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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Artificial Intelligence and Deep Learning for Upper Gastrointestinal Neoplasia

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Upper gastrointestinal (GI) neoplasia account for 35% of GI cancers and 1.5 million cancer-related deaths every year. Despite its efficacy in preventing cancer mortality, diagnostic upper GI endoscopy is affected by a substantial miss rate of neoplastic lesions due to failure to recognize a visible lesion or imperfect navigation. This may be offset by the real-time application of artificial intelligence (AI) for detection (computer-aided detection [CADe]) and characterization (computer-aided diagnosis [CADx]) of upper GI neoplasia. Stand-alone performance of CADe for esophageal squamous cell neoplasia, Barrett's esophagus–related neoplasia, and gastric cancer showed promising accuracy, sensitivity ranging between 83% and 93%. However, incorporation of CADe/CADx in clinical practice depends on several factors, such as possible bias in the training or validation phases of these algorithms, its interaction with human endoscopists, and clinical implications of false-positive results. The aim of this review is to guide the clinician across the multiple steps of AI development in clinical practice.

Keywords: Artificial Intelligence; Convoluted Neural Networks; Deep Learning; Upper GI Endoscopy; Gastric Cancer; Esophageal Cancer; Barrett's esophagus.

Upper gastrointestinal (GI) neoplasia accounts for 35% of GI cancers and 1.5 million cancer-related deaths every year, worldwide.[1] Disappointingly, the 5-year survival is still dismal, primarily because of the poor 5-year survival in the most advanced stages of the disease.[1,2] Moreover, the incidence is expected to remain high in the next decade because of the increasing aging population.[3] At the current time, early detection and screening/surveillance of high-risk patients represents the most effective intervention to reduce such burden by down-staging already prevalent cancer or preventing its incidence by interrupting the progression from precancerous to invasive phases of the disease.[4–8] Upper GI endoscopy was associated with an additional 67% reduction of gastric cancer vs radiography, and its mortality was significantly reduced by endoscopic, but not by radiologic, screening.[9–13] Similarly, surveillance of Barrett's esophagus (BE)–related neoplasia (BERN) has been shown to reduce late-stage cancers.[14]

For upper GI diseases, proper histologic sampling allows for risk stratification for patients with precancerous lesions or conditions.[4,15,16] More recently, optical diagnosis has been shown to in vivo predict histology-based stratification, including assessment of the depth of invasion, resulting in a more effective strategy of targeted biopsies.[4,17,18]

However, diagnostic upper GI endoscopy is far from being an optimal technique. By pooling 22 studies, the overall rate of missed gastric cancer (GC) at endoscopy was estimated to be 9.4% (95% confidence interval [CI], 5.7–13.1), with a rate of 10% in studies including patients with negative findings on esophagogastroduodenoscopy (EGD) followed over time, 8.3% in studies including patients with GC, and 23.3% in studies evaluating the proportion of missed synchronous lesions.[19] Similarly, a 20%–40% miss rate of visible neoplastic lesions in Barrett's esophagus has been shown.[20] The 2 most plausible pitfalls are represented by the visual failure of the endoscopist to recognize a lesion that has been exposed and an incomplete exposure of the entire GI mucosa because of imperfect navigation. The former is to be attributed to issues such as lack of training, the low prevalence of early neoplastic lesions, the flat and subtle appearance of upper GI neoplasia, and a suboptimal inspection time.[21–23] The latter depends on well-defined blind spots for gastric mucosa assessment, reluctance to adopt pre-endoscopic preparation with mucolytic and anti-foam agents, inadequate cleaning of the mucosa, and lack of the use of advanced imaging techniques for the detection of subtle lesions.

By exploiting the setting of validation studies for artificial intelligence (AI), we recently evaluated the visual miss

Abbreviations used in this paper: **AI, artificial intelligence; BE, Barrett's esophagus; BERN, Barrett's esophagus–related neoplasia; CADe, computer-aided detection; CADx, computer-aided diagnosis; CI, confidence interval; DL, deep learning; EGC, early gastric cancer; ESCN, esophageal squamous cell neoplasia; GC, gastric cancer; GI, gastrointestinal; IPCL, intrapapillary capillary loop; NPV, negative predictive value; PPV, positive predictive value; SD, standard deviation.**

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rate of human endoscopists for detecting expert-selected cases of upper GI neoplasia and its associated factors.[24] By extracting data on 122 endoscopists, we estimated an 18% miss rate for upper GI neoplasia detection.[24] In detail, such a miss rate was statistically significantly lower for Eastern vs Western endoscopists (13% [95% CI, 11–16] vs 25% [95% CI, 22–28]), and for expert vs nonexpert endoscopists (15% [95% CI, 13–17] vs 29% [95% CI, 25–33]).[24]

What Is Artificial Intelligence for Upper Gastrointestinal Neoplasia?

