Review Article

Artificial intelligence in esophageal cancer diagnosis and treatment: where are we now?—a narrative review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Artificial intelligence (AI) use is becoming increasingly prevalent directly or indirectly in daily clinical practice, including esophageal cancer (EC) diagnosis and treatment. Although the limits of its adoption and their clinical benefits are still unknown, any physician related to EC patients' management should be aware of the status and future perspectives of AI use in their field. The purpose of this review is to summarize the existing literature regarding the role of AI in diagnosis and treatment of EC. We have focused on the aids AI entails in the management of this pathology and we have tried to offer an updated perspective to maximize current applications and to identify potential future uses of it.

Methods: Data concerning AI applied to EC diagnosis and treatment is not limited, including direct (those specifically related to them) and indirect (those referring to other specialties as radiology or pathology), applications. However, the clinical relevance of the discussed and presented models is still unknown. We performed a research in PubMed of English and Spanish written studies from January 1970 to June 2022.

Key Content and Findings: Information regarding the role of AI in EC diagnosis and treatment has increased exponentially in recent years. Several models, including different variables and features have been investigated and some of them internally and externally validated. However, the main challenge remains to apply and introduce all these data into clinical practice, and, as some of the discussed studies argue, if the models are able to enhance experienced endoscopists' judgement. Although AI use is increasing steadily in different medical specialties, the truth is, most of the time, the gap between model development and clinical implementation is not closed. Learning to understand the routinely application of AI, as well as future improvements, would lead to a broadened adoption.

Conclusions: Physicians should be aware of the multiple current clinical uses of AI in EC diagnosis and treatment and should take part in their clinical application and future developments to enhance patient care.

Keywords: Artificial intelligence (AI); esophageal cancer; diagnosis; treatment

Submitted Aug 12, 2022. Accepted for publication Apr 21, 2023. Published online Jun 08, 2023.
doi: 10.21037/atm-22-3977
View this article at: https://dx.doi.org/10.21037/atm-22-3977

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Introduction

Esophageal cancer (EC) remains a challenging disease regarding not only its diagnosis but also its management and clinical outcome. Different strategies based in artificial intelligence (AI), including endoscopic, radiologic, clinicopathologic and genetic variables have been developed to try to improve its poor prognosis.

As it happens with different tumors, early detection has proven to be the best weapon to improve treatment and prognosis of esophageal carcinoma. Thus, most of the efforts of AI in the EC field have been focused in detection of early stage squamous cell carcinoma and adenocarcinoma arising from Barrett's esophagus (BE) (1).

Since its advantages in medical practice were perceived, AI set the frame for machine-learning (ML). ML is the field of AI where machines are trained by experts to recognize patterns based on different data and make predictions taking into account the inputs obtained from these data. Algorithms' performance in ML improves as they are exposed to increased data. Furthermore, deep-learning (DL) is based on multilayered neural networks that learn from vast amounts of data and that improve over time based on their own accuracy and results.

Despite multiple models assessing their accuracy, sensitivity and specificity, large datasets, multicenter studies and internal and external validations, the results, when compared to those of experienced endoscopists, remain controversial (2).

Whether or not AI can help expert endoscopists to enhance their clinical decision-making appears still the main challenge to be answered.

Larger datasets, real time models, probably video-enhanced and randomized controlled trials are still needed to answer this important question, specifically taking into account EC patients' particular needs.

The purpose of this review is to summarize the existing literature regarding the role of AI in diagnosis and treatment of EC. We have focused on the aids AI entails in the management of this pathology and we have tried to provide an updated perspective to maximize current applications and to identify potential future uses of it. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3977/rc).

Methods

The search strategy is described in *Table 1*. We searched PubMed for articles written from January 1970 to June 2022. Manuscripts in English and Spanish were taken into account. The search strategy included the words 'Artificial Intelligence' and 'Esophageal Cancer' 'Barrett's esophagus' or 'Esophageal Adenocarcinoma' or 'Esophageal Squamous carcinoma'.

