Review paper

Videosurgery

Endoscopic methods in the treatment of early-stage esophageal cancer

Wiesław Janusz Kruszewski[1,2]

[1]Division of Propedeutics of Oncology, Medical University of Gdansk, Poland
[2]Oncological Surgery Department, Gdynia Centre of Oncology, Maritime Hospital, Gdynia, Poland

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Abstract

Most patients with early esophageal cancer restricted to the mucosa may be offered endoscopic therapy, which is similarly effective, less invasive and less expensive than esophagectomy. Selection of appropriate relevant treatment and therapy methods should be performed at a specialized center with adequate facilities. The selection of an endoscopic treatment method for high-grade dysplasia and early-stage esophageal adenocarcinoma requires that tumor infiltration is restricted to the mucosa and that there is no neighboring lymph node metastasis. In squamous cell carcinoma, this treatment method is accepted in cases of tumors invading only up to the lamina propria of mucosa (m2). Tumors treated with the endoscopic method should be well or moderately differentiated and should not invade lymphatic or blood vessels. When selecting endoscopic treatments for these lesions, a combination of endoscopic resection and endoscopic ablation methods should be considered.

Key words: *Barrett's esophagus, endoscopic treatment, early cancer.*

Introduction

Esophageal cancer is a treatment-resistant lesion of poor prognosis [1]. In the early stage, T1a, and in the precancerous stage as a high-grade dysplasia (HGD), this type of lesion is still managed by esophageal resection [2]. Increasing evolution of endoscopic techniques identified the alternative treatment of selected types of early-stage esophageal cancers as a less invasive approach. Endoscopic treatment does not usually require patient hospitalization and is less expensive than surgical resection [3]. This method is recommended only in situations when the risk of lymph node metastasis is lower than the risk of perioperative mortality following esophageal resection [4]. In a meta-analysis published in 2012, involving 70 reports, the pooled data from 1874 patients with HGD and/or intramucosal cancer in Barrett's esophagus after esophagus resection were presented. Lymph node metastases were observed in 1.39% of all cases. There was no lymph node metastasis in 524 patients with HGD without the diagnosis of cancer, while lymph node metastasis was observed in 1.93% of 1350 patients with confirmed intramucosal cancer. Therefore, in the cases of tumors restricted to the mucosa, the authors of the analysis estimated the risk of metastasis at almost 2% [5]. In esophageal adenocarcinoma invading the submucosa, the risk of metastasis is even higher and accounts for 20% of all cases [6]. The perioperative mortality rate following esophagectomy usually exceeds 2%. Morbidity rates following this type of surgery are significant and the risk of disease recurrence in cases of lymph node metastasis remains high. One report pooled data from 7502 British pa-

Address for correspondence:
Prof. Wiesław Janusz Kruszewski, Division of Propedeutics of Oncology, Medical University of Gdansk, 9B Powstania Styczniowego St, 81-519 Gdynia, phone: +48 58 726 02 50, fax: +48 58 726 02 50, e-mail: wjkrusz@gumed.edu.pl

tients after esophageal resection within a period of 4 years, beginning in April 2009. The mortality rates within the period of 30 days following less invasive surgery using videosurgery and surgery with the body cavity open were 4% and 4.3%, respectively. Perioperative morbidity rates in both patient groups were 38% and 39.2%, respectively, whereas necessity of further hospitalization was required in 13.1% and 13% of patients, respectively [7]. Therefore, surgical esophagectomy, as well as surgery using less invasive methods, should be considered as burdened with significant morbidity and mortality. As emphasized by the authors of one of the reviews, at specialized centers with great experience in esophageal cancer treatment, the perioperative mortality rate is no higher than 2–3% [3, 8]. This rate is lower in postoperative patients with HGD, but, as it was estimated following the analysis of 6 reports, even in the case of this group, the perioperative mortality rate was approximately 1% [3, 9]. Taking into consideration that HGD is not associated with lymph node metastasis, even such a low mortality rate does not justify surgical intervention.

Overview of esophagectomy for high-grade dysplasia and cancer

There is increasing discussion on the relevance of esophagectomy in cases of HGD or intramucosal esophageal cancer. This method is still recommended, as there is a common opinion that the risk of esophageal cancer in patients with confirmed HGD is 30–40% [2]. However, the authors of several reviews refer to papers reporting this rate as much lower. They also suggested that in over 80% of HGD patients subjected to esophagectomy, this type of surgical intervention was not necessary [3, 10]. In addition, novel diagnostic techniques and endoscopic treatment methods of esophageal lesions are continuously developing. It is emphasized [11, 12] that the results of endoscopic treatment of early-stage esophageal cancer restricted to the mucosa are not inferior to those of surgical resection. For these reasons, esophagectomy is currently recommended in early-stage cancer invading the submucosa, in cases where lymph node metastasis is suspected or after endoscopic treatment failure [3, 13, 14]. Surgical treatment is also avoided in some cases of elderly patients burdened with concomitant disease, increasing the risk of mortality following esophagectomy.

