Esophageal Cancer

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Esophageal cancer (EC) has a poor prognosis when the diagnosis is delayed, but curative treatment is possible if the diagnosis is timely. The disease subtly progresses before symptoms prompt patients to seek medical attention. Effective pre-symptomatic screening strategies may improve the outcome of the disease. Recent evidence provided insights into early diagnosis of EC via blood tests, advanced endoscopic imaging, and artificial intelligence. Accordingly, this entry reviewed available strategies to diagnose early EC.

diagnosis esophageal cancer early neoplasia

1. Introduction

In 2018 esophageal cancer (EC) was estimated to account for 508,000 deaths, being the seventh most common cancer and the sixth cause of cancer death worldwide [1]. Histologically, EC includes esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Usually, ESCC occurs in the middle or upper one-third of the esophagus, whereas EAC in the lower one-third or junction of the esophagus [2]. ESCC accounts for up to 90% of ECs in lower-income countries and in those regions spanning from Asian republics to north-central China, known as the “esophageal cancer belt” [3][4]. Complementarily, EAC accounts for around 20% of all ECs in Western Countries [3]. The replacement of esophageal squamous epithelium with intestinal metaplasia containing goblet cells defines Barrett’s esophagus (BE), which represents a well-known preneoplastic lesion for EAC. Interestingly, a recent meta-analysis revealed that around 12% of patients diagnosed with EAC had a prior BE diagnosis, and up to 57% of patients had concurrent diagnoses of BE and EAC [5].

Due to the late onset of clinical symptoms and the lack of early disease markers, EC is often diagnosed in advanced stages, when the prognosis is poor: ESCC has an overall 5-year survival rate of 18%, which decreases to less than 5%, when distant metastases are present at diagnosis [3]. Similarly, when EAC is diagnosed in advanced stages, the disease has a 5-year survival rate of less than 20% [1][6].

However, when early detection and management of EC is possible, the outcome improves significantly, and mortality decreases [7]. Therefore, several screening and preventive strategies are under investigation, each having its specific applicability, advantages, and disadvantages [8]. Of note, international guidelines do not currently include novel blood biomarkers, advanced endoscopy, or artificial intelligence (AI)-assisted endoscopy in the diagnostic work-up of EC. However, in recent years, the topic is increasingly being investigated, and a growing body of evidence is being provided. Accordingly, we reviewed the most recent literature addressing the early detection of ESCC and EAC via blood testing, advanced upper endoscopy, and novel AI systems.

2. Blood Biomarkers of Esophageal Cancer: A Liquid Biopsy

A biomarker is a biological molecule that can be found in the blood or in biological fluids or tissues of patients [9]. Blood biomarkers can be used for early diagnosis, prognosis, and clinical management of several cancer types [10]. There are some highly desirable characteristics that a cancer marker (CM) should possess, namely (i) high sensitivity in the screening of the general population, (ii) high specificity to a given type of tumor, (iii) be detectable in early cancers, providing a lead-time over clinical diagnosis, and (iv) correlate with the burden of a tumor, reflecting any tumor progression or regression [11]. Currently, the perfect CM does not exist, and circulating CMs recommended for clinical use are limited and include prostate-specific antigen, thyroglobulin, oncofetal antigens (e.g., carcinoembryonic antigen (CEA), alpha-fetoprotein) and carbohydrate antigens (CA) (e.g., CA125, CA19-9, CA15.3) [10].

