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# Construction of A Screening Platform for the Dominant Population of Neoadjuvant Immunotherapy for Esophageal Cancer Based on Radiomics Technology and Tumour Immune Microenvironment

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**KEYWORDS** Biomarkers. Machine Learning. Patient Selection. Precision Medicine. Predictive Value of Tests. Treatment Outcome

**ABSTRACT** This review aimed to evaluate the potential of combining radiomics with tumour immune microenvironment assessment to identify patients with esophageal cancer who are most likely to benefit from neoadjuvant immunotherapy. Relevant literature on radiomics, immune biomarkers, and neoadjuvant treatment was reviewed and synthesised. Radiomics can extract quantitative imaging features that reflect tumour heterogeneity and may be associated with immune characteristics such as programmed death-ligand 1 expression and cluster of differentiation 8 (CD8)-positive tumour-infiltrating lymphocytes. Tumour immune microenvironment assessment provides biologically relevant information but is limited by invasiveness, sampling bias, cost, and technical complexity. Integrating noninvasive radiomic features with immune markers may improve patient stratification, treatment selection, and response prediction. However, evidence in esophageal cancer remains limited, and standardised multicentre validation is required before clinical implementation. This integrated strategy may support the development of a practical precision-medicine screening platform for neoadjuvant immunotherapy.

## INTRODUCTION

Esophageal cancer (EC) is one of the common malignant tumours of the digestive system with highly aggressive nature and poor prognosis, which is the eighth most prevalent tumour. The *China Health Statistics Yearbook 2022* showed that the mortality rate of EC ranked 4$^{th}$ among all malignant tumours and was higher in men than in women (4th vs. 6th) (National Health Commission of the People's Republic of China 2022), and that Chinese patients accounted for approximately 50 percent of newly diagnosed 500,000 EC patients each year worldwide, with up to 188,000 deaths (Zheng et al. 2019). Therefore, China is faced with a relatively heavy burden of EC.

Currently, the treatment options for EC include radical resection of EC, chemotherapy, radiotherapy, neoadjuvant therapy, neoadjuvant chemoradiotherapy (nCRT), and immunotherapy (Demarest and Chang 2021; Huang and Yu 2016), among which surgery is still the main treatment. Nevertheless, most patients are already at a locally advanced stage at the time of treatment due to the insidious onset of EC, so the surgical resection rate is low with poor treatment effectiveness and high risk of postoperative metastasis and recurrence. In recent years, neoadjuvant treatment modalities have been increasing in importance in the treatment of EC and are recommended by both the National Comprehensive Cancer Network and Chinese Society of Clinical Oncology guidelines, which believe that these modalities can increase the pathological complete remission (pCR) and long-term survival rates of EC patients (Yang et al. 2021). Neoadjuvant treatment mainly includes nCRT combined with sequential surgery. However, it has been reported that some patients may suffer from tumour recurrence and distant metastasis after nCRT, with high distant metastasis rates (Eyck et al. 2021; Yang et al. 2021). Accordingly, the function of traditional nCRT technology for locally advanced EC is relatively limited and its therapeutic efficiency is still debatable. Of note, the emergence of immuno-

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therapy provides a new idea for the treatment of EC. The addition of immunotherapy to nCRT is an early exploration of neoadjuvant immune combination therapy.

With advances in cancer immunotherapy, immune checkpoint inhibitors have become an important systemic treatment option for advanced or metastatic esophageal squamous cell carcinoma (ESCC). Their clinical efficacy has been demonstrated in the ATTRACTION-3 trial of nivolumab (Kato et al. 2019), the ESCORT trial of camrelizumab (Huang et al. 2020), and the KEYNOTE-181 trial of pembrolizumab (Kojima et al. 2020). These studies provided important evidence supporting immune checkpoint blockade in advanced or metastatic ESCC, although this treatment setting differs from the neoadjuvant setting considered in the present review. Multiple clinical phase II trials of neoadjuvant immunotherapy combined with chemotherapy in China were outlined in the Doctor of Philosophy (Ph.D.) dissertation of Li Jingpei (Li 2022), which showed relatively low rates of perioperative mortality and postoperative adverse events and higher pCR rates than those of neoadjuvant chemotherapy, although the reported pCR rates varied widely (18.8% to 39.2%) (Wang et al. 2021).

Unfortunately, neoadjuvant immunotherapy cannot benefit all EC patients and may lead to unnecessary treatment delays and even more serious disease progression. In this review, the term "dominant population" refers to the subgroup of patients with esophageal cancer who, based on their clinical characteristics, radiomic features, and tumour immune microenvironment profiles, are more likely to respond to and derive meaningful clinical benefit from neoadjuvant immunotherapy. To screen patients who can truly benefit from neoadjuvant immunotherapy, some investigators have used many techniques at multi-omics levels, including multiple immunofluorescence assay techniques and peripheral blood circulating tumour DNA (ctDNA) monitoring, for aided diagnosis and treatment (Li 2022), and the results have indicated that these techniques, although useful, are mostly invasive in their operation. For individual patients, pre-treatment imaging examination is essential, which is non-invasive and highly acceptable to patients. It is of significance to develop personalised and precise medical treatment through comprehensive evaluation and screening of sensitive patients suitable for neoadjuvant immunotherapy using existing imaging data, combined with tumour immune microenvironment (TIME) monitoring, which is the key to future medical development and also can become a cost-effective screening tool. More recent studies have extended this concept by directly applying radiomics and deep-learning approaches to predict pathological response to neoadjuvant chemoimmunotherapy in ESCC. Multicentre studies published in 2025 and 2026 have demonstrated that radiomics-based and radiomics–deep learning fusion models may provide non-invasive information for pretreatment patient stratification, further supporting the rationale for integrating imaging phenotypes with tumour biological characteristics (Chen et al. 2026; Zhu et al. 2025).