With this criteria we found a total of 1,368 articles. Article types included original research, with both prospective and retrospective cohorts, previous reviews and editorials. Articles without full text available or incomplete or irrelevant data were excluded.

Furthermore, the risk of bias of the selected studies was assessed using standardized tools (3,4) by two investigators (Beatriz Merchán Gómez and María Rodríguez).

Current literature review and discussion

AI in EC diagnosis

EC includes mainly two types: esophageal adenocarcinoma and esophageal squamous cell carcinoma, which is the most frequent histological type, and it is more prevalent in Asian countries. In terms of incidence, EC remains the ninth most common cancer globally and it is the sixth cause of cancer mortality at the date (5). Despite several treatment advances (6), prognosis has not improved significantly, with an average 5-year overall survival of 20% (7). Furthermore, although the impact of early diagnosis is significant in survival, up to 6.5% of EC are missed during diagnostic gastroscopy (8,9). Endoscopic imaging diagnosis of EC and precursor lesions mainly depends on endoscopists' experience, and in consequence, it has a high interobserver variability (9). To minimize this variability and to improve interobserver agreement, several techniques have been developed to improve diagnosis at earlier stages. For example, virtual chromoendoscopy and magnification, optical coherence tomography (OCT), high-resolution microendoscopy (HRM), confocal laser endomicroscopy (CLE) and volumetric laser endomicroscopy (VLE) (1,10-13). AI-based technologies, which are characterized by ML and DL algorithms, are the latest and subsequent technological step (14-16). Up to date, they have been tested in esophageal adenocarcinoma and esophageal squamous cell carcinoma precursors and have shown an improvement in the sensitivity and specificity of r EC diagnosis by refining the accuracy of endoscopic image diagnosis.

In the diagnosis of BE, the most important precursor of esophageal adenocarcinoma, AI may help in detecting and delineating suspicious lesions in endoscopic images. van der Sommen (2) tested an algorithm in 2013 that could

Table 1 Search strategy summary

Items	Specification
Date of search	15th June–31st June 2022
Databases and other sources searched	PubMed
Search terms used	Search terms: 'Artificial Intelligence' and 'Esophageal Cancer' or 'Barrett's esophagus' or 'Esophageal Adenocarcinoma' or 'Esophageal Squamous carcinoma'
Timeframe	From January 1970 to June 2022
Inclusion and exclusion criteria	Inclusion criteria:
	(I) English and Spanish language articles
	(II) Article types:
	Original research including:
	Prospective cohorts
	Retrospective cohorts
	Reviews
	Editorials
	Exclusion criteria:
	(I) Articles without full text available
	(II) Articles with incomplete or irrelevant data
Selection process	There were two independent reviewers, MR and BMG, who reached a consensus about the manuscripts to be included in the review

identify changes in esophageal mucosas on high-definition endoscopy with an accuracy of 95.9% and an area under the curve (AUC) of 0.99. In the same lines, these authors employed a computer-aided diagnosis (CAD) system to automatically recognize a suspicious region in dysplastic BE (17) with high sensitivity and specificity, but with difficulties to locate early neoplastic lesions and to select the biopsy site. Horie *et al.* (18) created a deep convolutional network model to detect EC with light, virtual chromoendoscopy and near focus images with a 90% accuracy, with initial promising results for real time diagnosis. Furthermore, in order to improve the location of lesions, Ebigbo *et al.* (19) designed a CAD system based on DL using high definition white light images. Diagnostic accuracy was better when compared to general endoscopists' diagnosis and the coincidence rate between the lesions identified by the system as well as the experts was up to 72%. This system was validated in two different datasets showing more than 90% of sensitivity. de Groof *et al.* (20) also trained a system using state-of-the-art ML techniques and validated their model in five sequential data files. They obtained a high accuracy in the validation process in two different external cohorts (89% and 88% respectively) (20), one of them including 53 endoscopists with a wide range of experiences. Continuing with the challenge to obtain an adequate diagnosis, Hong *et al.* (21) reported their experience with convolutional neural network as a classifier to distinguish neoplasia from BE employing endo microscopic images (21). The model's accuracy was 80.77%. Swager *et al.* (22) also reported the use of a CAD system to identify neoplasia in *ex-vivo* VLE images (22). Later, van der Putten *et al.* (23) followed in his steps but this time using *in-vivo* images (23). The AUC, sensitivity and specificity were 0.95, 90%, and 93%, respectively.

