CIRUGÍA ESPAÑOLA

www.elsevier.es/cirugia

Editorial

Early Esophageal Cancer. A Western Perspective☆

Carcinoma precoz de esófago. Una perspectiva occidental

In western countries the diagnosis of ''early esophageal adenocarcinoma'' (EAC) is exponentially increasing due mainly to Barrett's esophagus patients surveillance, as recommended by most gastroenterological scientific societies,[1] and to an improvement in diagnostic techniques that allow precise identification of small lesions that might have been previously missed.[2] An accepted definition of ''early cancer'' is the presence of neoplastic cells confined to the mucosal and submucosal layer, in the absence of nodal metastasis.[3] This correspond to the stage 0–1 of AJCC-UICC TNM classification and comprises Tis, T1a and T1b lesions, classified as stage 1, provided that no nodes are involved (N0). Tumors confined to the mucosa layer (Tis) are also called high-grade dysplasia (HGD). With the diffusion of local endoscopic therapies that effectively resect only the neoplastic tissue, it became necessary a further stratification of T1 tumors in T1a and T1b lesions, according to their risk of nodal involvement. T1a tumors are defined as tumors extending beyond the mucosa and invading the Lamina propria up to the muscolaris mucosa. A further subdivision according to the Paris Classification[4] divided superficial lesions into m1 (limited to the mucosa and corresponding to Tis-HGD), and the proper T1a lesions in m2 (limited to the *lamina propria*) and m3 limited to the *muscolaris mucosae*. T1b lesions – i.e. tumors invading the submucosa layer up to the *muscularis propria* – were classified in 3 subtypes: sm1, sm2, and sm3 according to the depth of invasion, using a conventional criteria of dividing the submucosa in 3 parts of 500 μm each: in this way the risk for nodal invasion is more accurately defined, assuming that the more superficial lesions (Tis, T1a) had no or minimal risk for nodal metastasis, T1b sm1 has a low risk and T1b sm2/3 has a consistent risk of nodal involvement. According to Fotis et al. the risk for nodal involvement is 29% for sm1, 71% for sm2 and 42% for sm3, and the grade of tumor differentiation (G) also plays a modulating relevant role.[5]

The major player in the diagnosis of EAC is the endoscopist: narrow band imaging and magnified endoscopy allow the identification of any irregular areas; chromoendoscopy with either Lugol and/or methylene blue staining facilitates the identification of the squamous epithelium, and enhances any area of intestinal metaplasia.[2] Biopsies should be aimed at any abnormal findings in addition to the random biopsy protocol according to Seattle.[6] If pathology shows the presence of neoplastic tissue additional procedures must be aimed to obtain an accurate stage of the tumor. The role of EUS is questionable if aimed to define the precise T of an early tumor, since it has been proven unable to consistently accurately distinguish intramucosal from submucosal tumor invasion,[7] but can accurately detect loco-regional nodes. Suspected nodes may be further investigated with fine needle biopsy. CT scan and PET can be used to detect distant metastases or nodes, but they are not routinely recommended in EAC, given the rarity of these findings.[8] The biopsy specimen should be pinned and fixed for permanent rather than frozen section and, a second opinion by a pathologist is strongly recommended.[9]

Esophagectomy is one of the most demanding surgical procedures and is associated with a not negligible mortality, between 2% and 5%, a considerable morbidity (50%), a substantial impact on quality of life, especially in the first years after the operation. It is therefore clear that an organ preserving treatment that could allow the removal of the cancer with reduced procedural associated risks and leaving the esophagus is appealing. According to the USA national cancer database, in the years from 2004 to 2010 endoscopic treatments for T1a tumors increased from 19% to 53% and from 6.6% to 23% in T1b tumors.[10] The modalities of endoscopic therapies constantly evolve, but simply, they can be classified into ablative therapies and resective therapies that can be used alone or in combination. Ablative therapies aims to destroy the epithelium by chemical means (porphyrine) or thermal means such as argon beam, cryoablation and radiofrequency (RFA).[11] This latter therapy is now the most popular, both for ablating diffuse Tis (HGD) lesions, where a ''target'' lesion is not evident and as a complement

☆ Please cite this article as: Zaninotto G, Markar S. Carcinoma precoz de esófago. Una perspectiva occidental. Cir Esp. 2018;96:463–465.

to endoscopic resection with the purpose to eliminate any remnant Barrett's epithelium.[12] Using this combined approach Phoa et al. reported a 90% remission rate at 5 years in a cohort of 54 patients.[13] The major drawbacks of ''ablative'' therapies is that there are no diagnosis of the extension in terms of tumor depth by the pathologist.

