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Artificial Intelligence in the Diagnosis, Treatment, and Prognosis of Hypopharyngeal Carcinoma: A Scoping Review

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Hypopharyngeal carcinoma (HPC) has one of the poorest prognoses among all types of head and neck squamous cell carcinoma (HNSCC). Artificial intelligence (AI) is a scientific field that is in the spotlight, especially in the last decade, and AI has also been widely used in the research field of HPC. This scoping review aimed to describe the improvement of HPC clinical cares brought by AI. Literatures utilizing AI and machine learning in HPC were searched in PubMed, EMBASE, and Web of Science, and 116 articles from 1987 to 2024 were retrieved. After removing duplicate and irrelevant articles, 85 were further selected for detailed review. AI helps analyze large amounts of data from HPC patients and develop models to facilitate clinical practice. The emergence of AI improves the endoscopic, radiologic, and pathologic diagnosis accuracy of HPC and guides personalized treatment and prognosis prediction. However, there are certain unmet challenges that need to be further elucidated, like interpreting the AI algorithms into features that can be observed by humans and promoting the AI models in larger and multi-centered cohorts.

Keywords: Artificial intelligence; Diagnosis; Hypopharyngeal carcinoma; Machine learning; Robotic surgery; Therapy

Introduction

Hypopharyngeal cancer (HPC) describes tumors arising between the level of the hyoid bone and the lower end of the cricoid cartilage, and squamous cell carcinoma (SCC) from the mucosal layer is the most common histology identified in 95% of the cases.[1] Patient management mainly includes surgery, radiotherapy, and chemotherapy. However, open surgery, like total laryngectomy, inevitably destroys patient laryngeal function, including breathing, speaking, and swallowing.[2] Other therapies might also lead to life-threatening complications, such as leukopenia, hepatotoxicity, and thyroid dysfunction.[3] Despite the effort and research in HPC fields, largely unmet challenges exist. HPC is still one of the worst prognostic type of head and neck squamous cell carcinoma (HNSCC), and the overall 5-year survival rate was only about 41.3%.[4] HPC increases the economic and societal burden, and novel techniques aiding clinical practice are warranted.[5]

In the last few decades, there is an increasing interest in artificial intelligence (AI) and machine learning, which refer to systems that perform human-like tasks, including to process, mine, learn, and respond to information gained from big data.[6] The computational and programming steps in AI and machine learning allow the analysis of large amounts of complex data for meaningful patterns and consequent knowledge. Deep learning helps in automatically identifying disease stages,

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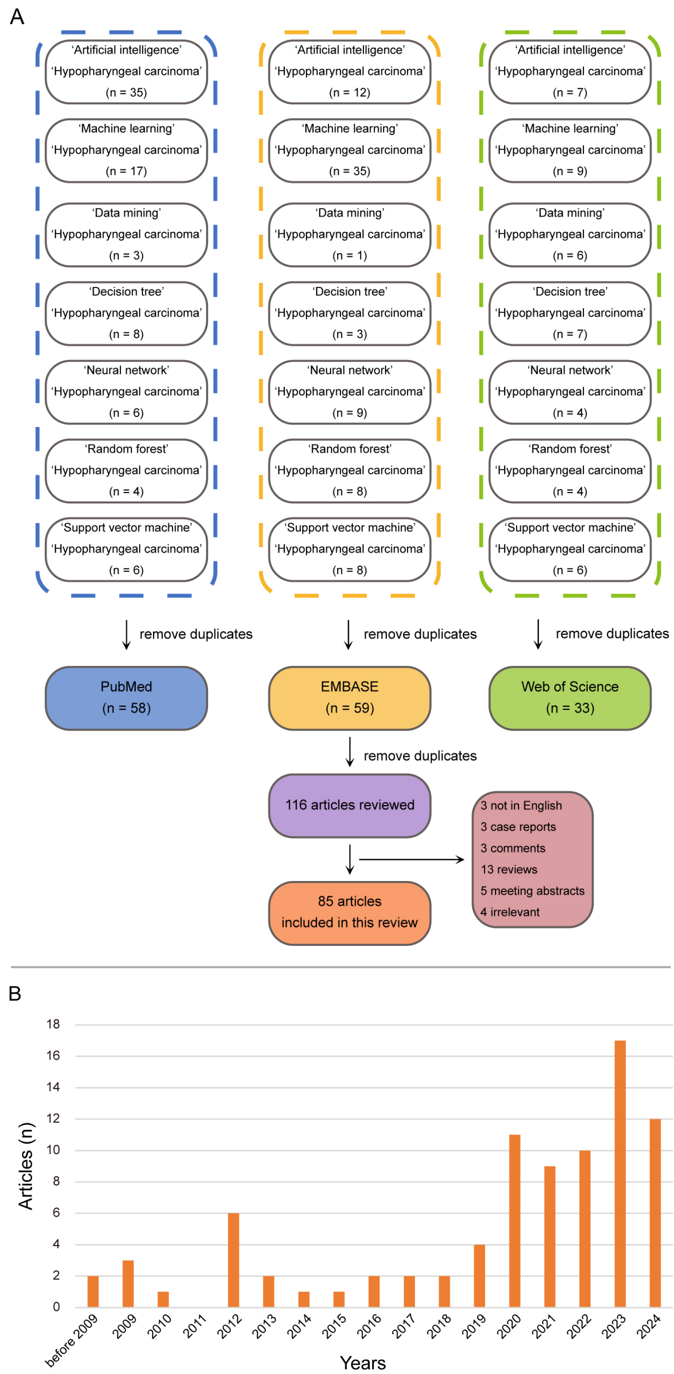
guiding patient therapy options, and predicting the prognosis.[7] Robotic surgery assisted by AI offers a minimally invasive approach, and it better aligns with the organ-preservation protocol and has developed rapidly in HPC management.[8,9] Molecular docking and molecular dynamics simulation help evaluate the bioactivity of promising agents against anticancer target.[10-14] Chat Generative Pre-Trained Transformer (ChatGPT) provides timely and convenient responses to common patient questions and can serve as a supplementary tool for patient education.[15] Indeed, AI improves the levels of HPC clinical workflow and facilitates decision-making in clinical practice.

