Review Article

Early Squamous Neoplasia of the Esophagus: The Endoscopic Approach to Diagnosis and Management

Kesavan Kandiah, Fergus J. Q. Chedgy, Sharmila Subramaniam, Sreedhari Thayalasekaran, Arun Kurup, Pradeep Bhandari

Department of Gastroenterology, Queen Alexandria Hospital, Portsmouth, United Kingdom

Address for correspondence:
Prof. Pradeep Bhandari, Department of Gastroenterology, Queen Alexandria Hospital, Portsmouth, PO6 3LY, United Kingdom.
E-mail: pradeep.bhandari@porthosp.nhs.uk

ABSTRACT

Considerable focus has been placed on esophageal adenocarcinoma in the last 10 years because of its rising incidence in the West. However, squamous cell cancer (SCC) continues to be the most common type of esophageal cancer in the rest of the world. The detection of esophageal SCC (ESCC) in its early stages can lead to early endoscopic resection and cure. The increased incidence of ESCC in high-risk groups, such as patients with head and neck squamous cancers, highlights the need for screening programs. Lugol's iodine chromoendoscopy remains the gold standard technique in detecting early ESCC, however, safer techniques such as electronic enhancement or virtual chromoendoscopy would be ideal. In addition to early detection, these new "push-button" technological advancements can help characterize early ESCC, thereby further aiding the diagnostic accuracy and facilitating resection. Endoscopic resection (ER) of early ESCC with negligible risk of lymph node metastases has been widely accepted as an effective therapeutic strategy because it offers similar success rates when compared to esophagectomy, but carries lesser morbidity and mortality. Endoscopic submucosal dissection (ESD) is the preferred technique of ER in lesions larger than 15 mm because it provides higher rates of en bloc resections and lower local recurrence rates when compared to endoscopic mucosal resection (EMR).

Key Words: Early esophageal squamous cell carcinoma, electronic imaging, endoscopic mucosal resection, endoscopic submucosal dissection, Lugol's iodine, radio frequency ablation, synchronous head and neck cancer, virtual chromoendoscopy

Received: 16.02.2016, Accepted: 09.04.2016

How to cite this article: Kandiah K, Chedgy FJ, Subramaniam S, Thayalasekaran S, Kurup A, Bhandari P. Early squamous neoplasia of the esophagus: The endoscopic approach to diagnosis and management. Saudi J Gastroenterol 2017;23:75-81.

Esophageal cancer is the eighth most common cancer in the world, with an estimated incidence of 456,000 cases and 400,000 deaths in 2012.[1] Considerable focus has been placed on esophageal adenocarcinoma in the last ten years due to its rising incidence in the West. However, squamous cell cancer (SCC) continues to be the most common type of esophageal cancer in the rest of the world. The "esophageal cancer belt" extends from the Middle East to northeast China, with the highest-risk of developing esophageal SCC (ESCC).[2-4]

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.203366

Patients with advanced ESCC, where the carcinoma extends into the submucosal layer (T1b–T4), are often symptomatic on presentation. In contrast, patients with superficial ESCC, where the carcinoma is limited to the mucosa (T1a), are often asymptomatic.[5,6] Patients with advanced ESCC carry a poor 5-year survival rate of 54.9%. On the other hand, early ESCC conveys a higher 5-year survival rate of up to 80%.[7-9] Such patients can be cured by endoscopic resection of the early squamous neoplasia. This highlights the importance of early detection and treatment of ESCC without the need for radical therapies such as chemoradiotherapy or esophagectomy. This review aims to summarise the current evidence for the endoscopic diagnosis and treatment of early squamous neoplasia.

Risk factors

Awareness of the risk factors leading to the development of ESCC leads to better identification of patients who would be at high risk of developing ESCC. An alcohol intake of more than 12.5 g/day increases the relative risk (RR) of ESCC to 2.62 when compared to abstinence. The RR increases to 5.54 when the daily alcohol intake exceeds 50 g.[10-12] Cigarette smoking carries an RR of 2.63 when compared to nonsmokers. The RR of developing ESCC is exponentially increased with the combination of alcohol consumption and cigarette smoking (RR 8.05).[13] An increasingly recognized risk factor of ESCC is the concurrent diagnosis of head and neck SCC. The incidence of esophageal squamous cell neoplasia in patients with head and neck cancer in screening studies range between 9.4 and 14%.[14,15] This high incidence of synchronous ESCC calls for an urgent need of a screening program in this population.