Real-time application of AI for the detection and characterization of upper GI neoplasia is primarily based on deep learning (DL) algorithms.[17,25] Different from human-engineered machine learning, DL implies an automatic extraction of the input features required for pattern recognition. These inputs are arranged in a multilayered convoluted algorithm that is able to provide an instantaneous output for real-time endoscopy to the same extent as object or face recognition for nonmedical applications of DL. A unique advantage of DL as compared to the human eye is its ability to explore all the pixels of each image for all of the consecutive images of an upper GI endoscopy without any transitory lack of attention or tiredness. The output is generally provided as a square or circle around the lesion or suggested diagnosis, that is, the bounding box. Heat or spatial maps may also be used. The main limitation of DL algorithms is the lack of information on how the algorithms actually work. This represents a distinct difference from human-based machine learning, where the algorithm is based on simple and clear rules. In theory, any decision-making process in the clinical setting should be driven by combinations of appropriate data features in the context of GI endoscopy. Thus, efforts to improve the transparency, explainability, and intelligibility of these DL algorithms are warranted, and possible techniques have been proposed.[26]

The 2 main tasks required from DL are real-time detection, also named as computer-aided detection (CADe), and characterization, that is, computer-aided diagnosis (CADx). CADe usually results in both detection and localization (also called segmentation) of the suspected area, whereas CADx is expected to clinically differentiate between 2 or more diagnosis. CADe has been applied for the detection of both esophageal squamous cell neoplasia, BERN, and early GC, whereas CADx may predict the depth of invasion of visible neoplastic lesions and differentiate between neoplastic and nonneoplastic tissue or the presence of precancerous conditions, such as gastric atrophy. The usual layout of a CADe output is the real-time overlapping of a bounding square/circle that outlines the borders of a suspected lesion/condition, whereas CADx provides a diagnostic output, such as the likelihood of a lesion being precancerous and/or prediction of depth of invasion. A mix of the 2 can also be used by providing the endoscopist with the most suspicious area in which to perform targeted biopsies, usually in the shape of a heat map. Additional tasks performed by DL systems are represented by the identification of anatomic landmarks and blind spots, measurement of withdrawal speed, assessment of the level of cleansing of the mucosa, and delineation of the lesion.

Usually, for GI endoscopy, DL is specifically based on a supervised training that consists of a large database of histologically verified endoscopic images that have been manually annotated.[25] Manual annotation of each single frame represents, by far, the most laborious and time-consuming phase of DL development, and dedicated software to propagate the annotation from the initial to the subsequent frames is currently under development.[27] In DL construction, training databases are usually split into a training and tuning database, with multiple methodologies to partition the database. Such tuning activity is sometimes termed *validation* in engineering jargon. However, such terms should be avoided in the clinical setting to preserve the difference between the tuning that is executed with images already included in the training data set and the clinical validation that is performed on an independent data set. In other words, tuning outputs should never be considered to predict AI discrimination accuracy in the clinical setting.

DL tasks are extremely narrow, strictly depending on the training database that has been used.[25] For instance, if a DL algorithm has been instructed to detect BERN, this should not be applied for BE characterization, or vice versa. For this reason, it is of critical importance that the gastroenterologist, before using an AI system, be fully aware of the clinical population that has been used for the supervised training, as well as of the several biases that may prevent the generalizability of this training data set to his/her own clinical population. The main features of the training data set are the actual number of patients, disease prevalence, practice setting (ie, tertiary centers), endoscopist number and experience, and the technical characteristics, such as the use of white light, advanced imaging, and optical magnification, as reported in Table 1. Several biases may affect the DL learning process at the level of the patient population, skill of the endoscopist, and technique used (Table 2). This is the case with selection bias when the database is not representative of a consecutive or average-risk population. For instance, the predictive values measured in tertiary centers with diseased patient enrichment may not be applicable in community centers with a lower disease prevalence. Selection bias may be more frequent in upper, compared with lower, GI neoplasia because of the low prevalence of disease that prevents the collection of databases with consecutive patients. However, such bias may be softened by data augmentation techniques involving the manipulation of the original image to create surrogate images that may be used for training purposes, such as flipping, cropping, rotation, and zooming. Alternatively, an operator bias may occur when only a few expert endoscopists have collected the training data set. Third, a spectrum bias may occur when only cases clearly representative of the disease or healthy status are enrolled. For instance, when only cases of high-grade dysplasia or early cancer in BE are included, the system may miss an advanced cancer. Fourth, the DL algorithm may have been trained with a suboptimal number of