In this review, we systematically searched the literature for articles that employed AI or machine learning techniques in HPC clinical practice, including predictive models for diagnosis, treatment, and prognosis, AI-assisted surgical systems, and AI-assisted investigation of marker genes in disease underlying mechanisms. Then, we classified these literatures into HPC diagnosis, treatment, and prognosis prediction. This review attempts to map the existing literature of AI application in HPC and summarize current improvement.

Methods

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR),[16] we systematically searched the literature through June 5, 2024 for articles using AI or machine learning techniques in HPC research. We searched three databases (PubMed, EMBASE, and Web of Science) using the following terms: ‘artificial intelligence’ AND ‘hypopharyngeal carcinoma’; ‘machine learning’ AND ‘hypopharyngeal carcinoma’; ‘data mining’ AND ‘hypopharyngeal carcinoma’; ‘decision tree’ AND ‘hypopharyngeal carcinoma’; ‘neural network’ AND ‘hypopharyngeal carcinoma’; ‘random forest’ AND ‘hypopharyngeal carcinoma’; ‘support vector machine’ AND ‘hypopharyngeal carcinoma’; ‘artificial intelligence’ OR ‘machine learning’ OR ‘data mining’ OR ‘decision tree’ OR ‘neural network’ OR ‘random forest’ OR ‘support vector machine’ AND ‘hypopharyngeal carcinoma’ (Figure 1A). No limits were imposed on the publication year. After removing duplicates, we retrieved 58, 59, and 33 literatures from PubMed, EMBASE, and Web of Science, respectively. Then, totally 116 articles were further screened, and articles not in English (n = 3), case reports (n = 3), comments (n = 3), reviews (n = 13), meeting abstracts (n = 5), and irrelevant (n = 4) were removed. Finally, 85 articles were included in this study.

Figure 1B presents the distribution of studies using AI or machine learning techniques for HPC research over the course of approximately 20 years, from 2009 to 2024. During the first decade there was minimal use of such techniques for HPC, while from 2019 on, we observed a considerable and progressive increase. In Figure 1C, the distribution of geographical location by continent of included studies are shown, and studies from Asia accounted for the largest proportion (58%).



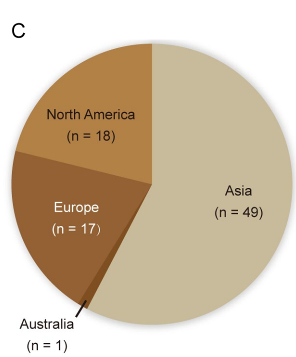


Figure 1. (A) Flowchart of the literature search; (B) Distribution of articles published per year that employed artificial intelligence (AI) and relevant machine learning techniques for hypopharyngeal carcinoma (HPC) research; (C) Distribution of geographical location by continent of included articles.