Endoscopic detection and characterization of early esophageal squamous cell cancer

On standard non-magnified endoscopy, intra-mucosal cancer commonly appears flat with little impact on the contour of the mucosal surface (Paris classification 0-IIa, IIb, IIc) making it difficult to detect [Figure 1]. On the other hand, advanced cancer is easily seen as elevated (0-I) or excavated (III) or a combination of the two.[16]

Lugol's iodine chromoendoscopy

The detection of early ESCC is augmented by the use of Lugol's iodine staining. Lugol is a vital stain that contains iodine and is actively taken up by glycogen found in normal esophageal squamous cells. The cells in areas of esophageal neoplasia are glycogen poor, resulting in a reduced uptake of the iodine in Lugol dye, appearing as Lugol voiding areas, otherwise known as the "pink-color sign" [Figure 2].[17,18] The sensitivity and specificity of Lugol chromoendoscopy in detecting early ESCC ranges from 96 to 100% and 57 to 64%, respectively, making it the gold standard detection test.[14,19] Lugol dye spray in the esophagus can lead to minor adverse events such as hypersensitivity to iodine, laryngitis, pneumonitis, chest discomfort and nausea. Spraying the esophagus with sodium thiosulphate following the administration of Lugol dye has been shown to reduce chest discomfort usually experienced with Lugol chromoendoscopy.[20]

ELECTRONIC ENHANCEMENT TECHNIQUES

Narrow band imaging

Narrow band imaging (NBI) is an optical image enhancing technique that provides a detailed assessment of the mucosal surface and microvasculature within the mucosa of the gastrointestinal tract.[21] The mucosal vessel pattern in squamous mucosa was described by Inoue *et al.* as intrapapillary capillary loops (IPCL). They described five different IPCL patterns corresponding to normal squamous mucosa to various grades of squamous neoplasia [Table 1].[22-24] NBI with magnification has been shown to diagnose the depth of invasion with an accuracy of 76.8 to 85.2%.[25-27] However, a well-powered multicenter prospective study carried out by Ebi *et al.* was not able to demonstrate an improved accuracy in diagnosing the depth of invasion of ESCC using NBI with magnification when compared with high definition white light alone.[28]

Blue Laser Imaging is a new optical image enhancement technology by Fujinon that uses laser light to transmit light with wavelengths of 410 and 450 nm. This provides for narrow band observation of mucosal vascular and surface patterns similar to NBI [Figure 3].

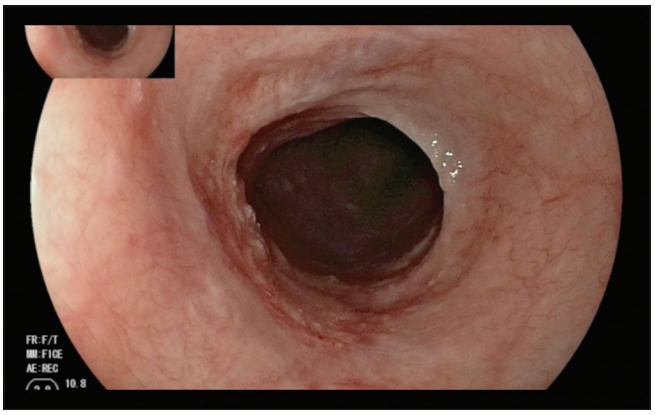


Figure 1: Early esophageal squamous cell neoplasia seen on standard white light endoscopy

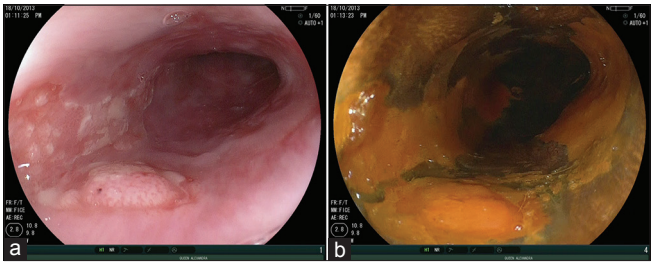


Figure 2: (a) 0-Ia esophageal squamous cell neoplastic lesion is clearly seen on white light endoscopy. (b) The addition of Lugol dye reveals multiple Lugol voiding areas indicating further areas of squamous neoplasia

