of our patients after mucosectomy, we excluded from the study the patients with a significant comorbidity and synchronous cancer. In both (1.4%) our patients with relapse, adenoma was too of a larger size. We removed residual adenoma tissue by electroresection with a snare or "hot biopsy forceps".

Perforation after EMR was shown in 1–2% of cases and bleeding in about 2% of the cases. These complications can be successfully endoscopically managed with hemoclips [21, 29]. We had 1 (0.7%) examinee with bleeding following mucosectomy of a large rectal adenoma, which was sanated with hemoclips. Post-coagulation syndrome occurs because of transmural bowel wall damage in 0.51–3.7% of cases. It manifests most frequently from the first to the fifth day after the polypectomy, with the symptoms of localised abdominal pain, febrility, peritonitis and leukocytosis. Conservative therapy is usually sufficient for resolution of the symptoms [22, 30]. In one (0.7%) of our patients, after caecal adenoma mucosectomy appeared post coagulation syndrome, which could not be sanated with drug treatment, and the patient was operated on.

Conclusion

With well-defined indications, EMR is an efficient, safe, as well as minimally invasive method of removing flat and sessile adenomas in the colon and rectum, and in many cases it has replaced surgical methods. During a long follow-up period after complete removal of adenoma there is a very low percentage of their recurrence, which is important in secondary prevention of colorectal carcinoma.

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