In addition, as interpretation of endoscopic images alone was proven challenging, the role of pathologic morphology has also been investigated. Sabo *et al.* (24) developed and validated a computerized nuclear morphometry model to discriminate the degree of dysplasia in BE (24). This model could differentiate between BE without dysplasia and with low-grade dysplasia; and between BE with low-grade dysplasia and high-grade dysplasia, both with high accuracy

(89% and 86% respectively).

Regarding esophageal squamous cell carcinoma, Liu *et al.* (25) developed an algorithm that detected 90.75% of EC with an AUC of 0.95 (25). Furthermore, Horie *et al.* (18), with their convolutional neural network model, reported a diagnostic accuracy of 99% for esophageal squamous cell carcinoma, 99% for superficial and 92% for advanced cancer, with high sensitivity and specificity. In 2019, Cai *et al.* (26) developed and validated a novel CAD system using a deep neural network to localize and identify early esophageal squamous cell carcinoma under conventional endoscopic white-light imaging. This model, trained with standard white-light images, could detect 91.4% of early esophageal squamous cell carcinoma (26). However, there weren't s any significant differences between the CAD system and senior endoscopists' diagnostic accuracy, questioning its utility. Similarly happened with the model of Ohmori *et al.* (27). They evaluated magnified and non-magnified images, including chromoendoscopy images using a convolutional neural network model. Although the accuracy was 77% or higher in all cases, with high sensitivity and moderate specificity, their results were similar to those achieved by experienced endoscopists. On the other hand, Zhao *et al.* obtained a higher sensitivity for type A microvascular intrapapillary capillary loop (IPCL) pattern than clinicians (71.5% *vs.* 28.2–64.9%), and the argued their model might avoid unnecessary radical treatment (28). Everson *et al.* validated another convolutional neural network model that could discriminate between types A and B with an accuracy of 93.3% (29). In the same research line, Nakagawa *et al.* aimed to predict invasion depths by developing a convolutional neural network system based on magnified and non-magnified images. The system's accuracy to correctly describe the submucosal invasion and differentiate between submucosal microinvasive (SM1) cancers and submucosal deep invasive (SM2/SM3) was high (91% for the total, 92.9% for non-magnified images, and 89.7% for magnified images) (30). Luo *et al.* developed a multicenter study, to create a gastrointestinal AI diagnostic system (GRAIDS) based on the concept of DeepLab's V3+®. For this purpose, they employed a total of 1,036,494 endoscopic images. The accuracy varied from 91.5% to 97.7% and it was validated in internal, external, and prospective validation datasets. This system obtained high sensitivities which were proximate to expert endoscopists' and higher than junior endoscopists (31). In a systematic review and meta-analysis, Bang *et al.* determined the AUC, as well as the sensitivity, specificity, and diagnostic odds ratio of CAD algorithms in the diagnosis of esophageal cancer based on the analysis of endoscopic images (32). The study obtained an AUC of 0.97 [95% confidence interval (CI): 0.95–0.99], a sensitivity of 0.94 (95% CI: 0.89–0.96), a specificity of 0.88 (95% CI: 0.76–0.94), and a diagnostic odds ratio of 108 (95% CI: 43–273). The study also explored the depth of invasion for EC obtaining a pooled AUC of 0.96 (95% CI: 0.86–0.99), a sensitivity of 0.90 (95% CI: 0.88–0.92), a specificity of 0.88 (95% CI: 0.83–0.91), and a diagnostic odds ratio of 138 (95% CI: 12–1,569). No heterogeneity or publication bias were found.

