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Advancements in imaging of head and neck squamous cell carcinoma: A comprehensive review.

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ABSTRACT

As a prevalent malignancy with substantial incidence and mortality worldwide, head and neck squamous cell carcinoma (HNSCC) originates from multiple locations of different tissues, which level up the difficulty and complexity of the cancer detection. The diagnosis requires high-resolution imaging modalities and several approaches have been developed within recent decades to provide detailed anatomical information for HNSCC. This review aims to summarize basic knowledge of those mainstream modalities including ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET). Moreover, novel and advanced imaging techniques, such as radiomics and dual-energy computed tomography (DECT), will be described as newly developed approaches of quantitative and personalized medicine. By comparing the advantages and disadvantages of these techniques, we would like to additionally discuss the directions of next generation imaging approaches.

Keywords : *imaging; head and neck squamous cell carcinoma; MRI; CT; radiomics; DECT.*

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) ranks as the seventh most prevalent cancer worldwide, with 930,000 new cases and 470,000 deaths in 2020 [1]. The primary risk factors associated with HNSCC are tobacco, alcohol, environmental pollutants, human papillomavirus (HPV) and Epstein-Barr virus (EBV) [2]. Due to the subtle nature of early symptoms, the HNSCC lesions often go unnoticed and won't be diagnosed until late stages. More than half of HNSCC patients develop locoregional recurrence or distal metastasis, which are detrimental [3,4]. The therapeutic effect of many developed radio/chemo-therapies as well as immunotherapies are limited, with a 5-year survival rate of 68.5% [5]. This raises a significant desire to determine or predict the cancer and to access the related clinical risk as early as possible.
To better diagnose HNSCC, multiple imaging methods have been thrived in recent years, such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET) (**Fig. 1**). Among them, ultrasound acquires real-time, non-invasive soft tissue characteristics by employing high-frequency sound waves to probe internal tissues [6]. MRI offers high-resolution visualization of soft tissues without radiation exposure either [7]. As the preferred imaging modality, CT costs less but with rapid acquisition time and superior capability in evaluating osseous structures [8]. Compared to CT, PET/CT provides additional metabolic information with a higher sensitivity but a lower specificity [9]. We will next describe these imaging applications in HNSCC, followed by an introduction of the latest imaging technologies such as radiomics, dual-energy computed tomography (DECT) and the combined application of multimodal imaging technology.

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Figure 1

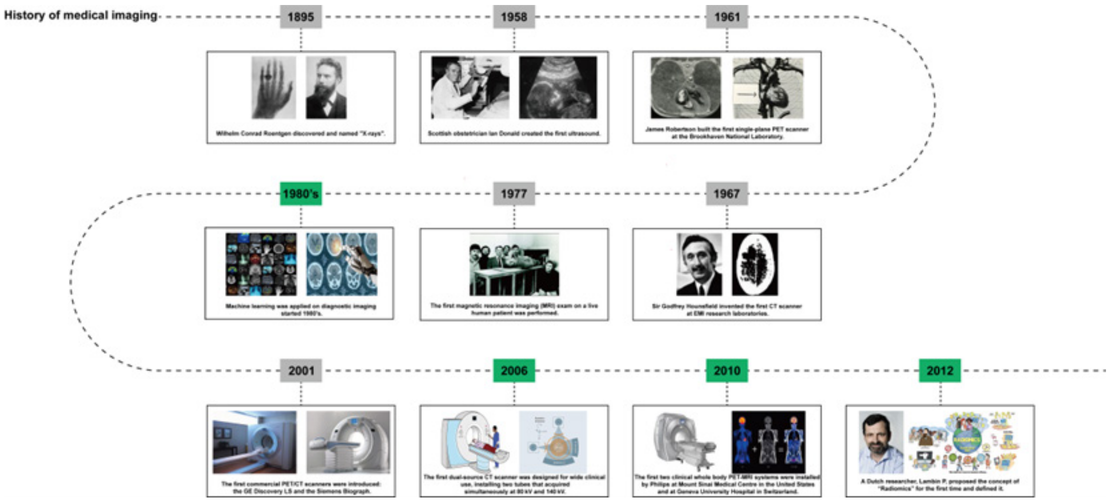

Figure 1. Developmental trajectory of medical imaging technology. Gray icons represent classical medical imaging modalities, while green icons denote relatively novel imaging technologies.