Results

HPC Diagnostics

Early diagnosis of HPC allows early intervention and improves long-term survival, and the AI models utilized in clinical variables, endoscopic, radiologic, and pathologic examination are summarized in Table 1.

Clinical Variables

Cervical lymph node status is crucial for guiding surgical approach, and primary tumor stage (T3/T4), blood neutrophil count (>5.0x10^9/L), and platelet count (>168x10^9/L) offer valuable guidance for personalized prediction of lymph node metastasis (LNM) in HPC patients.[17]

Confocal Laser Endomicroscopy (CLE)

CLE allows surface imaging of hypopharyngeal mucosa *in vivo* at a thousand-fold magnification, and corkscrew-like vessels, dilated intraepithelial capillary loops, and increased capillary leakage are significantly more frequently detected in malignant lesion compared to the healthy epithelium.[18,19] By Cellvizio Viewer software, a vessel diameter of 30 μm in capillary loops was considered as a cut-off value aiding malignance identification.[20] A point-wise spatial attention network model trained by endoscopic imaging could reach an average accuracy of 96.3% in automatically performing semantic segmentation and tumor recognition.[21] As for real-time HPC identification, the diagnostic accuracy of a Laryngopharyngeal Artificial Intelligence Diagnostic System (LPAIDS) in both white-light imaging (WLI) and narrow-band imaging (NBI) achieved more than 0.940, which is comparable to experts and can be adapted in various centers.[22] Endoscopy can also evaluate the overall function of the larynx, and novel models involving this factor might further enhance the diagnosis accuracy and guide the resection margin of surgery.[23]

Radiology

Computed tomography (CT) is the most used clinical tool in HPC diagnosis, tumor-node-metastasis (TNM) staging, and organs-at-risk (OARs) delineation.[24] T stage is essential for patient treatment, in which ≤ T2 staging is defined as early, and ≥ T3 staging is advanced stage. Several studies have leveraged CT-based radiomics to predict T-stage,[25,26] consistently reporting high accuracy (area under receiver operating characteristic [ROC] curve [AUC] >0.90). However, these models were developed on relatively small, single-center cohorts, and the specific radiomic features used often differed, highlighting a critical need for external validation and feature standardization before clinical application. Radiomics-based models also helped in LNM diagnosis and histological grades.[27,28]

Magnetic resonance imaging (MRI) also provides useful data for machine learning. DeepLab V3 + and U-Net models showed good performance in automated segmentation and MRI feature extraction and held great potential for facilitating more efficient clinical workflow.[29] MRI could also be used preoperatively for LNM prediction.[30] Additionally, in up to 5% of head and neck cancer cases, LNM was first detected within the head and neck region, while the location of the primary tumor was unknown.[31] AI identifies the significant difference of radiomic features in LN, and then predicts different primary tumor sites.[32] While promising, this model was validated on only 38 patients,[32] underscoring the risk of overfitting. Moreover, the multimodality image combination of CT, MRI, and position emission tomography (PET) might further improve tumor segmentation.[33]

Pathology

The pathological biopsy represents the gold standard for HPC diagnosis, and cancer cell identification on histological images by AI is increasingly applied in clinical practice. Compared to other sub-cellular components, nuclei especially exhibit more cancer-related information, like variations in nuclear shape and size, atypical mitotic figures, and hyperchromasia. A study developed hyperspectral imaging (HSI) for automatic SCC nuclei detection, and the average AUC and accuracy reached 0.94 and 82.4%, respectively.[34,35] Koyuncu et al.[36] further defined tumor cell multinucleation index (MuNI) using a deep learning model, defined as three tumor cells in the high-power field (HPF) with three or more nuclei in the same cell, which is strongly related to depletion of effector immunocyte subsets and reduced survival rate in HPC patients. Perineural invasion (PNI) has a negative prognostic impact on HNSCC patients, and it can be diagnosed by the domain knowledge enhanced yield (Domain-KEY) algorithm, whose accuracy was 89.01%.[37] Another study created a linear support vector machine classifier based on the whole-slide images (WSI) immunohistochemistry (IHC) staining of CD45 and Ki-67 to distinguish intratumor heterogeneity.[38] By probe electrospray ionization mass spectrometry (PSEI-MS), mass spectra were developed, and could help define the borders of the cancerous regions.[39] However, these studies are based on small sample size, and more data from larger population are needed to create robust classifiers and reduce the overfitting risk and interbatch intensity variability.