Table 1. Characteristics of Studies of AI for Upper GI Neoplasia

First author (year)	Design (training)	Setting	Light	Clinical vs offline	External validation	Patient in training set	Total images for training	Patients in test set	Total images in test set
SCC detection									
Guo (2020)[33]	M	E/W	WLI/mag blue light	Offline	Y	—	6473	59	6671
Guo (2020)[33] (videos)	M	E/W	WLI/mag blue light	Offline	Y	—	6473	60	168,865 (frames)
Cai (2019)[34]	M	E	WLI	Offline	N	746	2428	52	187
Zhao (2019)[59]	U	E	Mag blue light	Offline	N	—	—	—	—
Ohmori (2020)[70]	U	E	WLI/blue light/iodine	Offline	N	—	—	—	—
Horie (2019)[35]	U	E	WLI/mag blue light	Offline	N	384	8428	47	1118
Shiroma (2021)[36]	U	E	WLI/mag blue light	Offline	N	384	8428	72	—
Tang (2021)[37]	U	E	WLI	Offline	Y	1078	4002	243	1033
Waki (2021)[38]	U	E	Mag blue light	Offline	N	1572	18,797	100	Videos
SCC invasion depth > SM1									
Nakagawa (2019)[71]	U	E	WLI/blue light/mag iodine	Offline	N	—	—	155	914
Tokai (2020)[72]	U	E	WLI/blue light	Offline	N	—	10,179	55	279
Uema (2021)[73]	U	E	Mag blue light	Offline	N	336	1777	336	747
BAR + EAC detection									
de Groof (2020)[39]	M	W	WLI	Clinical	Y	509	1544	20	144
Ebigbo (2020)[42]	U	W	WLI/blue light	Clinical	Y	—	129	14	62
de Groof (2020)[40]	M	W	WLI	Offline	Y	509	1544	160	160
de Groof (2019)[41]	M	W	WLI	Offline	N	—	—	60	60
Ebigbo (2019)[43]	U	W	WLI/blue light	Offline	N	—	248	—	—
Ghatwary (2019)[44]	U	W	WLI	Offline	N	39	100	39	100
Hashimoto (2020)[45]	U	W	WLI/mag blue light	Offline	N	65	916	39	458
van der Sommen (2016)[46]	U	W	WLI	Offline	N	—	—	44	100
Horie (2019)[35]	U	E	WLI/mag blue light	Offline	N	384	8428	47	1118
Gastric cancer detection									
Wu (2021)[68]	U	E	WLI	Clinical (RCT)	Y	—	—	—	—
Wu (2022)[67] (Detection + invasion depth + differentiation status)	M	E	WLI/mag blue light	Clinical	Y	—	—	100	—
Hirasawa (2018)[74]	M	E	WLI/blue light	Offline	Y	—	—	69	2296
Hu (2021)[55]	M	E	Mag blue light	Offline	Y	170	—	120	—
Ueyama (2021)[56]	U	E	Mag blue light	Offline	N	—	5574	—	2300
Ishioka (2019)[75]	M	E	WLI	Offline	Y	—	—	62	—
Wu (2019)[48]	M	E	Mag blue light	Offline	Y	—	9151	—	200

