

Endoscopic Submucosal Dissection (E.S.D.) vs. Endoscopic Mucosal Resection (E.M.R.) in Colombia. Advocating E.M.R.

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Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD) provide new alternatives for minimally invasive treatment of superficial malignant neoplasms of the gastrointestinal tract. The procedures are safe and yield results that are comparable to surgery. They also result in lower morbidity rates and better quality of life because of tissue preservation than does traditional surgery. The two techniques have staying power and are perhaps the first approximations to true intraluminal resectioning of malignant gastrointestinal lesions. We must work together to produce our own statistics and participate in their development.

In western countries Endoscopic Mucosal Resection (EMR) has been clearly accepted, especially for the treatment of Barrett's neoplasia and colorectal adenomas (10). In contrast, Endoscopic Submucosal Dissection is seldom performed in western countries for many reasons. The first and most important one is that Endoscopic Submucosal Dissection has a difficult learning curve because of the low volume of early gastric cancer diagnosis. There are also few training centers to make the technique available, which limits population studies that would produce guidelines or criteria for using this procedure. In fact, only about 13 out of more than 340 publications about Submucosal Endoscopic Dissection originate from western countries. For this reason, more efforts and opportunities will be required to make this technique available as a therapeutical tool that is effective and safe.

EMR has been widely accepted for local management of gastric and esophageal carcinomas confined to the mucosal layer, high-grade intraepithelial neoplasia in Barrett's esophagus, elevated or depressed ampullary adenomas, and colorectal adenomas. It has been demonstrated in a variety of studies- mostly not controlled studies, that the different EMR techniques are effective and safe for the treatment of early cancers of the gastrointestinal tract (2, 7, 8). EMR techniques with transparent cap or with ligation-and-cut are most widely used in western countries. Clinical results are equivalent to each other, so deciding which technique to use depends on the size, the area where the lesion is located, and especially on the professional experience of those performing the procedure in that particular location.

A complete local resection of a lesion is possible with endoscopic mucosal resection. Also, it can be performed upon most adequately selected patients. For this reason, it is considered a potentially curative technique for the treatment of early lesions when no submucosal infiltration is reported by pathology. It is also used to obtain large diagnostic biopsies and for local staging of a tumor. In select cases, EMR can be combined with

local ablative techniques (argon plasma coagulation, photodynamic therapy, radiofrequency ablation) to destroy residual neoplastic tissue or metachronous lesions. This last point highlights the importance of endoscopic follow-up of these resections to detect residual tissue, recurrence, or metachronism.

The great majority of EMR studies have been performed in Japan. Western experience is limited. There are several possible explanations for this. Perhaps it is due to differences in the incidences of these lesions among these two populations, or maybe it is due to the different detection percentages, or the different medical communities' acceptance of this local therapy that is a potential cure for malignant lesions. In any case, the number of potential candidates for EMR is increasing in Europe and in western countries. This is due to more widely used screening programs based on local epidemiology, warning signs, and the availability of high resolution endoscopes and imaging techniques that can identify a larger number of early lesions. This makes it possible to spot lesions suitable for endoscopic treatment and for which endoscopic mucosal resection has been evaluated as an effective tool for resection of mucosal lesions with a very low morbidity rate (5, 6). Of course, this technique has its limitations. Among these limitations the most important is the restriction according to the size of the lesion. This implies limited ability for block resection in lesions more than 20mm with its consequent partial elimination. Partial elimination leads to uncertainty regarding whether or not the tumor has been completely resected. It also leads to an increased percentage of local recurrences due to the difficulty of histological analysis.

These technical limitations and the recurrence percentage motivated Japanese professionals to develop a new technique. By using cutting devices the mucosal lesion is dissected in block from the adjacent mucous membrane. This technique is known as ESD (Endoscopic Submucosal Dissection). It makes it possible to avoid difficulties and to limit, control and completely dissect the lesion.