THE OVERVIEW OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

HNSCC is a complex and heterogeneous disease often seen as lip and oral cavity cancers, as well as larynx cancers [10]. The malignant transformation starts with squamous epithelial cells lining the mucosal surfaces of the head and neck region. The common early symptoms of HNSCC, such as neck mass, sore throat and dysphagia [11], are similar to the ones of cold or other inflammation types. Therefore, over 60% of patients won't be diagnosed until advanced-stage cancers [12]. HNSCC patients frequently undergo intensive treatments, leading to disfigurement, speech or taste impairment and chewing difficulties [13]. HNSCC primary tumors are often accompanied with the migration of cancer cells to nearby lymph nodes (LN). LN metastasis results in a 50% decrease in the five-year survival rate of HNSCC patients [14]. At advanced stages of HNSCC, the common metastatic sites include the lungs, bones and livers, which cause additional symptoms or complications [15]. Roughly 5% of the total HNSCC cases appear with unknown primary sites (UP). This subpopulation usually has cervical lymphadenopathy and is misdiagnosed for lack of symptoms of primary tumor. To access HNSCC staging, the TNM system is employed to estimate the tumor size and anatomical extent, which aids physicians to evaluate the tumor growth rate while formulating treatment plans. Traditional risk factors for HNSCC include tobacco and alcohol use. Tobacco use was considered as the most predominant risk factor [16], and larynx is accordingly the most susceptible tissue. The odds ratio (OR) of the smokers for HNSCC development is 2.13, approximately ten times greater than that of non-smokers [13,17]. Cigarette smoking has been shown to promote tumor cell proliferation, migration, invasion, metastasis and angiogenesis [17,18]. For example, carcinogens in tobacco induce HNSCC occurrence by forming DNA adducts that disrupt the DNA structure, and termination of tobacco usage can improve the prognosis of HNSCC patients [19]. Similar to tobacco, alcohol is positively associated with HNSCC establishment. The combination of both factors greatly enhances the risk possibilities of HNSCC development [20]. Besides, betel nut is another risk factor for oral and oropharyngeal cancers [21]. Other viral pathogens have also been proposed to contribute to HNSCC carcinogenesis. Approximately 25% of all the cases worldwide are associated with high-risk (HR) HPVs with the highest incidence observed in oropharyngeal squamous cell carcinoma (OPSCC)[22-24], whereas EBV has been primarily detected in nasopharyngeal cancer patients. In addition, HNSCC is also associated with oral hygiene, female hormone levels, and occupational exposure, as well as food factors such as high-fat, processed meat and sugary dietary patterns [5,25].

The prevalence of HNSCC is projected to surge 30% by 2030, reaching 1.08 million new cases worldwide annually [2]. The incidence of HNSCC varies with regions, sexes, ages, social status, and economic levels [5]. In southeast Asia, the high incidence of oral cancer is significantly due to betel nut usage, while in the United States and Europe, oropharyngeal cancer is mainly associated with HPV infection [26]. Males has higher chances to develop HNSCC than females, with a male to female ratio of 2:1 globally [1], [5,27]. At least 1 in 5 new cases of HNSCC in the United Kingdom fall into the population aged 75 years or older. HNSCC incidence can also be impacted by socioeconomic status (SES), which encompasses household income, insurance status and the educational level. HNSCC patients with low SES face a risk of death within 5 years, which is three times higher than that of high SES patients [28].

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CLASSICAL IMAGING MODALITIES FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

It is pivotal to apply medical imaging techniques to better access HNSCC patients. Ultrasound, MRI, CT, and PET bring their specific advantages into the diagnosis, staging, treatment planning, and prognosis evaluation for HNSCC patients. This section will outline the principles, strengths, weaknesses, and applicable scenarios of these imaging tools.

Ultrasound

Ultrasound employs high-frequency sound waves to explore within tissues, converting acoustic wave properties into real-time grayscale images [29]. The advantages of ultrasound include easily access, economic expense, and devoid of radiation. Particularly, ultrasound offers excellent spatial resolution and clear visualization of small nodules like the vagus nerves, which is often challenging for CT or MRI [30]. Therefore, ultrasound is exceptionally well for thyroid cancer when imaging neck lumps, salivary gland lesions and lymph nodes [31]. It is often combined with fine-needle aspiration for cytology (FNAC) to enhance diagnostic accuracy in evaluating thyroid nodules [32]. Meanwhile, ultrasound is used to detect UP of the oropharyngeal tumor by visualization of anatomical features of tongue malignancy bases, which are usually difficult to be identified by other methods [33]. Ultrasound-guided surgery allows more precise resection of lesion margins and reduces the need for adjuvant radiotherapy [34]. On the other side, ultrasound has certain limitations. The quality of ultrasound imaging significantly relies on the operator's experience and technical proficiency. The image clarity and resolution can be reduced by constraints such as depth, experiencing attenuation and scattering when penetrating deep tissues.