Table 1. Continued

First author (year)	Design (training)	Setting	Light	Clinical vs offline	External validation	Patient in training set	Total images for training	Patients in test set	Total images in test set
Horiuchi (2020)[49]	U	E	Mag blue light	Offline	Y	—	2570	—	258
Yoon (2019)[76]	U	E	WLI	Offline	Y	—	—	—	—
Li (2020)[50]	U	E	Blue light/ mag FICE	Offline	N	—	2088	—	341
Miyaki (2013)[51]	U	E	Blue light/ mag FICE	Offline	N	—	493	46	92
Kanesaka (2018)[52]	U	E	Mag blue light	Offline	N	127	126	127	81
Sakai (2018)[53]	U	E	WLI	Offline	N	58	926	58	9650
Gastric cancer categorization AGC, EGC, HGD, LGD NC									
Cho (2019)[52]	—	—	WLI	Offline	Y	1066	4205	200	200
Gastric cancer invasion depth									
Yoon (2019)[76]	U	E	WLI	Offline	Y	—	—	—	—
Zhu (2019)[77]	U	E	WLI	Offline	Y	790	790	203	203
Detection of all upper GI cancers									
Luo (2019)[57]	M	E	WLI	Clinical	Y	15,040	125,898	84,425	894,927

NOTE. Adapted and updated from Arribas et al.[31]
AGC, advanced gastric cancer; E, Eastern; EGC, early gastric cancer; FICE, Fuji Intelligent Color Enhancement; HGD, high-grade dysplasia; LGD, low-grade dysplasia; mag, magnification; M, multicenter; N, no; NC, no cancer; RCT, randomized controlled trial; SCC, squamous cell cancer; SM1, upper third submucosal; U, single center; W, Western; WLI, white light imaging; Y, yes.

cases or too homogeneous pattern of lesions so that it memorizes rather than learns. This is termed *overfitting bias* and may be more frequent for upper, rather than lower, GI neoplasia because of the much lower prevalence of upper GI neoplasia. Thus, an appropriate sample size of the training database remains a critical need for DL development. Fifth, the use of advanced imaging in the training set should be considered. Although DL algorithms are extremely robust to exogenous factors, such as blue light or magnified endoscopy,[28] it seems more appropriate to apply any AI system with the same light that has been used in training. However, there is emerging evidence showing comparable performances of AI systems across different imaging modalities.[29]

How Should We Evaluate Artificial Intelligence Studies of Upper Gastrointestinal Neoplasia?

Similar to any device aiming to improve the quality of diagnostic endoscopy, AI must be clinically validated before it is incorporated into clinical practice.[17,25] Such validation, also named *testing* in engineering jargon, should entail those principles that ensure a high reproducibility and generalizability of the findings, including a rigorous reference standard or comparator, and the definition of patient-centered outcomes that are usually represented by a neoplastic and healthy status against which the discrimination power of the system is validated. A unique advantage of AI validation in upper GI endoscopy is that the reference standard is generally strengthened by histologic verification. This is, for instance, the case with CADe validation, where the accuracy of the machine is tested against the detection of lesions histologically defined as neoplastic, as well as that of CADx, where the comparator is directly represented by histology. However, there are also cases in the validation of AI software for upper GI endoscopy where the reference standard cannot be histologically verified. For example, this is the case when aiming to identify the hot spot for targeted biopsies or the accuracy in the delineation of early GC.[20] In these cases, only an expert-derived verification represented by endoscopist raters can be performed. To minimize the variability of the criterion standard, an average among multiple raters is generally recommended.

AI systems, however, have a unique feature that somewhat simplifies their validation. In the pre-AI era, the diagnostic benefit of new devices was validated in randomized trials between the standard and the new endoscopic modalities. Such randomization was needed for 2 main reasons: (1) to adjust for the intergroup disease prevalence by balancing for patient-related risk factors and (2) to prevent selection and operator bias due to the tendency to favor the new technique.[30] This is not the case when validating AI algorithms. The stand-alone performance of DL is based on an unbiased intrapatient comparison of AI discrimination against a human ground truth. In other words, stand-alone performance studies address the

Table 2. Common Biases in Endoscopic AI Studies

Biases	Description
Training bias (ground truth)	
Selection bias	Only the most suitable patients are selected in a nonconsecutive sequence from 1 or a few centers.
Spectrum bias	Only cases with a clear pattern of the disease are selected. For instance, only adenomas or hyperplastic polyps are included, whereas sessile serrated lesions are excluded from a mixed imaging pattern.
Operator bias (training)	Image annotation and/or image acquisition was made by 1 or a few expert physicians.
Overfitting bias (training)	The system has been trained to memorize but not to learn. Thus, a substantial drop in performance is observed in the testing phase.
Testing bias	
Overfitting bias (testing)	Severe: The system has been tested on frames or cases that overlap with the training set. In this case, training performance and test performance can be equally high, but if the system is tested with new cases, the performance will drop. Mild: The system has been tested on frames or cases that do not overlap with the training set but come from the same center and/or the same physician that provided the training set.
Operator bias (testing)	The system is tested against the ground truth but not against other comparators (ie, benchmarking endoscopists).

simple question: how often does AI detect what was detected by human endoscopists?