Isolated resection of esophageal tissue is usually performed by means of endoscopic mucosal resection (EMR) that remains the most popular method in western countries. The target mucosal lesion is lifted by injecting saline and then is resected using a band ligation device and a snare. Endoscopic submucosal dissection (ESD) is performed with a specific endoscopic knife: the target lesion is marked circumferentially with a cautery, progressively lifted with saline injection and resected along-with the submucosal tissue.[14] Both therapies allow sampling of neoplastic tissue for adequate pathology examination and tumor staging. Pech et al. reported an excellent result (93.6% of complete remission at long term follow-up of 56.6 months) in a cohort of 1061 patients with intramucosal carcinoma[15] and 83.6% of complete remission in a select cohort of 61 patients with ''low risk'' T1b tumor at 47 months of follow-up.[16] According to the National Cancer Comprehensive Network (NCCN) guidelines[17] however, any submucosal tumor (T1b) or deeper should have surgical resection, given the high risk of nodal involvement. A recent review on 7000 patients, reported that nodal metastases were present in 27%–54% of T1b patients.[18]

To date there are no randomized controlled trial to directly compare the two options. A large population based study of over 2000 patients with EAC (Tis, T1a, T1b) comparing surgery (1586 pts.) and endoscopic therapies (430 pts.) and 2 systematic reviews[19–21] failed to demonstrate any differences in survival between endoscopic and surgical therapies for EAC, though patients with endoscopic therapies had a greater incidence of recurrence and a higher mortality due to non-neoplastic causes.[19] Surgery had higher cost, higher complication and higher mortality rate than the endoscopic approach, however.[21]

Few data exist on how manage ''failure'' after endoscopic local treatment. In general, the scenario of failures has the following patterns: (1) Insufficient radicality, as shown by margin involvement. In this case, if the lateral margin is involved, further endoscopic retreatment is most commonly used. If the deep margin is involved the risk for nodal invasion should prompt the referral of the patient for surgical resection. (2) Persistence of neoplasia in other areas than those resected: a new local resection can be attempted or, if there are no visible lesions, RFA can be used. If the extent of BE is long and EAC is multifocal, not amenable with limited therapies, and the patient is fit, surgical resection can be considered. (3) Recurrence of the neoplasia during the follow up. All patients with early esophageal cancer managed with endoscopic therapies should be kept under endoscopic surveillance with short intervals. In case the tumor recurs it should be staged again and endoscopic therapy can be re-performed, provided that the tumor is confined to T1a and there are no sign of metastasis to the local or distant nodes. When the recurrent tumor extends deeper, surgical resection±neoadjuvant therapy, or radio-chemotherapy or local radiotherapy, depending on the patient fitness and tumor stage are employed.

Although an excellent survival of resected patients after failure of endoscopic treatment is reported from single high-volume center cohorts,[22] some alarming data came from the Cologne group[23]: they compared the outcome of 62 patients that had esophagectomy after endoscopic resection to a matched group of patients with early cancer who had surgery resection as first therapy. The patients with previous endoscopic therapy had a significant reduction of 5-year survival rate compared to those who had primary surgery, (91% vs 98% $P<.05$). Eleven percent of patients who had previous endoscopic therapies showed a T2/T3 tumor at operation; the interval between endoscopic therapy and surgery of more than 3 months and surgery within the first post-intervention year were associated with a worse outcome. A reason for the worse outcome of esophagectomy after endoscopic resection lies probably in the diffusion of endoscopic management of EAC outside referral centers: in the USA more than 20% of esophageal endoscopic resections are performed in community hospitals.[10] Endoscopic therapy of EAC certainly requires highly skilled endoscopists, but differently from more complex cancer surgeries that require an assortment of expertise, as anesthesiologists, ICU specialists, radiologists, oncologists, nutritionists, pathologists, it can be performed even in hospitals where only these endoscopic skills are available. Moreover, the reductive concept that endoscopic resection of EAC is an easy and unconsequential maneuver, prompted many endoscopist to perform it as the first approach, considering EMR-ESD as a ''macro-biopsy'' rather than a resection and starting the therapeutic process of an esophageal cancer patient before discussing the patient at the multi-disciplinary cancer-board and without a careful planning of the whole treatment.

In conclusion, as EAC is becoming more frequent and local endoscopic therapies are more commonly employed, a tendency to treat these patients without referring them to specialized centers is also increasingly adopted, especially if the physician deems that only endoscopic procedures are needed. Nevertheless, though endoscopic therapy is far less dangerous than surgery, the management of EAC patients is not less complex than that of more advanced cancer and requires adequate expertise and technologies. A careful diagnostic approach and staging is mandatory before starting any therapeutic approach and these patients should be referred to specialized UGI cancer centers.