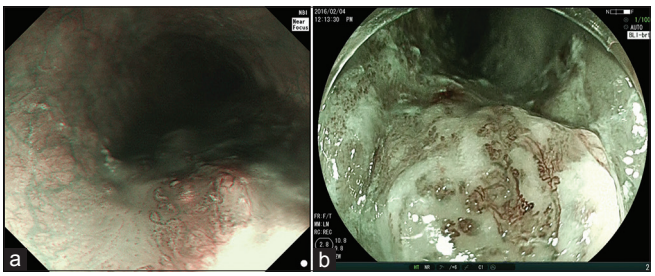
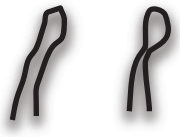
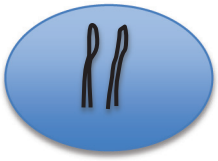


Figure 3: (a) NBI with DualFocus demonstrating type V2 intrapapillary capillary loop pattern. (b) BLI with zoom demonstrating Type V3 intrapapillary capillary loop pattern

Table 1: Intrapapillary Capillary Loop (IPCL) pattern classification

IPCL	Schematic drawing	Pattern description	Pathology
Type I		Smooth running, small diameter capillaries	Normal
Type II		Dilatation and elongation of Type I capillaries	Inflammation
Type III		Normal IPCL within a brownish lesion	Inflammation/LGN
Type IV		Increased vessel caliber and elongation of IPCL toward the epithelial surface	LGN/HGN
Type V1		Non-uniform, irregularly dilated IPCL	m1
Type V2		Elongation of Type V1 capillaries	m2
Type V3		Loss of loop configuration and spread to horizontal plane	m3/SM1
Type Vn		Vessel caliber 3x larger than V3 – new tumour vessels	SM2

(Modified from reference 24,25). IPCL pattern classification from IPCL type I to type V-1 is used for the tissue characterization of flat lesions (red outline). IPCL pattern classification from IPCL type V-1 to type VN reflects cancer infiltration depth

Fujinon intelligent color enhancement

FICE is a post-acquisition based image enhancement technique.[29] It is used to delineate tumor margins and degree of invasion by examining IPCLs.[30] Li *et al.* performed a prospective study comparing FICE and magnified FICE against Lugol chromoendoscopy and magnified Lugol chromoendoscopy. They found that the positive rates of early ESCC detection for FICE

and Lugol chromoendoscopy were similar, 92.6% vs. 88.9% ($P = 0.642$). The addition of magnification endoscopy did not significantly improve the detection rates of 96.3% vs. 92.6%, respectively ($P = 0.556$).[31]

i-scan

i-Scan is a post-acquisition image enhancement technology designed to enhance surface and vascular patterns. There is limited published data on the use of i-Scan in the detection and assessment of ESCC. However, in a single-center prospective non-inferiority sequential trial, the detection rate of early ESCC was 10.4% when compared to 12.9% detection rate with Lugol chromoendoscopy.[32]

Most studies highlight the difficulties in the detection of early ESCC with white light alone. However, enhancement techniques described above significantly improve the detection rate of early ESCC. We highly recommend the use of these techniques for the detection and characterization of early ESCC. Lugol chromoendoscopy remains the gold standard, but there is an urgent need of head-to-head studies comparing the detection rates of early ESCC using Lugol's versus virtual chromoendoscopy. This will help to decide if Lugol's can be replaced by virtual chromoendoscopy, which has a better safety profile.

Endoscopic management of early esophageal squamous cell cancer

Neoplasia restricted to the mucosa or with limited invasion into the superficial part of the submucosa is defined as early, irrespective of the risk of lymph node involvement. However, clinicians managing ESCC need to have a very clear understanding of the different stages of this cancer and the risk of lymph node metastasis [Table 2].[33-37]

Endoscopic resection vs. surgery/radical chemoradiotherapy

Endoscopic resection (ER) of early ESCC with negligible risk of lymph node metastases has been widely accepted as an effective therapeutic strategy because it offers similar success rates when compared to esophagectomy but carries lesser morbidity and mortality.[38,39]

Table 2: Risk of lymph node metastases according to depth of invasion of SCC

Depth	Lymph node risk %
Low/high grade dysplasia	0
m1	0
m2	0
m3	8-18.2
sm1	17-24
sm2	21-28
sm3	37-44

Historically, surgery has been viewed as the gold standard treatment for patients with esophageal carcinoma. However, esophagectomy is associated with a high risk of complications with a morbidity of 20–50% and a mortality rate of 3–11%, depending on volume of procedures.[40-42] Moreover, it has been shown that patients with early ESCC have a much greater mortality rate post-esophagectomy than those with early esophageal adenocarcinoma, 11% vs. 5%.[43]

Because of the significant risk of lymph node metastases in lesions extending to m^3 and beyond, curative endoscopic resection should only be offered to those patients with early ESCC, extending as far as the m2 layer.