These studies are usually done in an artificial setting by exposing AI to the reference standard consisting of a database of images representative of the neoplastic lesion or healthy status as identified and selected by experts.[31,32] The main precondition for a meaningful validation of AI systems is the complete independence between the training/tuning databases and the validation database. Indeed, images that may be related to the same cases used for training/tuning should never be present in the validation database because this would artificially inflate the discriminatory ability of the system (overfitting bias). The best scenario is represented by a validation database that is extracted by a different patient population than the one adopted for DL training, possibly with the highest degree of heterogeneity in terms of endoscopists and centers. However, independence between databases is not the only precondition for a proper validation. Validation studies are also susceptible to several biases—such as spectrum or selection bias—that are quite similar to those anticipated for the training data set and are summarized in Table 2.

The output of validation studies is usually represented by its discrimination power, which is presented as accuracy values, that is, sensitivity and specificity, as well as positive predictive value (PPV) and negative predictive value (NPV) due to the occurrence of both false positives and negatives. Such values may be plotted in receiver operating characteristic curves to select the threshold that is more suitable for the specific clinical purpose. For instance, in the case of neoplasia detection, false negatives are much more relevant than false positives, which usually require only additional biopsies. Discrimination power should be provided in terms of both per-frame and per-lesion accuracy. Usually, the per-frame sensitivity is much lower than the per-lesion because most of the lesions are not identifiable in all of the sequential frames (per frame), whereas most of them are detected by the AI system in at least 1 frame (per lesion). Theoretically, per-lesion sensitivity is clinically more relevant because the detection of 1 lesion in only 1 frame is enough to alert the endoscopist to the suspected area. However, the per-frame value is more reassuring because it is not certain whether each lesion is exposed to the camera for more than 1 frame.

How Good Is Artificial Intelligence for the Detection/Characterization of Upper Gastrointestinal Neoplasia?

Several studies addressing the stand-alone performance of AI for the detection and characterization of upper GI neoplasia are summarized in Table 1.

Esophageal Squamous Cell Neoplasia

The stand-alone performance of AI for the detection of esophageal squamous cell neoplasia (ESCN) has been assessed in both white light and blue light as well as with magnified or unmagnified endoscopy, primarily in an Eastern setting on enriched-disease databases with images and/or videos. In a recent systematic review of 3 studies,[31,33–35] including a total of 176,841 images from 218 patients in the test set, the AI sensitivity, specificity, PPV, and NPV for ESCN were 93% (95% CI, 73–99), 89% (95% CI, 77–95), 77% (95% CI, 55–89), and 97% (95% CI, 88–100), respectively. In individual studies, these values favorably compared with the accuracy of expert endoscopists, which is reassuring regarding the clinical value of such algorithms. Overall, the quality of the included studies was graded low because of risk of selection, spectrum, and operator biases in the training sets of the studies. After the meta-analysis was published, a further 3 studies were published in Asian settings,[36–38] all of them reporting similarly very high values of accuracy, as reported in the

pooled analysis.[31] In detail, 1 Japanese study[38] assessed the performance of AI on videos simulating overlooked ESCN—that is, withdrawal speed constant throughout the esophagus—showing an 85.7% sensitivity, which was higher than that of 21 endoscopists (75%).