Historically, CEA has been used as serum CM in the diagnosis of EC [12]. In this regard, CEA levels have been shown to be significantly higher in EC patients compared to controls [13]. In a meta-analysis [14], the sensitivity and specificity of CEA ranged from 8% to 70%, and from 57% to 100%, respectively, while its positive likelihood ratio (PLR) was 5.94 (95% confidence interval [CI], 3.24–10.89) meaning that patients with EC have a six-fold higher chance of having increased CEA levels compared to patients without EC [14]. The same study also investigated the diagnostic performance of squamous cell cancer antigen (SCC-Ag) and cytokeratin 21-1 fragment (CYFRA21-1) in the diagnosis of EC. The sensitivity and specificity Cyfra21–1 ranged from 36% to 63% and from 89% to 100%, respectively. The study revealed that patients with EC have a 12-fold higher chance of being Cyfra21–1 test-positive compared with patients without EC, having a PLR of 12.11 (95% CI, 5.02–29.24). As regards SCC-Ag, its sensitivity and specificity ranged from 13% to 64% and from 91% to 100%, respectively, whereas its PLR was 7.66 (95% CI: 4.24–13.83).

More recently, the high level of technology of our era paved the way for novel substances that can be applied to the early detection of EC, providing insights into novel blood tests for screening and early diagnosis of EC (**Table 1**).

Table 1. Potential circulating blood molecules in the screening of esophageal cancer.

Type of Biomarker	Disease	Panel
miRNA		miR-25, miR-100, miR-193-3p, miR-194, miR-223, miR-337-5p, miR-483-5p
	ESCC [15][16][17]	miR-10a, miR-22, miR-100, miR-148b, miR-223, miR-133a, miR-127-3p
		MiR-21, miR-375
	EAC [18][19][20]	miR-92a-3p, miR-151a-5p, miR-362-3p, miR-345-3p, miR-619-3p, miR-1260b, and miR-1276
		RNU6-1/miR-16-5p, miR-25-3p/miR-320a, let-7e-5p/miR-15b-5p, miR-30a-5p/miR-324-5p, miR-17-5p/miR-194-5p

Type of Biomarker	Disease	Panel
lncRNA	ESCC [21][22]	miR-25-3p, miR-151a-3p, miR-100-5p, miR-375
		POU3F3, SCCA
		Linc00152, CFLAR-AS1, POU3F3
Metabolite	ESCC [12][23]	propanoic acid, linoleic acid, glycerol-3-phosphate, and L-glutamine
		propanoic acid, L-leucine, and hydroxyproline
		α-glucose, choline, glutamine, glutamate, valine, and dihydrothymine
Antibody	ESCC [24]	Antibody against p53, NY-ESO-1, MMP-7, Hsp70, Prx VI, Bmi-1
	EAC [25]	Antibody against amino acid L-proline, ketone body 3-hydroxybutyrate, carbohydrate D-mannose
	ESCC/EAC [4]	anti-p53, anti-HSP70, anti-p16, anti-cyclin B1, anti c-Myc, anti-LY6K
Blood cells	EAC [26][27]	Neutrophil-lymphocyte ratio
		Erythrocyte mutant frequency

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Esophagogastroduodenoscopy (EGDS) is the gold standard test for EC and its precursor lesions [28]. At present, dysplasia and cancer surveillance in BE follows the Seattle protocol with random 4-quadrant biopsies every 2 cm, which is expensive, time-consuming, and has a sensitivity ranging from 28% to 85% for the detection of high-grade dysplasia (HGD)/EAC [29]. These drawbacks contribute to <50% adherence to the Seattle protocol in clinical practice [30]. Unlike BE, random sampling in ESCC screening would be unpractical because the entire esophageal mucosa can harbor ESD, and this requires extensive biopsy sampling [28]. Moreover, endoscopic recognition of early ESCC is challenging, as lesions often pass unrecognized with standard WLE, which may miss up to 40% of early ESCC even in high-risk populations [31]. Accordingly, the sensitivity of targeted biopsies for ESD may be as low as 7.7% [32].

In order to improve the diagnostic yield of standard WLE procedures, novel endoscopic techniques have been investigated, namely dye spray chromoendoscopy, virtual chromoendoscopy (VCE), confocal laser endomicroscopy (CLE), and volumetric laser endomicroscopy (VLE) (**Table 2**).

Table 2. Performance of advanced endoscopic imaging in the diagnosis of esophageal cancer according to systematic reviews and meta-analyses.