Timely diagnosis of early gastric cancer, defined as cancer that compromises the mucosal and/or submucosal layer with or without lymph node invasion, is of great clinical relevance. Patients' prognoses are excellent with a 95% five-year survival rate when treated. However, the risk of nodal metastases is 1% to 3% in mucosal lesions and up to 20% in submucosal lesions. This makes choosing the best available therapy a challenge for gastroenterologists, surgeons and endoscopists. With the appearance of new diagnostic techniques such as endoscopic ultrasonography for staging early lesions, and the availability of techniques for treatment of early gastric cancer in our environment, it has become critically important to know what different studies have demonstrated for determining advantages and

limitations. The purpose of this article is to neither overestimate the new technologies nor undervalue conventional therapies.

Another aspect of this article is to reveal the low rates of early diagnosis of gastric cancer in Colombia compared to rates of up to 50% in Japan. We have a long way to go in learning how to implement early detection programs, diagnoses and suggestions of treatment options. The best therapy can then be consolidated based upon the available literature, and keeping in mind the reality of our environment that can often, in certain ways, hinder clinical decisions.

Historically, the treatment of early gastric cancer was surgical. However, the evolution of technology and the identification of patients who face high surgical risks, or who refuse surgery, has made possible the development of current endoscopic resection methods. They have proven to be sufficient when there is adequate and strict patient selection, and clinical results have been satisfactory with low morbidity and mortality rates. This is how new techniques such as Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD) emerge for the treatment of early gastric cancer. Treatment is based on retrospective analyses of surgically resected specimens that have demonstrated that the risk of metastasis to lymph nodes in most gastrointestinal cancers confined to the mucous membrane is negligible. This led researchers to consider using EMR as a curative technique for intramucosal lesions. It has become an excellent, and less invasive, alternative to conventional surgical treatment. The risk of metastasis to lymph nodes is better defined by dividing the mucosa (m) and the submucosa (sm) into three sections each: m1 (epithelium), m2 (lamina propria), m3 (muscularis mucosa) and SM1 (upper third), SM2 (middle third) and SM3 (lower third). The risk of metastasis to lymph nodes in gastric carcinoma increases with the depth of penetration of the tumor. Lesions confined to the mucosa are associated with low risk of metastasis to lymph nodes (0% to 3%). The risk increases up to 20% in deep submucosal tumors. Gotoda et al presented a cohort analysis of 5,265 patients with early gastric cancer who underwent gastrectomy with meticulous lymph node dissection. Metastasis to lymph nodes was not found in well and moderately well differentiated carcinomas without lymphatic or vascular compromise. These findings were independent of the presence of ulceration for lesions less than 3cm and of the size of the tumor when there was no ulceration. The same happened with well or moderately well differentiated tumors less than 3cm with minimal submucosal invasion and without lymphovascular compromise. These findings are currently a source of controversy. All these parameters, especially lymphovascular invasion, can be evaluated in the EMR specimen. For many

this is the most accurate staging method. Also, it could be the method used to decide if local therapy is sufficient, or if it needs to be complemented with other endoscopic or surgical therapies. To attain this, communication with pathologists has to be very close. We need to begin by adequately labeling the excised lesion. The pathologist's answer has to be in terms of sub classification (m1, m2 o sm1, sm2, etc...). It also has to describe the presence or absence of ulceration, the neoplastic compromise of lateral and vertical borders, and vascular and/or lymph node invasion.

Accordingly, the technique to be implemented must be based on several points: the most solid scientific evidence, epidemiology, our environment, and, at least for now, the learning curve for physicians to be able to implement these techniques. Cost and morbidity and mortality rates also must be taken into account. For these reasons, it should be stressed that the best choice for endoscopic or surgical therapy must not be based on a single parameter. If we do, it will surely lead to erroneous or biased conclusions.