Risk of lymph node metastasis in early esophageal cancer

The risk of lymph node metastasis increases with the extent of cancer invasion. The most common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma originating within Barrett's esophagus [14]. Studies on squamous cell cancer indicate that it is reasonable to consider endoscopic treatment only in cases of cancer invading the mucosa (m1) and lamina propria of the epithelium (m2) [4]. Squamous cell cancer invading the muscularis mucosae (m3) or the upper third layer of the submucosa carries the risk of lymph node metastasis in 0–9% and 19% or more cases, respectively. Therefore, this stage of squamous cell cancer is a relative indication for endoscopic treatment [15–17]. The risk of lymph node metastasis can also be increased by poor histological tumor differentiation and invasion of cancer cells to lymphatic or blood vessels. In cases of adenocarcinoma of the same extent (invading up to the sm2 level), the risk of lymph node metastasis is assessed as lower than in squamous cell cancer [15, 18]. The risk is the same in both cancer types at the sm3 level [15]. The risk of metastasis is considered low in adenocarcinoma restricted to the mucosa [12, 19]. For that reason, little is known about the rate of risk in cases of adenocarcinoma invading subsequent layers of mucosa. The authors of a 2010 paper drew interesting conclusions after observing that the only reports on this subject included only retrospective studies based on material from archival surgical series [4]. A conclusion from these analyses was that in cases of adenocarcinoma at the m3 level, the risk of lymph node metastasis was assessed at up to 12%. The rate of metastasis occurrence in adenocarcinomas invading the submucosa ranged from 16% to 41%. When the depth of tumor invasion increased, a higher risk of lymph node metastasis was observed. As emphasized by the authors of that paper [4], these risk factors were estimated on the basis of retrospective studies on material obtained from patients subjected to esophagectomy at a time when the precise depth of adenocarcinoma infiltration through the esophageal wall had no significant influence on patient treatment. After esophagus resection, the tumor was routinely sectioned every 5 mm to obtain specimens for microscopic analysis. This allowed avoidance of the areas with the deepest tumor inva-

sion. Therefore, the evaluated rates of lymph node metastasis might actually refer to tumors of deeper invasion than estimated. The authors indicated the contrast between such microscopically analyzed material and the material obtained following endoscopic resection, where serial sectioning every 2 mm was the obligatory rule. Therefore, in these authors' opinion, it was worth considering their own results obtained following endoscopic resection in 82 patients with adenocarcinoma of the esophagus and cardia invading the muscularis mucosa (m3) or submucosa. The analyzed group included only patients with normal lymph nodes on transesophageal endoscopic ultrasound (EUS). Patients who were subjected to endoscopic treatment and subsequent esophagectomy had no lymph node metastasis. In cases of only endoscopically treated patients, there was no lymph node metastasis within the 26-month follow-up period. This report indicates that in cases of esophageal adenocarcinoma (m3), endoscopic resection may also be an appropriate treatment in selected cases of lesions invading the upper third layer of the submucosa (sm1). The cited authors [4] emphasized that in the retrospective analysis of outcomes from a surgical series, EUS was not performed on every patient prior to surgery, leading to patients with enlarged lymph nodes, which may have been detected on EUS, undergoing the surgical procedure. This could be another reason for the elevated rates of lymph node metastasis in m3 and submucosal esophageal adenocarcinoma observed following retrospective analysis. It is well known that enlarged lymph nodes disqualify patients from radical endoscopic treatment because of the higher risk of lymph node metastasis. In addition, the authors of the abovementioned report focused their attention on the phenomenon of the double muscularis mucosae. Doubling of this layer may result in false-positive staging of esophageal cancer. In microscopic assessment, identification of tumor invasion beyond the most superficial layer of the muscularis mucosae may result in the false diagnosis of lesions invading the submucosa. In the opinion of the authors of the mentioned study, the cancer cells' infiltration into the doubled muscularis mucosae should not change the risk of metastasis of neighboring lymph nodes in comparison with lesions invading only its more superficial layer. The authors of the mentioned study suggest that endoscopic treatment could also be extended to selected cases of esophageal adenocarcinoma invading the submucosa. These tumors should be well or moderately differentiated, should not invade lymphovascular vessels and should be at the sm1 stage. Other studies also suggest that in cases of esophageal adenocarcinoma and cardia T1sm1, the risk of lymph node metastasis is very low [20–22].