Author	Endoscopic Technique	Disease	Sensitivity (95% CI, %)	Specificity (95% CI, %)
Coletta et al. [33]	AA Chromoendoscopy	EAC	92% (83 to 97)	96% (85 to 99)
Morita et al. [34]	Lugol Chromoendoscopy	ESCC	92% (86 to 96)	82% (80 to 85)
Thosani et al. [35]	NBI	EAC	94.2% (82.6 to 98.2)	94.4% (80.5 to 98.6)
Morita et al. [34]		ESCC	88% (86 to 93)	88% (86 to 90)
Thosani et al. [35]	pCLE *	EAC	90.4% (71.9 to 97.2)	92.7% (87 to 96)
Kohli et al. [36]	VLE #	EC	81–97%	57–92%

References

1. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int. J. Cancer 2019, 144, 1941–1953.
2. Jemal, A.; Center, M.M.; DeSantis, C.; Ward, E.M. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol. Biomark. Prev. 2010, 19, 1893–1907.
3. Jamel, S.; Tukanova, K.; Markar, S. Detection and management of oligometastatic disease in oesophageal cancer and identification of prognostic factors: A systematic review. World J. Gastrointest. Oncol. 2019, 11, 741–749.
4. Zhang, H.; Xia, J.; Wang, K.; Zhang, J. Serum autoantibodies in the early detection of esophageal cancer: A systematic review. Tumor Biol. 2015, 36, 95–109.
5. Tan, M.C.; Mansour, N.; White, D.L.; Sisson, A.; El-Serag, H.B.; Thrift, A.P. Systematic review with meta-analysis: Prevalence of prior and concurrent Barrett's oesophagus in oesophageal adenocarcinoma patients. Aliment. Pharmacol. Ther. 2020, 52, 20–36.
6. Huang, L.-M.; Yang, W.-J.; Huang, Z.-Y.; Tang, C.-W.; Li, J. Artificial intelligence technique in detection of early esophageal cancer. World J. Gastroenterol. 2020, 26, 5959–5969.
7. Yamashina, T.; Ishihara, R.; Nagai, K.; Matsuura, N.; Matsui, F.; Ito, T.; Fujii, M.; Yamamoto, S.; Hanaoka, N.; Takeuchi, Y.; et al. Long-term outcome and metastatic risk after endoscopic

resection of superficial esophageal squamous cell carcinoma. Am. J. Gastroenterol. 2013, 108, 544–551.