REFERENCES

1. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of gastroeneterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014;64:7–42.
2. Mannath J, Ragunath K. Role of endoscopy in early esophageal cancer. Nat Rev Gastroenterol Hepatol. 2016;13:720–30.
3. Stein HJ, Feith M, Bruecher BLDM, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer. Pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005;242:566–75.

4. The Participants in Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Gastrointest Endosc. 2003;58. S3-43.
5. Fotis D, Doukas M, Wijnhoven BPL, Didden P, Bierman K, Bruno MJ, et al. Submucosal invasion and risk of lymph node invasion in early Barrett's cancer: potential impact of different classification on patient management. UEG J. 2015;3:505–13.
6. Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology. 1993;105:40–50.
7. Bergeron EJ, Lin J, Chang AC, Orringer MB, Reddy RM. Endoscopic ultrasound id inadequate to determine which T1/T2 esophageal tumors are candidates for endoluminal therapies. J Thorac Cardiovasc Surg. 2014;147:765–73.
8. Hermansson M, DeMeester SR. Management of stage 1 esophageal cancer. Surg Clin N Am. 2012;92:1155–67.
9. Jennifer R, Scudiere M. New treatments, new challenges: pathology's perspective on esophageal carcinoma. Gastroenterol Clin N Am. 2009;38:121–31.
10. Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, et al. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst. 2014. http://dx.doi.org/10.1093/jnci/dju133. pii:dju133.
11. Hammoud GM, Hammad H, Ibdah JA. Endoscopic assessment and management of early esophageal adenocarcinoma. World J Gastrointest Oncol. 2014;15:275–88.
12. Guarnere-Argente C, Buoncristiano T, Furth EE, Falk GW, Ginsberg GG. Long-term outcomes of patients with Barrett's esophagus and high-grade dysplasia or early cancer treated with endoluminal therapies with intention of complete eradication. Gastrointest Endosc. 2013;77:190–9.
13. Phoa NK, Pouw RE, van Viksteren FGI, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection. A Netherlands cohort study. Gastroenterology. 2013;145:96–104.
14. Ning B, Abdelfatab MM, Othman MO. Endoscopic submucosal dissection and endoscopic mucosal resection for early stage esophageal cancer. Ann Cardiothorac Surg. 2017;6:88–98.
15. Pech O, May A, Manner H, Behrens A, Pohl J, Braun K, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014;146:652–60.
16. Manner H, Pech O, Heldmann Y, May A, Pohl J, Bherens A, et al. Efficacy and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low risk sm1 invasion. Clin Gastroenterol Hepatol. 2013;11:630–5.
17. National Comprehensive Cancer Network. Esophageal cancer and esophagogastric junction cancers. Version 2-2017; 2017. Available from: https://www.nccn.org/professionals/physician_gls/esophageal.pdf [accessed 21.08.17]
18. Gockel I, Sgourakis G, Lyros O, Polotzek U, Schimanski CC, Lang H, et al. Risk of lymphnode metastasis in submucosal esophageal cancer: a review of surgically resected patients. Expert Rev Gastoenterol Hepatol. 2011;5:371–84.
19. Wani S, Drahos J, Cook MB, Rastogi A, Bansai A, Yen R, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population based study. Gastrointest Endosc. 2014;79:224–32.
20. Wu J, Pan Y, Wang T, Gao D, Hu B. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc. 2014;79:233–41.
21. Bennett C, Green S, DeCaestecker J, Almond M, Barr H, Bhandari P, et al. Surgery versus radical endotherapies for early cancer and high grade dyspasia (Review). Cochrane Database Syst Rev. 2012. http://dx.doi.org/10.1002/14651858.CD007334.PUB4. Art. No: CD007334.
22. Hunt BM, Louie BE, Schembre DB, Bohorfush AG, farivar AS, Aye RW. Outcomes in patients who have failed endoscopic therapy for dysplastic Barrett's metaplasia or early esophageal cancer. Ann Thorac Surg. 2013;95:1734–40.
23. Plum PS, Pacheco K, Bollschweiler E, Berlth F, Holscher AF. Prognosis of patients with early esophageal cancer who underwent endoscopic resection before esophagectomy. Presented at the *23 meeting of the European Surgical Association, ESA abstract book*. 2016. p. 67.

Giovanni Zaninotto*, Sheraz Markar
Departamento de Cáncer y Cirugía, Imperial College, London, United Kingdom

**Corresponding author.*
E-mail address: g.zaninotto@imperial.ac.uk (G. Zaninotto).

2173-5077/