Staging of esophageal pathology

Qualification for endoscopic therapy of esophageal cancer must be based on the precise staging of the tumor as well as on the distinction between lesions invading the mucosa and submucosa. The authors of several reviews specify that in this case, the efficacy rate of the experienced endoscopic specialist is 80–90%. Furthermore, in their opinion, endoscopic examination and transesophageal high-resolution ultrasonography are not considered ideal methods for stage assessment of early-stage esophageal cancer [11, 19, 23]. In this situation, the most advantageous tool for proper assessment is endoscopic resection and microscopic evaluation of the lesion specimen [14, 24]. Over the last few decades, numerous methods of endoscopic resection have been developed and upgraded, resulting in a safer procedure for patients, as well as in an improvement of assessment quality in resection of a whole lesion in one piece [25]. As emphasized by the review authors, endoscopic evaluation for the staging of early esophageal cancer and endoscopic treatment should be performed at specialized centers with extensive professional experience in these fields. It reduces the potential risk of false-positive diagnosis, establishing thorough, direct verification of the results obtained following preliminary endoscopic evaluation. In addition, patient hospitalization at the specialized center allows detection of lesions concomitantly present in Barrett's esophagus, which would remain untreated in other circumstances. This is particularly important if the patient is subjected to endoscopic treatment. Furthermore, the specialized centers often have integrated professional expertise. These include proficiency in the application of different endoscopic techniques, experience in the use of specialized endoscopy equipment, experience in resection and tissue material processing after biopsy or surgical resection for histopathological evaluation and experience in microscopic assessment. Additionally, the significance of such a large num-

ber of patient hospitalizations at specialized centers cannot be overlooked.

Endoscopic methods of resection at the esophagus level

In cases of HGD and early esophageal cancer, several methods of endoscopic resection (ER) have been developed. Two of them are widely used: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). An ideal situation is when it is possible to perform one-piece resection of a whole susceptible lesion. Considering the currently used EMR methods, it is usually possible to achieve one-piece resection in cases of lesions in the range of 15–20 mm. The ESD allows for en bloc resection of larger mucosal lesions [16, 25]. Which of the abovementioned methods are applied depends on the endoscopic equipment used and the specialists' experience. In cases of lesions identified in Barrett's esophagus, the main efforts are usually focused on endoscopic resection within the whole segment of Barrett's esophagus, simultaneously paying special attention to proton pump inhibition at the level of the stomach. Interesting results were published by the authors applying EMR as a stepwise radical endoscopic resection (SRER) of esophageal lesions to eradicate Barrett's esophagus with early-stage esophageal cancer. They performed the resection of the whole segment of Barrett's esophagus in 169 patients, repeating endoscopic resection every 4–8 weeks. Following complete eradication of neoplastic changes and intestinal metaplasia, they achieved the following rates: 165/169 (97.6%) and 144/169 (85.2%), respectively. After a median follow-up period of 32 months, the authors confirmed maintenance of the results following complete eradication of neoplastic changes in 95.3% of all patients (161/169) and complete eradication of intestinal metaplasia in 80.5% of all patients (136/169). However, in 50% of these patients, a symptomatic stenosis of the esophagus was observed. The esophageal stenosis rate was correlated with the length of esophagus resected [26]. The authors of the discussed report refer to promising results of studies on methods of prevention of esophageal stenosis occurrence after SRER, including the introduction of biodegradable stents, local injection of the treated area with steroids, prophylactic dilation of the healing region after resection and administration of autologous stem cells in this area [26–28].

The ESD is an interesting alternative to EMR for the treatment of HGD and early-stage esophageal cancer, as it allows for endoscopic en bloc excision of lesions in diameters exceeding 2 cm [16, 29–31]. The mean diameter of such removed lesions performed by Taiwanese authors was 33.7 mm [29]. They managed the whole lesion endoscopic resection as a one-tissue preparation with a success rate of 95.8% (22 of 26 cases). R0 resections constituted 87.5% of the cases. There were no applied method-dependent deaths among treated patients and there were no local disease recurrences observed. The ESD method has gained gradual acceptance, including in Europe, particularly in cases of lesions in the gastrointestinal tract qualified for endoscopic resection [14, 16]. In Japan, the ESD method has become the method of choice for the resection of superficial neoplastic lesions within the esophagus [31, 32]. The ESD method is perceived as a significant advance when compared to the EMR method. However, considering endoscopic technique, esophageal ESD is a more difficult procedure than EMR of pathological changes in this area, as well as being associated with a relatively high risk of serious complications [29, 33].