8. Marabotto, E.; Pellegatta, G.; Sheijani, A.D.; Ziola, S.; Zentilin, P.; De Marzo, M.G.; Giannini, E.G.; Ghisa, M.; Barberio, B.; Scarpa, M.; et al. Prevention Strategies for Esophageal Cancer—An Expert Review. Cancers 2021, 13.
9. Henry, N.L.; Hayes, D.F. Cancer biomarkers. Mol. Oncol. 2012, 6, 140–146.
10. Gion, M.; Trevisiol, C.; Fabricio, A.S.C. State of the art and trends of circulating cancer biomarkers. Int. J. Biol. Markers 2020, 35, 12–15.
11. Sharma, S. Tumor markers in clinical practice: General principles and guidelines. Indian J. Med. Paediatr. Oncol. 2009, 30, 1–8.
12. Zhang, S.; Lu, X.; Hu, C.; Li, Y.; Yang, H.; Yan, H.; Fan, J.; Xu, G.; Abnet, C.C.; Qiao, Y. Serum Metabolomics for Biomarker Screening of Esophageal Squamous Cell Carcinoma and Esophageal Squamous Dysplasia Using Gas Chromatography-Mass Spectrometry. ACS Omega 2020, 5, 26402–26412.
13. Bagaria, B.; Sood, S.; Sharma, R.; Lalwani, S. Comparative study of CEA and CA19-9 in esophageal, gastric and colon cancers individually and in combination (ROC curve analysis). Cancer Biol. Med. 2013, 10, 148–157.
14. Zhang, J.; Zhu, Z.; Liu, Y.; Jin, X.; Xu, Z.; Yu, Q.; Li, K. Diagnostic value of multiple tumor markers for patients with esophageal carcinoma. PLoS ONE 2015, 10, e0116951.
15. Wu, C.; Wang, C.; Guan, X.; Liu, Y.; Li, D.; Zhou, X.; Zhang, Y.; Chen, X.; Wang, J.; Zen, K.; et al. Diagnostic and prognostic implications of a serum miRNA panel in oesophageal squamous cell carcinoma. PLoS ONE 2014, 9, e92292.
16. Zhang, C.; Wang, C.; Chen, X.; Yang, C.; Li, K.; Wang, J.; Dai, J.; Hu, Z.; Zhou, X.; Chen, L.; et al. Expression profile of microRNAs in serum: A fingerprint for esophageal squamous cell carcinoma. Clin. Chem. 2010, 56, 1871–1879.
17. Komatsu, S.; Ichikawa, D.; Takeshita, H.; Tsujiura, M.; Morimura, R.; Nagata, H.; Kosuga, T.; Iitaka, D.; Konishi, H.; Shiozaki, A.; et al. Circulating microRNAs in plasma of patients with oesophageal squamous cell carcinoma. Br. J. Cancer 2011, 105, 104–111.
18. Fassan, M.; Realdon, S.; Cascione, L.; Hahne, J.C.; Munari, G.; Guzzardo, V.; Arcidiacono, D.; Lampis, A.; Brignola, S.; Dal Santo, L.; et al. Circulating microRNA expression profiling revealed miR-92a-3p as a novel biomarker of Barrett's carcinogenesis. Pathol. Res. Pract. 2020, 216, 152907.
19. Chiam, K.; Wang, T.; Watson, D.I.; Mayne, G.C.; Irvine, T.S.; Bright, T.; Smith, L.; White, I.A.; Bowen, J.M.; Keefe, D.; et al. Circulating Serum Exosomal miRNAs as Potential Biomarkers for

Esophageal Adenocarcinoma. J. Gastrointest. Surg. 2015, 19, 1208–1215.