HPC Treatment

The utilization of AI in HPC treatment mainly included three parts: AI-assisted surgical operation, prediction models by machine learning in the efficacy of radiotherapy and chemotherapy (Table 2), and AI-assisted investigation of new chemotherapy and immunotherapy targets.

Surgery

Compared to radical open surgery, the recent trend in surgical treatment of HPC is organ preservation, intending to maintain swallowing and speech function and quality of life as much as possible.[40-42] Transoral robotic surgery has been used in HPC patients since 2007,[43] and either the da Vinci Robotic System[44,45] or the Flex Robotic System[46] has been proven to be valid and

Publication	Model
Clinical variables (n = 1)	
Wu et al. 2024[17]	Lymph node metastasis (LNM) prediction by a nomogram.
Endoscopy (n = 4)	
Sievert et al. 2022[20]	The cut-off value of vessel diameter in capillary loops is defined as 30 μm by receiver operating characteristic (ROC) curve.
Zhou et al. 2023[21]	Semantic segmentation by a point-wise spatial attention network model.
Li et al. 2023[22]	Real-time automatically identifying HPC by a deep convolutional neural networks (CNN)-based Laryngopharyngeal AI Diagnostic System (LPAIDS).
Yumii et al. 2024[23]	Radiomic features extracted by Python and Pyradiomics software.
Radiology (n = 9)	
Gao et al, 2021[24]	Small organ segmentation by FocusNetv2.
Liu et al. 2024[25]	T2/T3 stage distinguished by radiomics-based prediction model using analysis of variance (ANOVA) feature selection and logistic regression (LR) classifier.
Guo et al, 2020[26]	Prediction of thyroid cartilage invasion by LR-support vector machine (SVM)-based synthetic minority oversampling (SVMSMOTE) method.
Liu et al. 2021[27]	LNM prediction by random forest (RF) classifiers built by radiomic or texture features extracted by TexRAD.
Zheng et al. 2023[28]	Histological differentiation grade prediction by a contrast-enhanced CT-based deep learning radiomics nomogram.
Lin et al. 2023[29]	Automated segmentation and radiomics features extraction of HPC by DeepLab V3 + and U-Net models.
Lu et al. 2020[30]	Preoperative LNM prediction by pre-treatment magnetic resonance imaging (MRI) radiomics.
Liu et al, 2024[32]	Primary tumor location determination by SVM classifier.
Ren et al. 2021[33]	Auto tumor segmentation by multimodal deep learning.
Pathology (n = 6)	
Ma et al. 2020[34]	Automatic detection of head and neck cancer cell nuclei on hyperspectral imaging (HIS).
Ma et al. 2021[35]	Head and neck cancer tissue detection on whole HSI using a modified Inception-based CNN.
Koyuncu et al, 2023[36]	Biological features of tumor cell multinucleation.
Lee et al. 2022[37]	Perineural invasion identification by domain knowledge enhanced yield (Domain-KEY) algorithm in digital slides.
Smits et al, 2023[38]	LPC classification based on CD45 and Ki-67 features.
Ashizawa et al. 2017[39]	Cancerous region border definition by mass spectra.

Table 1. Summary of AI and machine learning models in hypopharyngeal carcinoma (HPC) diagnosis (continued on page 155)

Abbreviations: HPC, hypopharyngeal carcinoma; LNM, lymph node metastasis; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value; HNSCC, head and neck squamous cell carcinoma; CNN, convolutional neural networks; LPAIDS, laryngopharyngeal AI diagnostic system; LPC, laryngopharyngeal cancer; CT, computed tomography; MICCAI'15, 'medical image computing and computer assisted interventions' conference head and neck auto