Barrett's Esophagus–Related Neoplasia

The stand-alone performance of AI for the detection of visible neoplastic lesions in BE lesions has been primarily assessed in Western settings with white light and advanced imaging, mainly with an unmagnified setting. We recently pooled 9 AI studies[39–47] regarding the detection of high-grade dysplasia/early cancer (BERN), and the total numbers of images and patients in the test set were 2,276 and 423, respectively. AI sensitivity, specificity, PPV, and NPV for BERN were 89% (95% CI, 83–93), 88% (95% CI, 84–91), 88% (95% CI, 84–91), and 89% (95% CI, 83–93), respectively. The quality for BE studies was higher because 2 were conducted in a real-time clinical setting, demonstrating the feasibility of using this software during clinical practice.[39,42] Of note, one study compared AI accuracy with that of 53 general endoscopists, showing a higher AI accuracy than any of the individual endoscopists[40] with comparable delineation performance. Real-time application of this software has also been shown.[39,42]

Gastric Adenocarcinoma

The stand-alone performance of AI for the detection of gastric cancer has been primarily assessed in Eastern setting using both white light and blue light, as well magnified and unmagnified endoscopy. By pooling 7 studies,[48–54] including a total number of images and patients in the test set, the sensitivity, specificity, PPV, and NPV were 88% (95% CI, 78–94), 89% (95% CI, 82–93), 88% (95% CI, 80–93), and 89% (95% CI, 80–94), respectively.

Although none of the studies was conducted in a real-time clinical setting, the quality was graded as medium, given the multicenter nature of the studies and the strict distinction between the training and testing phases. After the publication of the meta-analysis, 2 papers on gastric cancer detection were published, confirming a high AI accuracy with values favorably comparing to expert and junior endoscopists.[55,56]

When considering all upper GI neoplastic lesions, a very large multicenter study from China[57] assessed AI accuracy on more than 1 million endoscopy images coming from 84,424 patients, showing a 92.7% accuracy on the external testing database, which was similar to that of expert endoscopists and superior to that of junior endoscopists.

The use of AI for the characterization of specific endoscopically identifiable pathologic characteristics of upper GI cancers is another, newer frontier being studied.

Intrapapillary Capillary Loops for Early Esophageal Squamous Cell Neoplasia

Changes in intrapapillary capillary loop (IPCL) structures, seen with virtual chromoendoscopy (eg, narrow-band imaging), is a feature of early esophageal squamous cell carcinoma that also helps determine treatment options because it correlates with tumor depth of invasion. One proof-of-concept CADx system was trained to characterize IPCL patterns based on the Japanese Endoscopic Society classification. Using 7046 narrow-band imaging images from 17 patients and 5-fold cross-validation, the system performed with an overall accuracy of 93.7% (95% CI, 86.2–98.3), sensitivity of 89.3% (95% CI, 78.1–100), and specificity of 98% (95% CI, 92–99.7).[58] In another study, using a separate CADx system with real-time endoscopy, the model performed with 89.2% accuracy at the level of anatomic lesions and 93% accuracy at the pixel level. When compared to endoscopist classification with differing years of experience, the model performed significantly better than endoscopists with $<$15 years of experience in characterization of neoplastic lesions ($P < .001$).[59]

Depth of Invasion in Barrett's Esophagus–Related Neoplasia

The differentiation between T1a and T1b BERN is critical to allocate patients to the correct treatment (endoscopic vs surgical). A recent pilot study[60] assessed the performance of AI in differentiating T1a from T1b BERN in white light images. The accuracy of the system was 71%, similar to that of expert endoscopists used as the benchmark (70%).

Gastric Precancerous Lesions/Gastric Cancer

A pilot study[61] investigated the accuracy of an AI system fully dedicated to the detection of gastric atrophy conditions used to guide targeted biopsies and increase diagnostic power. This system showed a 93% accuracy, outperforming expert endoscopists (80%).

Gastric neoplasia can be subclassified into different categories (ie, low-grade dysplasia, high-grade dysplasia, early gastric cancer, advanced gastric cancer) that have different treatment options. An AI system showed comparable performance to that of experienced endoscopists in correctly classifying gastric neoplasia.[62]

Delineation of Gastric Cancer

Similar to IPCLs for ESCN, the margins of early GC are an important characteristic visualized with virtual chromoendoscopy that helps determine treatment plans to ensure curative resection. Using 2 different neural networks trained on separate training image sets, investigators developed an AI system to detect GC followed by delineation of the margins. AI accurately delineated margins for differentiated GC at a rate of 82.7% (95% CI, 78.6–86.1) and at a rate of 88.1% (95% CI, 84.2–91.1) for undifferentiated GC. The system was then tested on endoscopy videos and was able to perform at video speeds for both differentiation and delineation.[63]

Blind Spots

Real-time quality improvement AI systems are being developed to assist endoscopists in areas such as identifying

blind spots and key anatomic landmarks related to upper GI neoplasia.