Recently, Fang *et al.* (33) developed a model using semantic segmentation, a method of classification of pixels, so that various abnormal areas can be marked. In the method developed in this study, particularly the narrow band images, squamous cell carcinoma, and dysplasia were marked with high accuracy (84.72%). Tsai *et al.* (34) used hyperespectral imaging and a DL model using a single-shot multibox detector that classify the different stages of EC and identify its locations. The accuracy of this model using white-light images was 88% and 91% when narrow band images were used. An important remark is that the model's accuracy using white light and narrow band images was increased by 5%, confirming that the hyperspectral imaging method significantly improves the diagnostic accuracy. Wang *et al.* (35) created a single-shot multibox detector using a convolutional neural network for diagnosing various histological grades of esophageal neoplasms. The diagnostic sensitivity, specificity, and accuracy were 96.2%, 70.4%, and 90.9%, respectively; and the accuracy o in differentiating the histological grade was 92%. AI systems with endo-cytoscopy (36) and high resolution microendoscopic images (37) have also been developed. The main characteristics of the previous studies are shown in *Tables 2,3*.

AI in EC treatment and outcome prediction

AI has proven its utility not only in the diagnosis but also in the treatment and outcome prediction in EC patients. Opposing the traditional primary tumor, lymph nodes and distant metastasis (TNM) staging system, Sato *et al.* (38) trained an artificial neural network with 65 clinicopathologic, genetic and biologic variables for 1-year survival and 60 variables for 5-year survival. The AUC, sensitivity and specificity were 0.88, 78.1%, 84.7% for 1-year survival and 0.88, 80.7%, 86.5% for 5-year survival, respectively.

Another advantage of AI is the possibility of making

Table 2 Barrett' esophagus/adenocarcinoma models

Author	Year	Number of images/patients	Type of image	Model of AI	Validation	Accuracy (%)	Sensitivity (%)	Specificity (%)
van der Sommen *et al.*	2016	100	Endoscopy	–	Yes	–	86	87
Horie *et al.*	2019	8,428	Endoscopy	Convolutional neural network	No	90	–	–
Ebigbo *et al.*	2019	Two data sets of 148 and 139	Endoscopy, white light, NBI	Convolutional neural network	Yes	–	92–97	80–100
de Groof *et al.*	2020	1,704	Endoscopy, high resolution	Hybrid ResNet-UNet model CAD system	Yes	88–89	90–93	83–88
Hong *et al.*	2017	262	Endomicroscopy	Convolutional neural network	No	80.77	–	–
Swager *et al.*	2017	60	Endomicroscopy	Convolutional neural network	No	–	90	93
van der Putten *et al.*	2020	23	Endomicroscopy	Convolutional neural network	Yes	82	–	–
Sabo *et al.*	2006	97	Biopsies	–	No	86–89	–	–

AI, artificial intelligence; NBI, narrow band images; CAD, computer-aided diagnosis.

Table 3 Squamous cell carcinoma models

Author	Year	Number of images/patients	Type of image	Model of AI	Validation	Accuracy (%)	Sensitivity (%)	Specificity (%)
Liu *et al.*	2016	1,130	Endoscopy	–	No	90.75	–	–
Horie *et al.*	2019	8,428	Endoscopy	Convolutional neural network	No	99	–	–
Cai *et al.*	2019	2,428	Endoscopy, white light	Deep neural network	Yes	91.4	97.8	85.4
Ohmori *et al.*	2020	22,562	Endoscopy, white light, NBI, magnification	Convolutional neural network	Yes	75–77	90–100	56–76
Zhao *et al.*	2019	1,383	Endoscopy, white light, NBI, magnification	Double-labeling fully convolutional network	Yes	89.2–93	–	–
Everson *et al.*	2019	7,046	Endoscopy, white light, NBI, magnification	Convolutional neural network	No	93.7	89.3	98
Nakagawa *et al.*	2019	14,338	Endoscopy, white light, magnification	Deep neural network	Yes	91	90.1	95.8
Luo *et al.*	2019	1,036,496	Endoscopy	Deep neural network	Yes	91.5–97.7	–	–
Fang *et al.*	2022	165	Endoscopy, white light, NBI	Deep learning	No	84.72	–	–
Tsai *et al.*	2021	308	HSI, endoscopy, white light, NBI	Convolutional neural network	No	88–91	–	–
Wang *et al.*	2021	936	Endoscopy, white light, NBI	–	No	90.9	96.2	70.4