Endoscopic mucosal resection vs. endoscopic submucosal dissection

Experience of endoscopic resection for early ESCC began in the early 1990s in Asia; since then, techniques have significantly developed. Initial experience came from the strip biopsy technique, which was further refined with the suck-and-cut technique.[44] A randomized control trial comparing cap-assisted versus multi-band endoscopic mucosal resection (EMR) found that both methods are equally safe and efficacious; with multi-band EMR being significantly more cost-efficient and faster technique.[45] However, the en-bloc resection rates are low with large lesions requiring piecemeal resection making adequate histological assessment difficult. EMR has been demonstrated to have recurrence rates of 4–26%.[46-48]

Endoscopic submucosal dissection (ESD) has the advantage of being able to provide an en-bloc resection regardless of lesion size or submucosal fibrosis, allowing accurate histological staging at the expense of procedure duration, steep learning curve, and greater risks.[49] Ono *et al.*[50] treated 107 early ESCC in 84 patients, achieving a 100% en-bloc resection rate, with only 1 patient suffering from recurrence, and a perforation rate of 4%. They were able to achieve a 100% 5-year survival rate in patients whose lesions were limited to the m2 layer.

Takahashi *et al.* published a retrospective review of 300 consecutive patients undergoing ER for early ESCC. One hundred and eighty four patients underwent EMR and 116 underwent ESD.[51] They demonstrated that the en-bloc resection rates (53.5% vs. 100%) and local recurrence rates (9.8% vs. 0.9%) were significantly better in the ESD group when compared with the EMR group. However, they also demonstrated that when EMR is performed for lesions <15 mm, no local recurrence was seen, further supporting the report from Ishihara *et al.*[52] The overall efficacy of ESD in the management of early ESCC was demonstrated in a meta-analysis of 15 studies encompassing

776 ESD-treated lesions.[53] In this study, the pooled estimate of en-bloc resection rate was above 95% and the complete resection rate was 89%.

Careful selection of cases is key for an optimum outcome following endoscopic resection. In both their studies, Mizuta and Ono *et al.* found that lesions with a greater depth of invasion (>pT1m2) led to higher stricture rates. Lesions and resection margins extending over 59% and 71% of the esophageal circumference, respectively, were also found to be strong predictors of post-ESD esophageal stricturing.[54,55] However, post-ESD esophageal stricturing can be successfully managed by endoscopic dilatation with or without the use of locally injected or orally administered steroids.[56,57]

We would, therefore, suggest that ER is performed with curative intent in patients with ESCC limited to m^2 layer. Lesions <15 mm can be effectively treated with either cap-assisted EMR or ESD, but lesions >15 mm should be treated by ESD where the expertise is available.

ER offers a real potential of cure in patients with low grade dysplasia, high grade dysplasia, m1 and m2 cancer with well differentiation and without lymphovascular invasion. In cases of M3 or SM1 cancer, ESD could be considered as an alternative to radical therapy (surgery or chemoradiotherapy) when histology shows R0, well-differentiated cancers without lymphovascular invasion, especially in elderly patients or in patients with significant comorbidities.[58]

Radio frequency ablation for esophageal squamous cell cancer

Radiofrequency ablation (RFA) for esophageal neoplasia involves the application of heat generated by an energy waveform. The heat is delivered to a depth of 800 μm via a bipolar electrode array to the esophageal mucosa. The electrode is located either on the outside of a balloon, on an articulating platform attached to the distal end of an endoscope, or on the end of a through-the-scope catheter. The role of endoscopic RFA in the management of Barrett's dysplasia is well established. However, similar success has not been demonstrated with RFA in the management of early ESCC.