A single-blind, 3-parallel-group randomized controlled trial compared the blind spot rate of unsedated ultrathin transoral endoscopy, unsedated conventional EGD, and sedated conventional EGD with or without AI. The blind spot rates for all AI subgroups were significantly lower than all non-AI subgroups ($P < .001$). Sedated conventional EGD with AI assistance achieved the lowest blind spot rate of all parallel groups ($P < .05$).[64]

Anatomic Landmarks

In an initial proof-of-concept study showing that landmark identification with AI training is possible, investigators used 3704 images labeled with 11 anatomic landmarks as identified in the British and Japanese guidelines for appropriate endoscopic procedure documentation. The AI systems performed with a mean accuracy of 87.43% (standard deviation [SD], 4.25) to 88.11% (SD, 4.62) using 4 test sets. To be clinically relevant in patients with suspected upper GI diseases, this capability must be applied to real-time endoscopy.[65]

It could be argued that such stand-alone performance represents a worst-case scenario for AI systems because the ground truth that has been selected by experts does not necessarily represent the current standard of endoscopy. For this reason, a methodology adopted quite frequently is to administer the same cases used for AI testing to a group of physicians who were not involved in the collection of the ground truth in the first place. Such a benchmarking group usually consists of a mix of experienced and less-experienced endoscopists rating multiple images from different patients (in a blinded fashion) from AI output. The characterization studies for IPCL and GC delineation are examples that used this methodology to assess the superiority of their AI systems. Such methodology is also named *multicase multireader methodology*, and it has been extensively used in AI applications in medicine. As already summarized, AI performances favorably compared with human performances.[24] A second limitation of our pooling of data extracted from an artificial setting is that there are possible methodologic pitfalls related to the intrinsic bias of the individual studies, such as selection or technical bias, that prevent an immediate translation of these point estimates to community practice endoscopy.

What Is the value of Artificial Intelligence for Upper Gastrointestinal Neoplasia in Clinical Practice?

Despite its consistency, the simple evidence of a robust stand-alone performance of an AI system for the detection or characterization for upper GI neoplasia does not ensure additional value when AI is incorporated into clinical practice. AI systems are considered low-risk devices expected to assist but not replace the endoscopist. Thus, the AI output does not necessarily correspond to the physician diagnosis because it may be affected by the interaction between the physician and the machine. For instance, when the AI system flags a true positive, this may be rejected by the physician and considered as a false positive. Vice versa, a false positive may trigger an unnecessary resection with detrimental rather than incremental effects on patient care and endoscopist performance. On the other hand, a false negative result by the machine may be compensated for by an autonomous diagnosis by the physician, resulting in a unique human–machine diagnostic ability that depends on each of the 2 sides separately. The relevance of these pitfalls is increased by the following 2 observations. Different from colorectal polyps, neoplastic lesions in the upper GI tract are usually subtle and flat. In addition, inflammatory changes may mimic such neoplastic changes, requiring a careful differential diagnosis between the 2. Second, most of this software has been tested against high-grade dysplasia and early cancer for both BERN and gastric lesions, and the additional detection of low-grade dysplasia may result in an overdiagnosis, also increasing the cost of surveillance and treatment.

For this reason, clinically controlled trials with randomized or tandem design are needed to define the additional value of AI in the diagnostic process. The usual design is the comparison between standard endoscopy vs AI-assisted endoscopy with patient-centered outcomes, as summarized earlier. To date, one system (EndoAngel; Wuhan University, Wuhan, China) has been extensively validated with a more rigorous methodologic approach, for which 4 published clinical trials are currently available.[64,66–68] Briefly, in these various clinical trials, this system has been shown to increase the inspection time of the gastric mucosa (5.40 minutes [SD, 3.82] vs 4.38 minutes [SD, 3.91]; $P < .001$), to reduce the percentage of blind spots during upper GI endoscopy (21% [95% CI, 1.6–40] vs 38.9% [95% CI, 0.8–68.3]; $P < .001$), and to reduce the miss rate[68] in a tandem methodology design (6.1% [95% CI, 1.6–17.9] vs 27.3% [95% CI, 15.5–43.0]; relative risk, 0.224 [95% CI, 0.068–0.744]; $P = 0.015$). In addition, the same system showed sensitivity rates for detecting gastric neoplasia and diagnosing early gastric cancers (EGCs) of 87.81% and 100%, respectively, significantly higher than those of endoscopists (83.51% and 87.13%, respectively).[67] Accuracy rates of the system for predicting EGC invasion depth and differentiation status were comparable to those of the endoscopists.[67] When passing from preclinical to clinical validation studies, not only bias related to deep AI validation should be considered, because other types of bias purely related to the blinding of the operator and the randomization process may occur.