Combining endoscopic resection with local ablation in the treatment of esophageal pathology

An unequivocal recommendation for an appropriate treatment method for early-stage esophageal cancer has not yet been developed [14]. In cases of cancer within Barrett's esophagus mucosa, the ER method with ablation of mucosa residues is still strongly recommended [11, 34]. The authors applying the SRER method emphasize that the first endoscopic resections always concern the lesions of the highest susceptibility, and hence those of the highest stage. This reduces the risk of overlooking and, consequently, leaving more advanced lesions that would influence the results of the microscopic evaluation necessary for selection of an adequate course of radical treatment [26]. This method justifies the significance and safety of local ablation for eradication of residues after applying ER techniques. High effectiveness in the eradication of residues after endoscopic resection of pathologically changed muco-

sa of Barrett's esophagus was determined following radiofrequency ablation (RFA). The combination of both methods, ER and RFA, is intended to reduce the risk of consecutive esophagus stenosis, even in cases of lesions of Barrett's type for long-segment Barrett's esophagus [34]. The mentioned report included the results of a prospective study on eradication effectiveness following the RFA application regarding residual neoplasm within the esophagus after endoscopic resection. In all patients (n = 21), complete eradication of residues of neoplastic changes was achieved, while complete eradication of intestinal metaplasia was obtained in 96% of all patients (in 23 of 24 cases). In the opinion of the authors, these favorable results justify consideration of the RFA method as a leading ablation treatment method recommended for patients with flat-type neoplasia in Barrett's esophagus. Taking into consideration the usefulness of a wide variety of endoscopic eradication methods for the treatment of pathological changes of mucosa in Barrett's esophagus, it is important to consider the restrictions related to ER, photodynamic therapy (PDT), argon plasma coagulation (APC) and cryotherapy, as the separate application of each of these methods very rarely allows complete removal of intestinal metaplasia or of lesion-associated intraepithelial neoplasia in the esophagus. Application of these methods also constituted a source of serious complications [14, 35–37]. The ER method, as EMR or ESD, in combination with a local RFA procedure, is a relatively novel method of endoscopic treatment of Barrett's esophagus. It is widely recommended to combine ESD or EMR methods, including SRER, with the RFA technique, which allows the achievement of high effectiveness of oncological treatment without the risk of negative outcomes that can occur after the use of ablation techniques other than RFA [37, 38].

Conclusions

The selection of appropriate treatment and therapy methods for early esophageal cancer should be performed at a specialized center with adequate facilities. The criteria for endoscopic treatment selection of HGD and early-stage esophageal cancer of adenocarcinoma are the presence of neoplasia restricted to the mucosa and a lack of features of lymph node metastasis. In squamous cell cancer, this treatment is restricted to cases with tumor penetration up to the lamina propria of the mucosa (m2). Tumors treated with the endoscopic method should be well or moderately differentiated and should not invade lymphatic or blood vasculature. A combination of endoscopic resection and endoscopic ablation methods should be considered in endoscopic treatment decisions for these lesions.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. Ca Cancer J Clin 2011; 61: 69-90.
2. Reed MF, Tolis G, Edil BH, et al. Surgical treatment of esophageal high-grade dysplasia. Ann Thorac Surg 2005; 79: 1110-5.
3. Konda VJA, Ferguson MK. Esophageal resection for high-grade dysplasia and intramucosal carcinoma: when and how? WJG 2010; 16: 3786-92.
4. Herrero LA, Pouw RE, Vilsteren FGI, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010; 42: 1030-6.
5. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol 2012; 107: 850-62.
6. Leers JM, DeMeester SR, Oezcelik A, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma: a retrospective review of esophagectomy specimens. Ann Surg 2011; 253: 271-8.
7. Mamidanna R, Bottle A, Aylin P, et al. Short-term outcomes following open versus minimally invasive esophagectomy for cancer in England: a population-based national study. Ann Surg 2012; 255: 197-203.
8. Law S. Esophagectomy without mortality: what can surgeons do? J Gastrointest Surg 2010; 14 Suppl. 1: S101-7.
9. Fernando HC, Murthy SC, Hofstetter W, et al. The Society of Thoracic Surgeons practice guideline series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. Ann Thorac Surg 2009; 87: 1993-2002.
10. Wang VS, Hornick JL, Sepulveda JA, et al. Low prevalence of submucosal invasive carcinoma at esophagectomy for high-grade dysplasia or intramucosal adenocarcinoma in Barrett's esophagus: a 20-year experience. Gastrointest Endosc 2009; 69: 777-83.
11. Manner H, Pech O, Ell C. Barrett's: evolving techniques for dysplasia detection and endoscopic resection. Semin Thoracic Surg 2010; 22: 321-9.
12. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008; 57: 1200-6.
13. Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World J Gastroenterol 2013; 19: 1424-37.
14. Hunt BM, Louie BE, Schembre DB, et al. Outcomes in patients who have failed endoscopic therapy for dysplastic Barrett's