Effect measures	Sample size
C-index = 0.887 (95% confidence interval [CI] 0.835-0.933).	285 HPC patients.
Arer under ROC curve (AUC) = 91.5% (95% CI 87.1%-95.9%), sensitivity = 90.6%, specificity = 71.3%, positive predictive value (PPV) = 57.4%, negative predictive value (NPV) = 94.7%, accuracy = 77.1%.	10 head and neck squamous cell carcinoma (HNSCC) patients, 54 sequences, 23061 images.
AUC = 0.97, sensitivity = 94.39%, specificity = 98.68%, mIoU = 86.25%, pixel accuracy = 96.3%.	Cancerous: 101 HNSCC patients, 1742 images; normal or benign lesion: 200 patients, 6473 images.
Internal image test: accuracy = 0.956 (95% CI 0.951-0.960), video test: accuracy = 0.949 (95% CI 0.931-0.968); external tests: AUC = 0.965-0.987.	Internal training, verification, and test sets: 2382 laryngopharyngeal cancer (LPC) patients, 31543 images; external test set: 6806 LPC patients, 25293 images.
AUC = 0.868, sensitivity = 87.3%, specificity = 76.1%, accuracy = 83.3%.	95 LPC patients.
Average dice = 84.51, average dice of small organs = 77.34.	1164 collected computed tomography (CT) scans and 'medical image computing and computer assisted interventions' conference head and neck auto segmentation challenge 2015 (MICCAI'15) dataset.
Training AUC = 0.919; validation AUC = 0.857; test AUC = 0.817.	118 LPC patients, 851 images.
AUC = 0.905 (95% CI 0.863-0.937).	256 HPC patients.
$P < 0.001$.	241 LPC or HPC patients.
Training set: AUC = 0.878; test set: AUC = 0.822.	204 HNSCC patients.
DeepLab V3 + model: dice similarity coefficient (DSC) = 0.77 (0.74-0.79), Jaccard index = 0.67 (0.64-0.69), average surface distance (ASD) = 1.23 (1.12-1.34); U-Net model: DSC = 0.75 (0.69-0.77), Jaccard index = 0.62 (0.59-0.65), ASD = 1.89 (1.77-2.03).	222 HPC patients.
Training cohort: AUC = 0.906 (95% CI 0.840-0.972); validation cohort: AUC = 0.853 (95% CI 0.739-0.966).	155 HPSCC patients.
Accuracy = 75.3%.	38 LPC patients.
Dice score: 0.74.	153 HNSCC patients.
AUC = 0.94, accuracy = 82.4%.	15 LPC patients.
Accuracy = 0.73, sensitivity = 0.77, specificity = 0.69.	18 LPC patients.
$P < 0.001$.	436 patients from the TCGA HNSCC cohort.
Accuracy = 89.01%.	85 H&E-stained whole-slide images from 80 HNSCC patients.
Accuracy = 81%.	74 whole-mount tumor slides from 21 LPC patients.
Positive-ion modes accuracy: 90.48%, negative-ion modes accuracy: 95.35%.	19 HNSCC patients.

segmentation challenge 2015 database; ANOVA, analysis of variance; LR, logistic regression; SVM, support vector machine; SVMSMOTE, SVM-based synthetic minority oversampling; RF, random forest; DSC, dice similarity coefficient; ASD, average surface distance; MRI, magnetic resonance imaging; HSI, hyperspectral imaging.

Table 2. Summary of AI and machine learning models in radiotherapy and chemotherapy of hypopharyngeal carcinoma (HPC) patients

Publication	Model	Effect measures	Sample size
Radiotherapy (n = 3)			
Lin et al. 2024[55]	Baseline absolute peripheral lymphocyte counts (1.335*10^9/L) as a predictive indicator of the radiotherapy effectiveness.	Area under receiver operating characteristic (ROC) curve (AUC) = 0.770 (95% confidence interval [CI] 0.600-0.878).	133 HNSCC patients.
Hasegawa et al. 2020[56]	An artificial neural network (ANN) model using clinical factors and immunohistochemical staining of Ku70 in predicting radiotherapy results.	AUC = 0.901, sensitivity = 66.7%, specificity = 88.2%.	46 HNSCC patients.
Men et al. 2019[57]	A three-dimensional residual convolutional neural network (3D rCNN) deep learning model for predicting xerostomia due to radiotherapy.	Accuracy = 0.76, sensitivity = 0.76, specificity = 0.76, F-score = 0.70, AUC = 0.84 (95% CI 0.74-0.91).	784 HNSCC patients.
Chemotherapy (n = 7)			
Guo et al. 2020[58]	A nomogram for pretreatment prediction of response to induction chemotherapy.	AUC = 0.860 (95% CI 0.780-0.940); 3-fold cross-validation AUC = 0.864 (95% CI 0.755-0.973).	127 patients with locally advanced HPC.
Howard et al. 2020[59]	Machine learning models identifying intermediate-risk HNSCC patients who would benefit from chemoradiotherapy.	DeepSurv: hazard ratio = 0.79 (95% CI 0.72-0.85, $P < 0.001$); neural multitask logistics regression: hazard ratio = 0.83 (95% CI 0.77-0.90, $P < 0.001$); random survival forest models: hazard ratio = 0.90 (95% CI 0.83-0.98, $P = 0.01$).	35527 patients diagnosed with squamous cell carcinoma of the oral cavity, oropharynx, or larynx.
Surucu et al. 2016[60]	Decision trees predicting tumor shrinkage during chemoradiotherapy.	Accuracy = 88%.	48 patients treated with definitive concurrent chemoradiotherapy for squamous cell carcinoma of the nasopharynx, oropharynx, oral cavity, or hypopharynx.
Liu et al. 2022[61]	Multiparametric computed tomography (CT)-based radiomics model predicting treatment response and progression-free survival in HPC patients who underwent induction chemotherapy.	Training cohort: C-index = 0.899 (95% CI 0.831-0.967); validation cohort: C-index = 0.775 (95% CI 0.591-0.959).	112 patients with locally advanced HPC (training cohort: 78, validation cohort: 34).
Liu et al. 2024[62]	A multisequence magnetic resonance imaging (MRI)-based volumetric histogram metrics model for predicting pathological complete response in advanced HNSCC patients undergoing neoadjuvant chemo-immunotherapy.	AUC = 0.95.	24 patients with locally advanced HPC.
Zhong et al. 2018[63]	A 10-gene support vector machine (SVM) model predicting the response to docetaxel, cisplatin, 5-fluorouracil (TPF) treatment.	Sensitivity = 75.0%, specificity = 100%.	29 HPC patients (16 TPF-sensitive, 13 TPF-non-sensitive).
Tan et al. 2023[64]	A 6-gene signature predicting the response to induction chemotherapy and overall survival.	AUC = 0.949 (95% CI 0.864-1.000).	266 pre-treatment locoregionally advanced laryngeal and hypopharyngeal cancer samples.