EMR and ESD can be used as definitive therapy in pre-malignant lesions or in early stage malignant lesions of the digestive tract (T1N0M0). EUS is frequently used for initial staging before endoscopic resection to make sure that the tumor has not compromised the deepest layers of the wall or the lymph nodes. Neither of the two techniques should be attempted for lesions that do not rise during submucosal injection. A tumor that does not rise after injection is a predictor of deep invasion and is not subject to curative endoscopic removal. In studies, the non-rising signal has a sensitivity of 100%, specificity of 99% and VPP of 83% for invasive carcinoma at least for patients with early colon cancer (9).

This review will try to focus on the advantages and limitations of each of the techniques. Perhaps some points in the literature are very clear, but when adapted to our environment, they are not very obvious choices. Finally, the message is what we need to do to be on the cutting edge that the state of the art demands in the management of this pathology.

The beginning of this article will focus on the advantages of mucosectomy and then on the advantages of ESD by another author.

Although it seems evident, one of the most basic principles in endoscopy must be taken into account: EMR can be considered a variation of conventional polypectomy with special devices, while ESD is typically performed by endoscopists with experience in advanced endoscopic procedures and who are widely familiar with mucosal dissection techniques. However, the facts that both techniques are technically difficult and time consuming cannot be ignored (1). For large gastric lesions the reported time for a complete EMR is 25.8 + - 25.9 minutes while the average time

for ESD is 84.0 +-54.6 minutes (1). The initial advantage of EMR is that it is reasonably shorter. On the other hand, in EMR the positioning of the handle in the transparent capsule before capturing the tissue can be changed or manipulated by the endoscopist. This favors certainty in the resection just as there is certainty when using ligation that does not require prior handle positioning. It follows technical guidelines for variceal ligation prior to resection, and the band force is such that it is possible to capture mucosa and submucosa but not the muscle layer. This makes it a safe technique which is another potential advantage.

Finally, a complete sample is obtained in a single block for histological analysis. Lateral resection and invasion depth can be defined too. Nowadays, different mucosectomy methods are available, but they depend on local experience. The best technique will be the one that best adapts to the experience of the particular group.

CRITERIA FOR ENDOSCOPIC MUCOSAL RESECTION

In Japan, absolute indications for EMR include well or moderately well differentiated non-ulcerated carcinoma, raised lesions with ulcer scarring of less than 2cm for types I, IIa, and IIb, or smaller slightly depressed lesions of less than 1cm for type IIc lesions. For these types of lesions the risk of metastasis to the lymph glands is practically non-existent. It is considered that EMR should not be performed in undifferentiated lesions because of the risk of metastasis even in small lesions, nor should it be performed when there is signet ring cell carcinoma independent of the size of the lesion.

EMR Indications according to histology, size and lesion type

1. Well or moderately well differentiated adenocarcinoma of intestinal type.
2. Type I, IIa, and IIb lesion in ulcerated or non-ulcerated lesions less than 20mm, since there is no risk of nodal involvement.
3. Type IIc depressed lesion or non-raised and depressed type IIa + IIc lesion less than 10mm (11).

The border of the lesion is marked by electrocoagulation or argon to demarcate the area to be resected. The lesion is raised with a cushion of saline solution with epinephrine which rules out deep layer submucosal adherence or where penetration is only up to sm1 without risk of invasion. This is the most important point because in order for the procedure to be curative, the risk of invasion must be non-existent. After, the resection is performed through the submucosa. The piece is extracted, oriented from proximal

to distal and then sent to pathology. Pathology determines histology and with it the risk of recurrence can be predicted as follows: if the lesion is located more than 2mm away from the resection border, recurrence is 0%. Recurrence is 20% if it affects the safety border, and 50% if there are malignant cells on the other side of the safety border.

Besides this, it must be remembered that in the different series the risk of metastatic lesions in mucosal lesions is between 1% and 3%. In some series the risk rises to 5%, and in submucosal lesions it is between 15 to 25%. This risk requires a strict clinical, endoscopic, histological and radiological follow-up.