Several studies have demonstrated variable success of RFA in treating early ESCC. In a prospective single-center cohort study of Chinese patients, 96 patients with early flat (type 0-IIb) neoplasia (maximum depth of T1m2) underwent RFA.[59] In a 12-month follow-up, 81% of patients had complete response having had a mean number of 1.9 ± 0.8 RFA procedures. In contrast, a prospective cohort study from eight tertiary centers in the United Kingdom found that, in a 12-month follow-up period, only 50% of patients achieved complete eradication of early ESCC. Furthermore, 30% of patients progressed to invasive cancer at 1 year.[60]

There are several drawbacks in treating early ESCC with RFA. This technique does not allow for tissue acquisition and post–treatment analysis. Therefore, the histological examination for depth of invasion and lymphovascular involvement cannot be made. Unlike Barrett's, ESCC is more aggressive, and therefore, under treatment of inappropriately selected patients can be catastrophic.[55] We feel that the role of RFA in the management of ESCC is questionable and should only be performed under special circumstances.

CONCLUSION

ESCC is the major type of esophageal cancer worldwide; it can be readily treated provided it is detected early. Several high-risk groups have been recognized but patients with SCC of the head and neck are at a very high risk of developing ESCC. We highly recommend a screening program where one does not exist. White light endoscopy alone is insufficient to detect early ESCC and this is best done using Lugol's chromoendoscopy, which remains the gold standard technique. Safer techniques, such as virtual chromoendoscopy, on the other hand would be ideal, but studies comparing the sensitivity and specificity of the two techniques are sorely lacking. Early diagnosis of ESCC leads to early endoscopic curative therapy. Here, EMR can be carried out for lesions <15 mm and ESD for lesions >15mm.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M. GLOBOCAN, cancer incidence and mortality worldwide: IARC cancer base no. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013.
2. Rasool S, Ganai BA, Sameer AS, Masood A. Esophageal cancer: Associated factors with special reference to the Kashmir Valley. Tumori 2012;98:191-203.
3. Khuroo MS, Zargar SA, Mahajan R, Banday MA. High incidence of oesophageal and gastric cancer in Kashmir in a population with special personal and dietary habits. Gut 1992;33:11-5.
4. Li JY. Epidemiology of oesophageal cancer in China. Natl Cancer Inst Monogr 1982;62:113-20.
5. Chen LQ, Hu CY, Ghadirian P, Duranceau A. Early detection of oesophageal squamous cell carcinoma and its effects on therapy: An overview. Dis Esophagus 1999;12:161-7.
6. Sugimachi K, Ohno S, Matsuda H, Mori M, Matsuoka H, Kuwano H. Clinicopathologic study of early stage oesophageal carcinoma. Surgery 1989;105:706-10.