metaplasia or early esophageal cancer. Ann Thorac Surg 2013; 95: 1734-40.
15. Gockel I, Sgourakis G, Lyros O, et al. Risk of lymph node metastasis in submucosal esophageal cancer: a review of surgically resected patients. Expert Rev Gastroenterol Hepatol 2011; 5: 371-84.
16. Repici A, Hassan C, Carlino A, et al. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. Gastrointest Endosc 2010; 71: 715-21.
17. Takubo K, Makunchi H, Arima M, et al. Lymph node metastasis in superficial squamous carcinoma of the esophagus. Pathologe 2013; 34: 148-54.
18. Stein HJ, Feith M, Bruecher BL, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005; 242: 566-73.
19. Bollschweiler E, Baldus SE, Schröder W, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 2006; 38: 149-56.
20. Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol 2008; 15: 3278-88.
21. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment of early adenocarcinoma of the esophagus or gastroesophageal junction. Virchovs Arch 2005; 446: 497-504.
22. Manner H, May Y, Pech O, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with curative intent. Am J Gastroenterol 2008; 103: 2589-97.
23. Cho JW. The role of endoscopic ultrasonography in T staging: early gastric cancer and esophageal cancer. Clin Endosc 2013; 46: 239-42.
24. Prasad GA, Wu TT, Wigle TA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 2009; 137: 815-23.
25. Pouw RE, Bergman JJ. Endoscopic resection of early oesophageal and gastric neoplasia. Best Pract Res Clin Gastroenterol 2008; 22: 929-43.
26. Pouw RE, Seewald S, Gondrie JJ, et al. Stepwise radical endoscopic resection for eradication of Barrett's oesophagus with early neoplasia in a cohort of 169 patients. Gut 2010; 59: 1169-77.
27. Rajan E, Gostout C, Feitoza A, et al. Widespread endoscopic mucosal resection of the esophagus with strategies for stricture prevention: a preclinical study. Endoscopy 2005; 37: 1111-5.
28. Nieponice A, McGrath K, Qureshi I, et al. An extracellular matrix scaffold for esophageal stricture prevention after circumferential EMR. Gastrointest Endosc 2009; 69: 289-96.
29. Chiu PWY, Chan KF, Lee YT, et al. Endoscopic submucosal dissection used for treating early neoplasia of the foregut using a combination of knives. Surg Endosc 2008; 22: 777-83.
30. Lee CT, Chang CY, Tai CM, et al. Endoscopic submucosal dissection for early esophageal neoplasia: a single center experience in South Taiwan. J Formos Med Assoc 2012; 111: 132-9.
31. Toyanaga T, Man IM, East JE, et al. 1,635 endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. Surg Endosc 2013; 27: 1000-8.
32. Shimizu Y, Takahashi M, Yoshida T, et al. Endoscopic resection (endoscopic mucosal resection/endoscopic submucosal dissection) for superficial esophageal squamous cell carcinoma: current status of various techniques. Dig Endosc 2013; 25 Suppl. 1: 13-9.
33. Isomoto H, Yamaguchi N, Minami H, Nakao K. Management of complications associated with endoscopic submucosal dissection/endoscopic mucosal resection for esophageal cancer. Dig Endosc 2013; 25 Suppl. 1: 29-38.
34. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010; 8: 23-9.
35. Fayter D, Corbett M, Heirs M, et al. A systematic review of photodynamic therapy in the treatment of precancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess 2010; 14: 1-288.
36. Halsey KD, Chang JW, Waldt A, Greenwald BD. Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. Endoscopy 2011; 43: 844-8.
37. Pouw RE, Sharma VK, Bergmann JJ, Fleischer DE. Radiofrequency ablation for total Barrett's eradication: a description of the endoscopic technique, its clinical results and future prospects. Endoscopy 2008; 40: 1033-40.
38. Neuhaus H, Terheggen G, Rutz EM, et al. Endoscopic submucosal dissection plus radiofrequency ablation of neoplastic Barrett's esophagus. Endoscopy 2012; 44: 1105-13.

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