Abbreviations: HPC, hypopharyngeal carcinoma; ROC, receiver operating characteristic; AUC, area under ROC curve; CI, confidence interval; HNSCC, head and neck squamous cell carcinoma; ANN, artificial neural network; 3D rCNN, three-dimensional residual convolutional neural network; CT, computed tomography; MRI, magnetic resonance imaging; SVM, support vector machine; TPF, docetaxel, cisplatin, 5-fluoruracil.

Publication	Model	Effect measures	Sample size
Clinical predictors (n = 4)			
Kotevski et al. 2023[76]	Nomogram prognostic modeling for 2-year survival.	C-index = 0.73.	2953 HNSCC patients.
Li et al. 2023[77]	XGBoost algorithm predicting the 3-year survival status.	Accuracy = 80.9%, sensitivity = 92.6%, specificity = 62.9%, area under receiver operating characteristic (ROC) curve (AUC) = 77.7%, kappa value = 58.1%.	295 HPC patients.
Yang et al. 2019[78]	Important cancer-related parameter identification influencing patient survival.	Gini index of age for HPC: 2.56%.	28639 HNSCC patients.
Liu et al. 2023[79]	The association of positive lymph node ratio (LNR) with recurrence-free survival and disease-specific survival.	LNR cut-off value: 8.6%.	101 patients with pyriform sinus cancer.
Radiomics (n = 6)			
Fatima et al. 2021[80]	The support vector machine (SVM) classifier using quantitative ultrasound (QUS) predicting recurrence in node-positive HNSCC patients.	Week 1: accuracy = 80%, AUC = 0.75; week 4: accuracy = 82%, AUC = 0.81.	51 HNSCC patients.
Bernatz et al. 2023[81]	Dual-energy computed tomography (DECT) material decomposition for survival prognostication.	Elastic net (EN): AUC = 0.784 (95% confidence interval [CI] 0.775-0.812); random survival forest (RSF): AUC = 0.785 (95% CI 0.759-0.812).	50 HNSCC patients.
Li et al. 2020[82]	CT-based radiomic signature predicting early recurrence.	Training set: AUC = 0.83 (95% CI 0.76-0.90), sensitivity = 0.8, specificity = 0.83; validation set: AUC = 0.83 (95% CI 0.67-0.99), sensitivity = 0.69, specificity = 0.71.	167 HPC patients who underwent partial surgery (training cohort: 133, validation cohort: 34).
Chen et al. 2022[83]	A magnetic resonance imaging (MRI)-based radiomics-clinical nomogram for the overall survival (OS) prediction.	C-index: training cohort 0.78, internal validation cohort 0.75, external validation cohort 0.75.	190 HNSCC patients.
Kim et al, 2022[84]	Radiomics features from apparent diffusion coefficient (ADC) map to diagnose local tumor recurrence.	Internal validation set: AUC = 0.76 (95% CI 0.62-0.89); external validation set: AUC = 0.77 (95% CI 0.65-0.88).	285 HNSCC patients (training: 161; internal validation: 54; external validation: 70).
Zhong et al. 2021[85]	Baseline integrated 2-[^{18}F]-fluoro-2-deoxy-d-glucose positron-emission tomography computed tomography (FDG PET-CT) predicting disease progression in squamous cell carcinoma (SCC) patients receiving (chemo)radiotherapy.	Training cohort: AUC = 0.93, validation cohort: AUC = 0.94.	40 hypopharynx SCC patients, 32 larynx SCC patients.
Stadler et al. 2020[86]	Suvmax changes between two sequential post-therapeutic FDG PET predicting recurrence in HNSCC patients.	Hazard ratio: 4.17 (95% CI 1.89-9.2).	337 oral, oropharyngeal, laryngeal, and hypopharyngeal SCC patients.
Martens et al. 2022[87]	MRI and FDG PET-CT predicting 2-year locoregional recurrence-free survival.	AUC = 0.81	57 histopathologically-proven HNSCC patients with curative (chemo)radiotherapy.
Marker genes (n = 1)			
Chung et al. 2014[88]	p16 protein expression predicting prognosis.	Hazard ratio for progression-free survival (PFS): 0.63 (95% CI 0.42-0.95, *P* = 0.03); for OS: 0.56 (95% CI 0.35-0.89, *P* = 0.01).	356 oral cavity, hypopharynx, and larynx SCC patients.