Magnetic resonance imaging (MRI)

As a magnetic field-based imaging technology, MRI has been widely applied for HNSCC diagnosis with various parameters such as T1 relaxation time, T2 relaxation time and proton density. Compared to ultrasound, MRI provides superior soft tissue contrast for better visualization of tumor size, extent and the relationship with adjacent structures [35,36]. In particular, MRI plays unique roles in visualizing perineural invasion, extracapsular extension and muscle invasion [37]. Tumor and inflammation in laryngeal and hypopharyngeal HNSCC can be better distinguished by MRI analysis according to the signal intensity of T1 and T2 sequences [38]. The enhanced signals on T2-weighted MRI images help to distinguish chondroid neoplasms from invasive nasopharyngeal carcinoma [6]. MRI is friendly to pregnant women and children who are vulnerable to radiation. In addition, two functional MRIs have been developed to predict chemoradiotherapy outcomes for patients with advanced HNSCC [39]. High apparent diffusion coefficients (ADCs) of diffusion-weighted imaging (DWI) are associated with poor outcome in pre-treated HNSCC patients. Another indicator so referred to as Ktrans, generated by dynamic contrast-enhanced MRI (DCE-MRI), positively predicts outcome of the treatment [40].

Despite its' advantages, MRI scans require a longer scanning time compared to CT, and patients must remain still to ensure clear images, which may be troublesome for those who cannot tolerate prolonged scans. Additionally, MRI is not suitable for patients with metal implants, pacemakers, or claustrophobia. The high cost also poses a challenge for certain regions and patients.

Computed tomography (CT)

Based on X-ray and computational reconstruction techniques, CT is extensively used to obtain high-resolution cross-sectional images of head and neck region. The generated images provide accurate information about the size, shape and location of HNSCC. CT also helps to identify the number of adjacent LN and to determine the status of metastasis. These data contribute to clinical TNM staging of HNSCC as well as subsequent treatment options. Furthermore, CT scans can detect recurrence and metastases of HNSCC patients timely, contributing to early intervention and prognosis improvement [41]. To prevent that the regional LN is missed or faulty diagnosed, administration of intravenous (IV) is performed to better distinguish tissues with similar contrast and to determine lesions observed on the scan. Some side effects of IV have been found in HNSCC patients, such as anaphylaxis, renal dysfunction and extravasation [42]. The limitations of CT include potential exposure to ionizing radiation from X-rays, difficulties in visualizing soft tissues, and a lack of capability to assess functional information like blood flow [43,44].

Positron emission tomography (PET)

PET provides physiological, biochemical, and metabolic information by utilizing positron emission from radioactive isotopes. It is often combined with CT, especially for the locoregionally advanced disease, to identify distant metastases and second primary tumors (SPTs) [15,45]. These combined PET/CT images fuse metabolic and anatomical data, using 18F-FDG as a common tracer for the disease [46]. PET/CT has better accuracy in distant metastases screening at advanced HNSCC stages, compared to CT and MRI imaging [47,48]. Without PET/CT scans, 19.3% of patients would have been improperly staged or misdiagnosed for SPTs that are main causes of long-term mortality [49]-[51]. Moreover, early PET/CT scanning between 8 and 12 weeks after patients' chemoradiotherapies provides valuable predictive values for residual viable nodal disease [52,53], which can spare

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patients from unnecessary neck dissection. Whether 8-12 week is the optimal timing still needs more discussion for the PET/CT scan following the completion of therapy. One disadvantage of PET/CT could bring potential false-positive results due to the fact that 18F-FDG might be more uptaken by infections, inflammation or radiation therapy-induced ulcers [9], [54]. This will increase the patient's unnecessary anxiety as well as redundant tests. The high cost also poses a certain burden to the patients. The principles, advantages and disadvantages of these methods are presented in **Table 1**.