Until now the range of probabilities of recurrence after mucosectomies has gone from 2.3% up to 35% while in submucosal dissection the probability of recurrence is 0.5%. One of the elements involved in the percentage of recurrence is partial resection. Partial resection makes it difficult to adequately and thoroughly analyze histopathology. This analysis is needed to determine the durability of the lesion, especially for lesions larger than 20 mm because the reorganization of multiple fragments makes staging uncertain. The latter is the critical point of mucosectomy, which as mentioned earlier, motivated the development of techniques that would make complete resection possible for larger lesions with block resections. Finally, it must be stressed that in order for mucosectomy to be successful, it must follow strict selection criteria. The goal is to be closer to the 2.3% recurrence rate than the 35% rate at the other extreme. The higher rate probably depends on broadened criteria for resection of early cancers (lesions up to 3cm in some series). In fact, in Japan ESD is being used increasingly for well or moderately well differentiated non-ulcerated carcinomas of any size, and for lesions smaller than 30mm if there is ulceration or if the lesion has minimal submucosal compromise.

EFFICACY AND LONG TERM RESULTS

The greatest experience in endoscopic treatment of early gastric cancer has been reported in Japan, where about 50% of tumors are diagnosed early.

Previously described findings from studies of surgical specimens led Japanese professionals to develop some guidelines. These guidelines emphasize that early cancer should only be treated endoscopically when lesions, due to their size and location, can be resected in a single piece. Results in an early initial Japanese study of 1,872 patients with early gastric cancer who were treated with EMR and ESD demonstrated complete resection in 73.9% of patients. The percentage of complications was 1.9% (1.4% bleeding and 0.5% perforation) (3). Later, in order to clarify the effectiveness of EMR as a curative treatment for

early gastric cancer, Kojima et al (13) performed a review of 1,832 cases from 12 Japanese centers. In 10 of the centers the above criteria was used. The other two centers used a combination of raised lesions less than 30mm, of depressed lesions less than 20mm, and of ulcerated lesions less than 10mm. Different EMR techniques were also used. Block resection was performed in 75.8% of the cases with an average follow-up time of 4 months to 11 years. Complete resection was performed in 1,353 of the cases (73.9%). In cases of incomplete resections, residual cancer was successfully treated with repeated endoscopic treatment or surgery. Recurrence after histopathological documentation of eradication was observed in 1.9% of the patients. Most of these cases derived from extended indications. Only one patient died from metastatic gastric cancer, demonstrating a 99% survival rate. Another important study was performed by Ono et al (12). It describes 445 patients with early gastric cancer treated with EMR over a period of 11 years. In this study patients were selected with the accepted criteria, although the maximum diameter of the treated lesions was extended to 30mm instead of 20mm. Among the 405 intramucosal cancers complete resection was only achieved in 278 of the patients (69%). The lateral margins were compromised in 43 cases (11%). Assessment of the integrity of the resections of the remaining 84 patients (20%) was prevented by diathermic burns, mechanical damage or failure to recover specimens. Local recurrence was reported in 5 cases of complete resections (2%) and in 17 (18%) of the 95 patients with incomplete or non-assessable resections. All these patients underwent surgery and remained disease free. No gastric cancer related deaths were observed.

In this article the author also reported that the initial experience with the IT knife made complete resection percentages possible in more than 90% of the cases. This was possible even for major lesions. Based on this, the authors replaced EMR with ESM over time. This decision was adopted by most of the Japanese centers. The efficacy of this decision is supported by the data presented by two Japanese institutions: The Shizuoka Cancer Center and The National Cancer Center. Complete block resections with tumor free borders have been achieved in 1,019 out of 1,167 (87%) patients treated with ESD compared to only 42% in patients treated with EMR. On the other hand, when the data was stratified by taking the size of the tumor as a reference, the advantages of ESD over EMR seem to be greater when the size of the lesion is larger (block resection in 96%, 91% and 83% with ESD vs. 45%, 24% and 0% with EMR for lesions less than 20mm, between 20 and 30mm and larger than 30mm respectively). These differences were ratified in a recent study by Watanabe et al. It reports significantly higher numbers of block resections with ESD than with EMR for lesions larger than 10mm (91.3 vs. 63.6%).