Table 3. Summary of AI and machine learning models in prognosis of hypopharyngeal carcinoma (HPC) patients

Abbreviations: HPC, hypopharyngeal carcinoma; HNSCC, head and neck squamous cell carcinoma; ROC, receiver operating curve; AUC, area under ROC curve; LNR, lymph node ratio; DECT, Dual-energy computed tomography; CI, confidence interval; MRI, magnetic resonance imaging; OS, overall survival; FDG PET-CT, 2-[^{18}F]-fluoro-2-deoxy-d-glucose positron-emission tomography computed tomography; SCC, squamous cell carcinoma.

feasible. Transoral robotic surgery is more suitable for patients with low risk of positive surgical margins.[47] However, complications might occur during transoral robotic surgery, including bleeding and need for tracheostomy or gastrostomy tube.[48-50] AI could analyze risk factors for complications based on big data preoperatively. For example, for prolonged postsurgical enteral feeding prediction, body mass index, previous radiotherapy, preoperative dysphagia, type of surgery, and flap reconstruction were independent factors.[51]

Radiotherapy

Adjuvant radiotherapy is standard of care for HNSCC patients with positive surgical margins or extracapsular extension.[52,53] Based on an in-house AI classification model, lymph nodes could be characterized as involved or suspicious, which guided different intensity of radiotherapy.[54] As for predicting the effectiveness of radiotherapy, higher absolute peripheral lymphocyte counts demonstrated a higher possibility to achieve a complete response (CR).[55] Pathological parameters, like the expression of Ku70 (involved in DNA repair mechanism), also predict radiotherapy result.[56]

Although radiotherapy is ontologically sound and reaches highly favorable quality-of-life outcomes, xerostomia and mucositis are common sequelae. With radiomics (CT images) and dosiomics (radiotherapy dose distribution) input, a hybrid predictive model of xerostomia comprising a 3D residual convolutional neural network was proposed, with AUC up to 0.84.[57] Individualized regimens and more reliable biomarkers are still in need for personalized radiotherapy treatment.

Chemotherapy

Currently, docetaxel, cisplatin, 5-fluoruracil (TPF) treatment is the major regimen of chemotherapy for HNSCC, but only half of all patients exhibit good response to TPF treatment.[5] For personalized treatment, AI identified that age, primary tumor stage, human papillomavirus (HPV) status, and Karnofsky performance status were indicative parameters of significant tumor volume reduction and survival benefit.[58-60] Radiomics signatures of CT and multisequence MRI could also predict progression-free survival and pathological complete response (pCR) in advanced HNSCC patients undergone induction chemotherapy.[61,62]

A study further identified a gene expression signature between TPF-sensitive and non-sensitive patients, and based on GATS, PRIC285, ARID3B, ASNS, CXCR1, FBN2, MYOM3, SLC27A5, and STC2, a support vector machine model was trained, with 88.3% sensitivity and 88.9% specificity.[63] Another study constructed a more precise six-gene signature (NRIP1, GIMAP27, CD72, THBS4, ABCA9, and SNED1) to predict tumor response and overall survival in locoregionally advanced HPC patients, and this gene model reached an AUC of 0.949.[64]. PPARG and its interconnectedness (AKT1, TP53, PTEN, MAPK1, NOTCH1, BECN1, PTGS2, SPP1, and RAC1) were also involved in the regulation of chemosensitivity.[65,66] SPP1 was closely related to M2 macrophages infiltration, LNM, and poor prognosis.[67] Clinical parameters and genetic characters all participate in patient response to chemotherapy, and recognizing TPF-sensitive patients in advance is necessary.