Table 1. Comparisons of various imaging techniques

Type	Principles	Techniques	Advantages	Disadvantages
	High-frequency sound waves	Ultrasound	Easily access Relatively inexpensive No radiation and safety Non-invasive approach Dynamic real-time images Shows soft tissues in great detail	Operator-dependent Limited tissue penetration Limited in imaging bone and air-filled structures
Traditional imaging modalities	Magnetic field Radio waves	MRI	Excellent soft tissue contrast Multiplanar imaging capability No radiation Non-invasive approach	Long scanning time High cost Contraindication (metal implants, pacemakers, claustrophobia)
	X-rays	CT	High-resolution cross-sectional images Fast scanning speed Wide availability	Ionizing radiation exposure Limited soft tissue contrast Limited in functional and metabolic information Potential for contrast agent allergies
	X-rays	PET/CT	Superior in cancer staging and detection Provides information on both function and structure	Ionizing radiation exposure Costly and not as widely available
	Radionuclide			Potential false-positive results High cost
	Data/analyse	Radiomics	Non-invasive process Comprehensively evaluate	Lack of clinical validation Poor reproducibility Lack of standardization Limited data
Emerging technologies	Two different energies of X-rays	DECT	Improved contrast agent effect Virtual non-contrast Quantitative assessment	Metal artifacts High cost
	Magnetic field	PET/MRI	Significantly reduced radiation exposure	Lack of protocol and standardization
	Radionuclide		Convenience of two scans in one	Limited flexibility
	Imaging fusion			High acquisition times of up to 60 min High cost

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FUTURE DIRECTIONS AND EMERGING TECHNOLOGIES

Beyond the established modalities like CT and MRI, there is a growing array of emerging technologies at the forefront of HNSCC diagnostic imaging. The most promising aspects are the integration of imaging techniques with artificial intelligence (AI), with current focal points involving whole slide imaging and radiomics. Additionally, multimodal collaborative diagnostic tools, such as PET/MRI, MRI/CT and SPECT/CT, have been developed to improve diagnosis. We'll highlight some of these technologies in this section.

Whole slide imaging (WSI)

The whole slide imaging (WSI) refers to digitalized scanning of conventional slides. Traditionally, pathological slides are read by light microscopy, which is usually slow, subjective and less reproducible. Instead, WSI generates more objective and reproducible digital datasets by digitization of pathological slides (so called "digital slides") using specialized hardware, with a combined AI-based analysis [55]. Many commercial WSI models are capable of processing up to 400 slides, which greatly reduce the analysis time. In this way, WSI is expected to automate pathology diagnosis and to better interpret parameters of the tumor microenvironment [56,57]. One barrier of WSI application is the large data space required for image acquisition (a typical 1,600 megapixel digital slide need about 4.6 GB of memory) as well as software processing abilities for those digital slides. Other limitations of WSI include image quality of conventional slides, inability of high-throughput scanning, pathologists' reluctance, etc. Most of these will be largely compensated by the integration of artificial intelligence/machine learning (AI/ML).

AI has been extremely developed within recent 2 decades, with the progression of supercomputational capability and fast data transportation. A well-known example could be "voice assistants", such as Siri, Alexa, and so on, who are able to recognize speech, complete voice commands, and communicate with humans. One great power of AI is its automated learning abilities, so called as machine learning (ML). ML is a feature of AI that effectively performs missions based on historical data and statistical algorithms without exact instructions. The high accuracy of ML has been validated in prediction of HNSCC prognosis as well as optimization of clinical decision-making, by integration of multi-modal data such as imaging, clinical data, genomic data, etc [58,59]. Therefore, AI/ML is now widely applied in otolaryngology-head and neck surgery for disease diagnosis, pathology detection and outcome prediction [60]. The scientific field of ML still faces certain potential challenges, such as black-box concern (models of opaque systems operation are not easy to access or interpret) and result or model interpretability [61]. In addition, AI/ML can be applied to many other imaging approaches such as radiomics.

Radiomics

Radiomics is a systematic imaging approach that extract detailed features by high-throughput data mining of a vast array of clinical images (including CT, MRI, and PET) combined with application of computational algorithms [62-64]. The employment of radiomics helps to distinguish HNSCC tissues from inflammatory or necrotic tissues and to comprehensively evaluate HNSCC information in depth, including HPV infection, tumor staging, metastasis, recurrence and survival [58,65-67]. These radiomic features can be better characterized by optimization of radiomics analysis as well as ML algorithms [68]. Due to variable location of primary tumors of HNSCC, the parameter of tumor location has been suggested to be considered in HNSCC radiomic research [69]. In addition, the combination of the quantitative data from radiomics analysis and genomic phenotypes (so called as radiogenomics) has also been developed to explore molecular expression in HNSCC [70,71].

Though radiomics can improve diagnosis, clinical decision-making and prognosis [62], the application is still constrained by many factors. For example, the difference between theory and clinical practice leads to the poor practicability of radiomics. Lack of standardization, technical deficiencies, and limited data often lead to poor reproducibility of radiomics [63,72]. Those limitations highlight the need for further improvement in radiomics.