AI, artificial intelligence; NBI, narrow band images; HSI, hyperspectral imaging.

real-time decisions. Although that is probably one of the theoretical-clinical practice more difficult to close gaps, an Iranian group trained a multilayer neural network with particle swarm optimization and error back propagation (EBP) algorithms, intending to clarify the most precise chemotherapy dose. The accuracy of their model was 77.3% (39). Not only to determine the best systemic treatment approach, but also to determine the best resection margin, Maktabi *et al.* (40) tested an hyperespectral image model that could detect cancerous tissue with 63% sensitivity and 69% specificity in one second. This system's potential relies on the fact that it may assist surgeons in the process of identification of tumor margins intra-operatively and in real time for an adequate resection.

Another still unmet challenge in EC is predicting cancer response. To overcome it, several investigators have also designed different AI models. Warnecke-Eberz *et al.* (41) trained an artificial neural network system to predict histologic response in neoadjuvant chemoradiotherapy naïve patients. They analyzed 17 genes with the TaqMan® low-density arrays, obtaining 75.0% sensitivity, 81.0% specificity and 78.1% accuracy. Also, to predict response to neoadjuvant chemotherapy, Ypsilantis *et al.* (42) developed a three-slice convolutional neural network that was able to extract data from pre-treatment positron emission tomography-computed tomography (PET-CT) images to predict the response to neoadjuvant chemotherapy. The accuracy was 73.4%, with sensitivity of 80.7% and specificity of 81.6%. Finally, Li *et al.* (43) conducted a prospective, multicenter study to determine the therapeutic efficacy of chemoradiotherapy in patients with locally advanced thoracic esophageal squamous cell carcinoma. They developed a 3-dimensional DL radiomics model (3D-DLRM) based on pretreatment CT images to predict the response to treatment, with a positive predictive value (PPV) of 100% and AUC over 0.8 in radiation therapy plan, radiation field and prescription dose used.

Although with this narrative review we have tried to summarize the current evidence regarding AI in EC, our study could be affected by the main limitations of narrative reviews. Among them, is that narrative-review methodology does not follow systematic evidence based criteria. Furthermore, in this type of studies a higher selection bias (aligned with author's expert opinion) have been observed. To mitigate this limitation two independent reviewers, from different departments have selected and reviewed each manuscript (44).

Furthermore, limitations of AI application in daily clinical practice, as patients data integration, clinical decision impact and influence in patients' outcomes still need to be addressed in larger, multicentric studies.

Conclusions

In conclusion, as the reviewed manuscripts highlight, the role of AI in the care of EC patients has considerably increased in later years. The unmet challenges remain the validation and application of these algorithms into the daily clinical practice, the possibility to use them in real-time patient diagnosis and to test not only their efficacy, something that most of them have already proven, but also their real efficiency in different healthcare settings.

The future for AI in a complex pathology as EC seems bright, but we, as clinicians need to be aware of the most recent advances and help to introduce them in our daily practices.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3977/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3977/coif). MR serves as an unpaid editorial board member of *Annals of Translational Medicine* from April 2022 to March 2024. MR reports personal fees from Abex and AstraZeneca outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Merchán Gómez B, Milla Collado L, Rodríguez M. Artificial intelligence in esophageal cancer diagnosis and treatment: where are we now?—a narrative review. Ann Transl Med 2023;11(10):353. doi: 10.21037/atm-22-3977