20. Zhang, K.; Wu, X.; Wang, J.; Lopez, J.; Zhou, W.; Yang, L.; Wang, S.E.; Raz, D.J.; Kim, J.Y. Circulating miRNA profile in esophageal adenocarcinoma. Am. J. Cancer Res. 2016, 6, 2713–2721.
21. Hu, H.B.; Jie, H.Y.; Zheng, X.X. Three Circulating LncRNA Predict Early Progress of Esophageal Squamous Cell Carcinoma. Cell. Physiol. Biochem. 2016, 40, 117–125.
22. Tong, Y.S.; Wang, X.W.; Zhou, X.L.; Liu, Z.H.; Yang, T.X.; Shi, W.H.; Xie, H.W.; Lv, J.; Wu, Q.Q.; Cao, X.F. Identification of the long non-coding RNA POU3F3 in plasma as a novel biomarker for diagnosis of esophageal squamous cell carcinoma. Mol. Cancer 2015, 14, 3.
23. Yang, Z.; Liu, Y.; Ma, L.; Wen, X.; Ji, H.; Li, K. Exploring potential biomarkers of early stage esophageal squamous cell carcinoma in pre- and post-operative serum metabolomic fingerprint spectrum using (1)H-NMR method. Am. J. Transl. Res. 2019, 11, 819–831.
24. Xu, Y.W.; Peng, Y.H.; Chen, B.; Wu, Z.Y.; Wu, J.Y.; Shen, J.H.; Zheng, C.P.; Wang, S.H.; Guo, H.P.; Li, E.M.; et al. Autoantibodies as potential biomarkers for the early detection of esophageal squamous cell carcinoma. Am. J. Gastroenterol. 2014, 109, 36–45.
25. Sanchez-Espiridion, B.; Liang, D.; Ajani, J.A.; Liang, S.; Ye, Y.; Hildebrandt, M.A.; Gu, J.; Wu, X. Identification of Serum Markers of Esophageal Adenocarcinoma by Global and Targeted Metabolic Profiling. Clin. Gastroenterol. Hepatol. 2015, 13, 1730–1737.e1739.
26. Campos, V.J.; Mazzini, G.S.; Juchem, J.F.; Gurski, R.R. Neutrophil-Lymphocyte Ratio as a Marker of Progression from Non-Dysplastic Barrett's Esophagus to Esophageal Adenocarcinoma: A Cross-Sectional Retrospective Study. J. Gastrointest. Surg. 2020, 24, 8–18.
27. Haboubi, H.N.; Lawrence, R.L.; Rees, B.; Williams, L.; Manson, J.M.; Al-Mossawi, N.; Bodger, O.; Griffiths, P.; Thornton, C.; Jenkins, G.J. Developing a blood-based gene mutation assay as a novel biomarker for oesophageal adenocarcinoma. Sci. Rep. 2019, 9, 5168.
28. di Pietro, M.; Canto, M.I.; Fitzgerald, R.C. Endoscopic Management of Early Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus: Screening, Diagnosis, and Therapy. Gastroenterology 2018, 154, 421–436.
29. Sharma, P.; Savides, T.J.; Canto, M.I.; Corley, D.A.; Falk, G.W.; Goldblum, J.R.; Wang, K.K.; Wallace, M.B.; Wolfsen, H.C. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on imaging in Barrett's Esophagus. Gastrointest. Endosc. 2012, 76, 252–254.
30. Abrams, J.A.; Kapel, R.C.; Lindberg, G.M.; Saboorian, M.H.; Genta, R.M.; Neugut, A.I.; Lightdale, C.J. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. Clin. Gastroenterol. Hepatol. 2009, 7, 736–742, quiz 710.

31. Lee, C.T.; Chang, C.Y.; Lee, Y.C.; Tai, C.M.; Wang, W.L.; Tseng, P.H.; Hwang, J.C.; Hwang, T.Z.; Wang, C.C.; Lin, J.T. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy 2010, 42, 613–619.
32. Mwachiro, M.M.; Burgert, S.L.; Lando, J.; Chepkwony, R.; Bett, C.; Bosire, C.; Abnet, C.C.; Githanga, J.; Waweru, W.; Giffen, C.A.; et al. Esophageal Squamous Dysplasia is Common in Asymptomatic Kenyans: A Prospective, Community-Based, Cross-Sectional Study. Am. J. Gastroenterol. 2016, 111, 500–507.
33. Coletta, M.; Sami, S.S.; Nachiappan, A.; Fraquelli, M.; Casazza, G.; Ragunath, K. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: A meta-analysis. Gastrointest. Endosc. 2016, 83, 57–67.e51.
34. Morita, F.H.; Bernardo, W.M.; Ide, E.; Rocha, R.S.; Aquino, J.C.; Minata, M.K.; Yamazaki, K.; Marques, S.B.; Sakai, P.; de Moura, E.G. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: A systematic review and meta-analysis. BMC Cancer 2017, 17, 54.
35. Thosani, N.; Abu Dayyeh, B.K.; Sharma, P.; Aslanian, H.R.; Enestvedt, B.K.; Komanduri, S.; Manfredi, M.; Navaneethan, U.; Maple, J.T.; Pannala, R.; et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations thresholds for adopting real-time imaging–assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus. Gastrointest. Endosc. 2016, 83, 684–698.e687.
36. Kohli, D.R.; Schubert, M.L.; Zfass, A.M.; Shah, T.U. Performance characteristics of optical coherence tomography in assessment of Barrett's esophagus and esophageal cancer: Systematic review. Dis. Esophagus 2017, 30, 1–8.