Of course, the controversy continues regarding the use of ESD vs. mucosectomy in early cancer lesions of less than 20mm and for small lesions. Despite what has been presented here demonstrating the tendency of the most experienced Japanese centers to use ESD, Nakamoto and Sakay's study of 177 patients concludes that for small lesions of less than 15mm, the two methods are comparable. Endoscopic mucosal dissection can be recommended, a fact which is very applicable for our environment as opposed to the use of ESD in lesions larger than 20mm.

SAFETY AND COMPLICATIONS

Bleeding is the most common complication in both techniques. The literature has reported ranges between 1% and 45% with an average of 10%. Most bleeding occurs during the procedure or during the next 24 hours. Late bleeding after the first 72 hours occurs in 13.9% of patients. Bleeding is the most frequent complication of EMR. It occurs in between 1.5% and 24% of patients. The use of hemoclips is the method of choice for controlling bleeding because of their low perforation risk. No major bleeding percentages have been reported for ESD since hemostasia is performed simultaneously during dissection. Severe bleeding is more frequent in the stomach probably because of the higher caliber of the vessels. To prevent late bleeding risk and promote ulcer scarring, proton pump inhibitors are administered along with oral sucralfate, which can also be applied in spray form during the procedure.

Without a doubt, perforation is the biggest concern. It occurs more frequently during ESD than EMR. The perforation percentage reported for EMR is between 0.3% and 0.5%, while for ESD it is between 4% and 10% (4). Small perforations identified during the procedure can be managed with endoclips. However, large perforations require emergency surgery to prevent peritonitis. Despite its percentages of complication, ESD is considered to be a safe procedure. It can be performed on elderly patients with those with early gastric cancer who are in poor health.

One of these advantages of EMR is its lower rate of major complications such as perforations.

CONCLUSIONS

EMR, like ESD, has surfaced as an important therapeutic option for premalignant and malignant lesions in their early stages. The choice between these options must be made according to the type of the lesion, professional experience, institutional resources and health costs. However, despite existing studies, there are still no long term follow-up studies. It is no secret that the ongoing development of equipment used in these techniques will facilitate these

procedures. This could be reflected in mass use. A great variety of prospective and retrospective studies in Japan have demonstrated that ESD achieves higher block resection percentages and curative resections in early gastric lesions than EMR. This fact cannot be disregarded. This is reflected in lower rates of recurrence and residual tumors. However, ESD is more time consuming, is related to higher complication rates such as perforation, and its success clearly depends of the professional's experience. It yields excellent results only when it is performed by expert hands. Additionally, it cannot be ignored that ESD should be used more widely in our environment. However, today we have a reasonable alternative that offers good clinical results. For us, it can be an excellent alternative in the endoscopic management of small early gastric cancer (less than 2cm) with strict patient selection and use of the recommended criteria.

Meanwhile, more follow-up studies will be conducted and developed and the needed learning curve will be accomplished. Hopefully this will bring us close to what has been achieved in countries such as Japan. Without a doubt they are light years ahead of us in the development of these techniques. This will allow us in a near future to identify the best strategies for our environment.

I would like to note that, as is known, early gastric cancer is frequently associated with synchronous lesions. Also, metachronous cancers can occur after EMR. This mandates that the follow-up for our patients be of great relevance as some studies demonstrate. Studies even recommend yearly endoscopic examinations for timely diagnosis, and recommend endoscopic treatment of synchronous lesions and metachronous lesions. This can lead to preservation of the whole stomach for most patients with early gastric cancer after a successful EMR.

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