7. Surveillance Epidemiology and End Results (SEER) 18 2004-2010 [cited 2015 April 21st]; Available from: http://www.seer.cancer.gov
8. Kato H, Tachimori Y, Watanabe H, Yamaguchi H, Ishikawa T, Itabashi M. Superficial oesophageal carcinoma—surgical treatment and the results. Cancer 1990;66:2319-23.
9. Yoshinaka H, Shimazu H, Fukumoto T, Baba M. Superficial oesophageal carcinoma: A clinicopathological review of 59 cases. Am J Gastroenterol 1991;86:1413-8.
10. Islami F, Fedirko V, Tramacere I, Bagnardi V, Jenab M, Scotti L, *et al.* Alcohol drinking and oesophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: A systematic review and meta-analysis. Int J Cancer 2011;129:2473-84.
11. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW Jr, *et al.* Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337:1705-14.
12. Pandeya N, Williams G, Green AC, Webb PM, Whiteman DC. Australian Cancer Study. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology 2009;136:1215-24.
13. Steevens J, Schouten LJ, Goldbohm RA, van der Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: A prospective cohort study. Gut 2010;59:39-48.
14. Ina H, Shibuya H, Ohashi I, Kitagawa M. The frequency of a concomitant early oesophageal cancer in male patients with oral and oropharyngeal cancer. Screening results using Lugol dye endoscopy. Cancer 1994;73:2038-41.
15. Petit T, Georges C, Jung GM, Borel C, Bronner G, Flesch H, *et al.* Systematic oesophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. Ann Oncol 2001;12:643-6.
16. The Paris endoscopic classification of superficial neoplastic lesions: Esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S44-5.
17. Inoue H, Rey J, Lightdale C. Lugol chromoendoscopy for oesophageal squamous cell cancer. Endoscopy 2001;33:75-9.
18. Shimizu Y, Omori T, Yokoyama A, Yoshida T, Hirota J, Ono Y, *et al.* Endoscopic diagnosis of early squamous neoplasia of the esophagus with iodine staining: High-grade intraepithelial neoplasia turns pink within a few minutes. J Gastroenterol Hepatol 2008;23:546-50.
19. Shiozaki H, Tahara H, Kobayashi K, Yano H, Tamura S, Imamoto H, *et al.* Endoscopic screening of early oesophageal cancer with the Lugol dye method in patients with head and neck cancer. Cancer 1990;66:2068-71.
20. Kondo H, Fukuda H, Ono H, Gotoda T, Saito D, Takahiro K, *et al.* Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. Gastrointest Endosc 2001;53:199-202.
21. Takenaka R, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, *et al.* Narrow Band Imaging Provides Reliable Screening for Oesophageal Malignancy in Patients With Head and Neck Cancers. Am J Gastroenterol 2009;104:2942-8.
22. Inoue H. Magnification endoscopy in the oesophagus and stomach. Dig Endosc 2001;13(suppl):40-1.
23. Minami H, Isomoto H, Inoue H, Akazawa Y, Yamaguchi N, Ohnita K, *et al.* Significance of background coloration in endoscopic detection of early oesophageal squamous cell carcinoma. Digestion 2014;89:6-11.
24. Inoue H, Honda T, Nagai K, Kawano T, Yoshino K, Takeshita K, *et al.* Ultrahigh magnification endoscopic observation of carcinoma *in situ* of the oesophagus. Dig Endosc 1997;9:16-8.
25. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial oesophageal lesions. Gastrointest Endosc 2004;59:288-95.
26. Higuchi K, Tanabe S, Azuma M, Katada C, Sasaki T, Ishido K, *et al.* A phase II study of endoscopic submucosal dissection for superficial oesophageal neoplasms (KDOG 0901). Gastrointest Endosc 2013;78:704-10.
27. Sato H, Inoue H, Ikeda H, Sato C, Onimaru M, Hayee B, *et al.* Utility of intrapapillary capillary loops seen on magnifying narrow-band imaging in estimating invasive depth of esophageal squamous cell carcinoma. Endoscopy 2015;47:122-8.
28. Ebi M, Shimura T, Yamada T, Mizushima T, Itoh K, Tsukamoto H, *et al.* Multicenter, prospective trial of white-light imaging alone versus white-light imaging followed by magnifying endoscopy with narrow-band imaging for the real-time imaging and diagnosis of invasion depth in superficial oesophageal squamous cell carcinoma. Gastrointest Endosc. 2015;81:1355-61.
29. Miyake Y, Sekiya T, Yano T, Kubo S, Hara T. A new spectrophotometer for measuring the spectral reflectance of gastric mucous membrane. J Photogr Sci 1989:37:134-8.
30. Pohl J, May A, Rabenstein T, Pech O, Ell C. Computed virtual chromoendoscopy, a new tool for enhancing tissue surface structures. Endoscopy 2007;39:80-3.
31. Li YX, Shen L, Yu HG, Luo HS, Yu JP. Fujinon intelligent color enhancement for the diagnosis of early oesophageal squamous cell carcinoma and precancerous lesion. Turk J Gastroenterol 2014;25:365-9.
32. Guo J, Li CQ, Li M, Zuo XL, Yu T, Liu JW, *et al.* Diagnostic value of probe-based confocal laser endomicroscopy and high definition virtual chromoendoscopy in early oesophageal squamous neoplasia. Gastrointestinal Endoscopy 2015;81:1346-54.
33. Makuuchi H, Shimada H, Chino O. Survival of patients with superficial squamous cell carcinoma of the esophagus treated by oesophagectomy. Rinsho-Shokakinaika (Clin Gastroenterol) 1997;12;1749-56 (in Japanese).
34. Endo M, Takeshita K, Kawano T, Inoue H. Indication: Endoscopic treatment for early carcinoma of the esophagus. In Okubo A, Kimura K, Imawari M, Nakamura T eds. Shokaki-Shinryo practice. Tokyo: Bunkodo; 1998. p. 139-42.
35. Li B, Chen H, Xiang J, Zhang Y, Kong Y, Garfield DH, *et al.* Prevalence of lymph node metastases in superficial oesophageal squamous cell carcinoma. J Thorac Cardiovasc Surg 2013;146:1198-203.
36. Tajima Y, Nakanashi Y, Ochial A, Tachimori Y, Kato H, Watanabe H, *et al.* Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial oesophageal carcinoma: Analysis of 240 surgically resected tumors. Cancer 2000;88:1285-93.
37. Araki K, Ohno S, Egashira A, Saeki H, Kawaguchi H, Sugimachi K. Pathologic features of superficial esophageal squamous cell carcinoma with lymph node and distal metastasis. Cancer. 2002 Jan 15;94(2):570-5. PubMed PMID: 11900242.
38. Fujita H, Sueyoshi S, Yamana H, Shinozaki K, Toh U, Tanaka Y, *et al.* Optimum treatment strategy for superficial oesophageal cancer: Endoscopic mucosal resection versus radical oesophagectomy. World J Surg 2001;25:424-31.
39. Shimizu Y, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Long-term outcome after endoscopic mucosal resection in patient with oesophageal squamous cell carcinoma invading the muscularis mucosa or deeper. Gastrointest Endosc 2002;56:387-90.
40. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early oesophageal cancer: Pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005;242:566-73.
41. Thomas P, Doddoli C, Neville P, Pons J, Lienne P, Giudicelli R, *et al.* Oesophageal cancer resection in the elderly. Eur J Cardiothorac Surg 1996;11:941-6.

42. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, *et al.* Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-37.
43. Höelscher AH, Bollschweiler E, Schneider PM, Siewert JR. Comparison between adeno- and squamous cell carcinoma. Cancer 1995;76:178-86.
44. Tanabe S, Koizumi W, Kokutou M, Imaizumi H, Ishii K, Kida M, *et al.* Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. Gastrointest Endosc 1999;50:819-22.
45. Zhang YM, Boerwinkel DF, Qin X, He S, Xue L, Weusten BL, *et al.* A randomized trial comparing multiband mucosectomy and cap-assisted endoscopic resection for endoscopic piecemeal resection of early squamous neoplasia of the esophagus. Endoscopy 2016;48:330-8.
46. Pech O, Gossner L, May A, Vieth M, Stolte M, Ell C. Endoscopic resection or superficial oesophageal squamous-cell carcinomas: Western experience. Am J Gastroenterol 2004;99:1226-32.
47. Pech O, May A, Gossner L, Rabenstein T, Manner H, Huijsmann J, *et al.* Curative endoscopic therapy in patients with early oesophageal squamous-cell carcinoma or high-grade intraepithelial neoplasia. Endoscopy 2007;39:30-5.
48. Katada C, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005;61:219-25.
49. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, *et al.* Endoscopic submucosal dissection of oesophageal squamous cell neoplasms. Clin Gastroenterol Hepatol 2006;4:688-94.
50. Ono S, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, *et al.* Long-term outcomes of endoscopic submucosal dissection for superficial oesophageal squamous cell neoplasms. Gastrointest Endosc 2009;70:860-6.
51. Takahashi H, Arimura Y, Masao H, Okahara S, Tanuma T, Kodaira J, *et al.* Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus. Gastrointest Endosc 2010;72:255-64.
52. Ishihara R, Lishi H, Tackeuchi Y, Kato M, Yamamoto S, Yamamoto S, *et al.* Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. Gastrointest Endosc 2008;67:799-804.
53. Kim JS, Kim BW, Shin IS. Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: A meta-analysis. Dig Dis Sci 2014;59:1862-9.
54. Mizuta H, Nishimori I, Kuratani Y, Higashidani Y, Kohsaki T, Onishi S. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. Dis Esophagus 2009;22:626-31.
55. Ono S, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, *et al.* Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 2009;41:661-5.
56. Hashimoto S, Kobayashi M, Takeuchi M, SatoY, Narisawa R, Aoyagi Y. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc 2011;74:1389-93.
57. Yamaguchi N, Isomoto H, Nakayama T, Hayashi T, Nishiyama H, Onhita K, *et al.* Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Gastrointest Endosc 2011;73:1115-21.
58. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, de Ceglie A, *et al.* Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47:829-54.
59. He S, Bergman J, Zhang Y, Weusten B, Xue L, Qin X, *et al.* Endoscopic radiofrequency ablation for early oesophageal squamous cell neoplasia: Report of safety and effectiveness from a large prospective trial. Endoscopy 2015;47:398-408.
60. Haidry RJ, Butt MA, Dunn J, Banks M, Gupta A, Smart H, *et al.* Radiofrequency ablation for early oesophageal squamous neoplasia: Outcomes form United Kingdom registry. World J Gastroenterol 2013;19:6011-9.