Immunotherapy

Immunotherapy is the new treatment landscape of head and neck cancer, with checkpoint inhibitors including pembrolizumab and camrelizumab, and has been proven to be efficient and well-tolerated.[68-71] However, due to the complex microenvironment, primary resistance can be shown in patients who underwent PD-(L)1-targeted regimens.[72] The predictive and prognostic biomarkers of immunotherapy remain limited.

AI also recognizes active ingredients and new targets for HPC immunotherapy.[73,74] CD73 is a new therapeutic target induced by the epidermal growth factor (EGF)-EGF receptor (EGFR)-epithelial-mesenchymal transition axis, and mediates local invasion in especially advanced HPV-negative HPC. Except anti-EGFR cetuximab, a novel antagonizing antibody 22E6, might also be promising after appropriate processing.[75]

HPC Prognosis of Survival Status and Tumor Recurrence

<u>Clinical Predictors</u>

Age ≥60 years, advanced TNM stage (with lymphovascular, perineural, or thyroid invasion), poorly differentiated pathology, no adjuvant radiotherapy or chemotherapy accepted, and smoking were independent prognostic factors for 3-year survival status of HPC patients (Table 3).[76-79]

<u>Radiomics</u>

Quantitative ultrasound delta-radiomics during radical radiotherapy are efficient in predicting tumor recurrence, and its accuracy and AUC were 82% and 0.81, respectively.[80] Radiomic features from CT and MRI also aided in patient survival prediction and tumor recurrence diagnosis.[81-84] Furthermore, 18-fluorodeoxyglucose (FDG)-PET measures metabolic activity (maximum standardized uptake value, SUV max) of the local tumor area and the regional lymph nodes and predicts HPC progression.[85-87]

<u>Marker Genes</u>

Sequencing data showed a more frequent presence of tumor suppressor gene mutations than oncogene mutations, and p53 and p16 protein expression are important prognostic biomarkers in HPC development and response to treatment.[88] A study demonstrated that compared to laryngeal carcinoma, hypopharyngeal carcinoma had less central memory T cells, T follicular helper cells, transforming growth factor-β response, and $CD4^{+}$T memory resting cells.[89] By RNA sequencing, serum high resolution mass spectrometry, and secretomes, many genes, metabolites, and microRNAs were found to be aberrantly expressed in tumors,[90-97] but there is still no widely-accepted model. Further development of markers staining protocol and scoring system, as well as the more accessible serum proteomics, are warranted before broad application in the clinical setting.[98]

Discussion

This scoping review summarized current progress on the application of AI and machine learning on HPC clinical diagnosis, treatment, and prognosis. By establishing predictive models and enhancing treatment means, diagnostic accuracy increased and postoperative complications can be better avoided. AI and machine learning are gradually increasing in HPC research.

AI and machine learning are particularly useful for the analysis of large complex datasets, encompassing heterogeneous sources of information. Due to the complex microenvironment at the cellular level and long follow-up period in HPC patients, the utilization of AI on HPC is appropriate to gain new knowledge.[99] A cross-sectional review for the management of HPC is crucial for patient outcome and the reduction of disease burden.

Multi-omics approaches are urgently needed in identifying HPC heterogeneity and biological features underlying cancer pathology. However, current studies are all based on small sample sizes and single sequencing methods. Integrative multi-omics analysis with AI assistance can better guide precision therapy of HPC patients.

There are some limitations in this review. First, due to the complicated algorithms of AI, we cannot interpret the established models into characteristics that can be figured by humans. The underlying features of medical imaging remain to be explained. Second, how to promote the AI models on a national or global scale might be a future aspect, and a large patient cohort is still lacking.

Conclusions

AI/machine learning is undeniably a scientific field that is in the spotlight, especially in the last decades, and its utilization in medical applications of HPC research is on the rise. Big data from multi-center and standardized databases are needed for model training by AI techniques, and AI-based diagnostic or predictive models are eagerly anticipated to solve clinical dilemmas of every HPC stages.

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