Conclusions

AI does not represent a mere technological improvement for the management of upper GI neoplasia. By codifying expert skills in a real-time algorithm, it automatically transfers human knowledge from experts to the entire gastroenterology community. By AI assistance, patient outcome does not depend on the individual physician performing the procedure, but his/her individual pitfalls—such as miss rate or incorrect characterization of upper GI

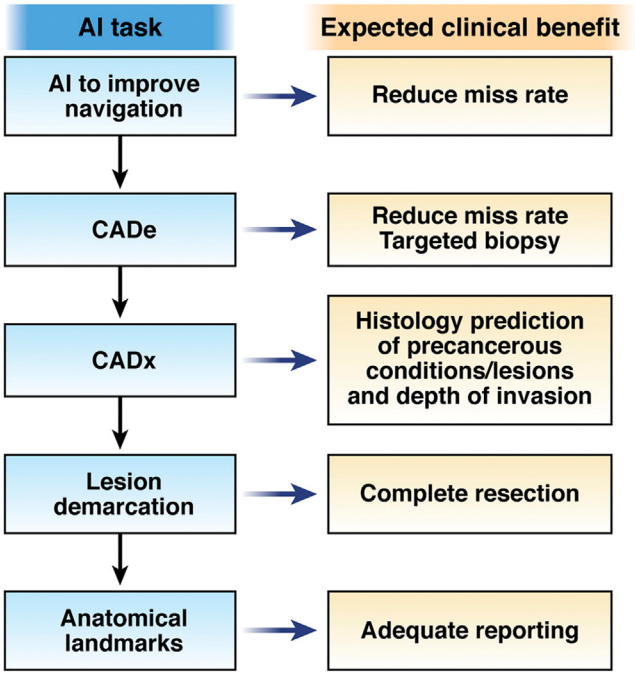

Figure 1. Integration of different individual AI tasks for the detection, characterization, treatment, and reporting of upper GI neoplasia.

neoplasia—may be prevented by the human–machine interaction.[17,69] AI also allows the perspective to be changed for quality assurance in upper GI endoscopy. Rather than intervening on the physician front, as several interventions in this field, AI shifts the focus on the patient. In this regard, it will be important to integrate all of the available stand-alone algorithms in a combined approach. For instance, navigation software can improve the exposure of the mucosa, maximizing the efficacy of CADe in lesion detection. In turn, CADx may indicate the need for further biopsy/treatment, and delineation software may simplify the subsequent resection (Figure 1). Thus, it is the patient who is protected from any suboptimal detection or characterization, irrespective of the competence of the endoscopist.

However, AI incorporation in clinical practice will result in new challenges. Because of the low prevalence of upper GI neoplasia, community endoscopists must be up-skilled to correctly differentiate between true and false positive AI activations. This is also related to the fact that the adoption of AI will accelerate the abandoning of random biopsies in favor of target biopsies. This, on one hand, will reduce the cost and burden of surveillance examination but, on the other, will pose the risk of missing subtle neoplastic lesions missed by AI but that would have been otherwise identified by random biopsies. In addition, nondedicated centers need to refer cases of upper GI neoplasia to tertiary centers, generating organizational challenges. Alternatively, false positive triggers may actually increase the costs and waste of resources, which are not limited to additional biopsies, also resulting in potential overtreatment, excessive surveillance, or patient anxiety.

In general, AI appears to be a promising tool to standardize the detection and characterization of upper GI neoplasia in diagnostic, screening, and surveillance endoscopy. In addition, it may prevent rare but catastrophic errors, such as missing an early or advanced cancer, which may occur because of physician exhaustion, distraction, or lack of expertise.

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