Dual-energy computed tomography (DECT)

Dual-energy CT, also known as spectral CT, is a computed tomography that uses two separate X-ray photon energy spectra to generate accurate anatomical and functional photographs. Compared with single energy CT, DECT is more suitable for ML to improve the performance of computational image analysis and biomarker prediction models [73,74]. DECT image reconstructions with quantitative analyses better characterize tumor tissues from surrounding structures [75], contributing to accurate determination of tumor staging and surgical resection boundaries or radiation therapy approaches [76]. Practically, DECT uses the differences in spectral Hounsfield unit attenuation characteristics between non-ossified thyroid cartilage and tumors to identify thyroid cartilage invasion [77]. This is of significant importance for patients with hypopharyngeal and laryngeal squamous cell carcinoma, as it is related to organ (laryngeal) preservation and postoperative quality of patient lives [76,78]. DECT also has valuable advantages in lymph node differentiation [79], because it can clearly distinct among normal, inflammatory and metastatic neck lymph nodes of squamous cell carcinoma. As for the disadvantage of DECT, metal dentures and orthodontic appliances often cause artifacts that can obscure certain lesions and degrade image quality. To avoid it, reducing metal artifacts on DECT images should be considered, which can be realized by the combination of DECT with iterative reconstructions [80,81].

PET/MRI

PET/MRI scan is a hybrid technology that combines the functional PET imaging with the high-resolution structural imaging of MRI to produce a more detailed and comprehensive image of the internal body. Compared to PET/CT, PET/MRI offers superior diagnosis of lesions, invasion assessment and detection of lymph node metastasis [82,83]. PET/MRI demonstrates strong concordance with histopathological results of pre-treatment T staging [84], which refers to the original tumor size and extent. In addition, PET/MRI reduces radiation exposure by approximately 50% and exhibits higher HNSCC detection rates than PET/CT due to its improved soft tissue contrast. These would be more beneficial in adolescent and child patients [85]. The combination of functional MR Sequences (DWI or DCE-MRI) as previously mentioned with PET may help to distinguish between inflammatory and neoplastic lymph nodes [86]. The cost of PET/MRI may be more expensive than the individual approach, causing a significant financial burden for patients.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this minireview, we firstly summarized the common imaging methods utilized in HNSCC management. Ultrasound is the initial choice for thyroid cancer assessment. MRI excels in soft tissue contrast and tumor visualization, while CT is the primary tool for HNSCC evaluation, offering insights into tumor morphology, lymph nodes, and recurrence. Moreover, PET/CT is good for identifying distant metastases and second primary tumors, and has the best predictive value for residual lymph nodes at 8-12 weeks after chemoradiotherapy. Besides conventional imaging, the combination of multiple imaging modalities such as PET/MRI greatly improves HNSCC diagnosis with reduced radiation. The convergence of AI and imaging technologies has become a promising direction. Radiomics has been the focus of research in recent years.

The effectiveness of radiomics in predicting treatment outcomes and survival of HNSCC highlights the reliable feasibility of radiomics combined with more bioinformatic analyses or AI-based advanced algorithms. Additional analytical approaches, such as transcriptomics, proteomics and metabolomics, are expected to be applied with radiomics to gain new insights into the disease's pathogenesis. Because AI-based image data analysis is still not well developed for early diagnosis and medicine development, progresses have to be achieved in all aspects such as technology, database establishment and even privacy protection. Addressing these challenges will foster a deeper integration of clinical practice and AI, enhancing HNSCC management.

Author Contributions

Contributed to study concept and design, Shiyuan Hong; acquisition of the resources, Zhenyu Chen, Yuhang Lei and Jianlin Tang; drafting of the manuscript, Zhenyu Chen; critical revision of the manuscript, Zhenyu Chen; supervision Shiyuan Hong. All authors have read and agreed to the published version of the manuscript.

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Ethical Statement

Our study did not require further ethics committee approval as it did not involve animal or human clinical trials and was not unethical.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Simple Summary

This review delves into the latest advancements of imaging detection techniques for head and neck squamous cell carcinoma (HNSCC), a prevalent and life-threatening cancer. By exploring methods such as ultrasound, MRI, CT and PET scans, we aim to provide a clear understanding of their strengths and limitations in HNSCC diagnosis. Emerging technologies like radiomics and dual-energy CT are additionally introduced, which offer promising avenues for personalized and precision medicine. Through this comprehensive comparison, the review endeavors to contribute valuable insights to HNSCC detection, with an effort of disclosing future integration of clinical diagnosis with artificial intelligence that benefit the management of HNSCC patients.

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