### Objectives

This review aims to evaluate the potential value of integrating radiomics with tumour immune microenvironment assessment to identify patients with esophageal cancer who are most likely to benefit from neoadjuvant immunotherapy. It also seeks to summarise the current evidence, identify the limitations of existing patient-selection approaches, and provide a rationale for developing a noninvasive precision-medicine screening platform.

## MATERIAL AND METHODS

### Literature Search and Review Approach

For this narrative review, relevant literature concerning radiomics, tumour immune microenvironment, immune biomarkers, and neoadjuvant immunotherapy in esophageal cancer was identified through targeted searches of PubMed, manual screening of the reference lists of relevant articles, and supplementary screening of previously identified relevant literature. Search terms included combinations of "esophageal cancer", "esophageal squamous cell carcinoma", "radiomics", "deep learning", "tumour immune microenvironment", "PD-L1", "CD8", "neoadjuvant immunotherapy", and "chemoimmunotherapy". Particular attention was paid to studies published in 2025 and 2026 during the final literature update. Relevant original studies, multicentre studies, clinical investigations, and key reviews were narratively synthesised with emphasis on predictive perfor-

mance, biological interpretation, clinical applicability, and methodological limitations.

## RESULTS

### Radiomics Technology

Traditional medical imaging is necessary for the diagnosis and treatment of EC but stores a large amount of complex information, which is difficult to be identified and utilised in daily X-ray, computerised tomography (CT) imaging, and magnetic resonance imaging (MRI). In this context, the concept of radiomics has emerged. The concept of radiomics was formally introduced by Lambin et al. in 2012 and was defined as the high-throughput extraction of quantitative features from medical images (Lambin et al. 2012). Kumar et al. (2012) further described radiomics as the high-throughput extraction and analysis of large numbers of quantitative imaging features from CT, MRI, and positron emission tomography (PET). After continuous exploration, radiomics forms a non-invasive imaging biomarker by acquiring morphological, semantic, and textural features of lesion areas in medical images, which extracts numerous features from multimodal images based on the machine learning method, converts conventional images into high-dimensional quantitative data that can be deeply mined, and then assists clinical diagnosis, treatment plan development, and prediction of treatment effect and prognosis by analysing feature parameters (Peng and Feng 2021). Different from the conventional diagnostic imaging method, radiomics can better characterise the heterogeneity and biological properties of the tumour itself (Gillies et al. 2016), which are key factors in determining the effectiveness of tumour treatment. Radiomics can extract relevant features of tumours, such as tightness, three-dimensional (3D) diameter, sphericity, and other basic morphology, by drawing regions of interest, and analyse texture by calculating texture features of lesion images to reflect tumour heterogeneity (Peng and Feng 2021; Xie et al. 2017). Overall, radiomics is the quantitative analysis of medical images to infer the various phenotypes of tumours (Hu et al. 2017).

Many studies have used radiomics to predict the risk or prognosis of diseases. For example, Yang (2022) used a multidimensional deep learning model to explore the predictive ability of CT-based radiomics for the risk of radioimmune-associated pneumonia in patients with non-small cell lung cancer (NSCLC). Wu (2022) used a multimodal model to probe the predictive capability of CT-based radiomics for the efficacy of immunotherapy in patients with advanced NSCLC. Pan (2021) utilised PET-based radiomics to predict the prognosis of patients with diffuse large B-cell lymphoma. Chen (2021) performed a predictive study of type II endometrial cancer with MRI and radiomics. Radiomics based on CT, PET/CT, and MRI have been applied in the field of EC and especially have yielded certain achievements in clinical staging, efficacy evaluation, and prognosis assessment (Peng and Feng 2021).

In practice, different imaging methods have different advantages in the diagnosis of EC, and the combined examination of multiple imaging methods is of great value for the precise treatment of patients with EC. Specifically, the detection rate of X-ray esophageal barium examination is higher than that of CT imaging for EC, but EC at the early stage is still poorly identified under X-ray. CT imaging can demonstrate infiltration of proximal esophageal tissues and distant organs but is not clearly advantageous for preoperative T staging of EC. Esophagus endoscopic ultrasonography has certain advantages over other imaging examinations in the detection of local tumour infiltration and regional lymph nodes in EC, but its role in the staging of early EC is controversial. PET/CT is useful for the diagnosis of advanced EC, and the new PET/MRI is relatively sensitive in the N staging of EC (Wu et al. 2022). In terms of radiomics, parameters of CT-based radiomics have high diagnostic efficacy in identifying lymph node metastases in EC. PET/CT-based radiomics helps to quantify the distribution of 18F-fluorodeoxyglucose (18F-FDG) within the tumour and is complementary to spatial image information, such as tumour volume, total lesion glycolysis, and tumour morphology, in the diagnosis and treatment of EC. A prior study unveiled that models constructed based on MRI features had excellent predictive power for preoperative lymph node metastasis in EC patients (Yang et al. 2022). In addition, radiomics is certainly valuable in assessing the preoperative clinical staging of EC patients. Compared to traditional imaging techniques, radiomics can improve diagnostic accuracy and allow for stratified prediction of patients (Jiang et al. 2022), which has the potential to

be a new method for predicting the extent of local tumour invasion, lymph node metastasis status, and tumour staging.

However, the feature parameters extracted by radiomics are often highly correlated, with a very large amount of data. Hence, selecting more accurate prediction parameters through dimensionality reduction is an important research direction. Additionally, the prediction accuracy of radiomics is directly related to feature screening and algorithm selection, suggesting that the selection of the most appropriate features and models is the breakthrough point to elevate the prediction effectiveness of radiomics. Artificial intelligence models, including logistic models, convolutional neural networks, support vector machine models, random forest algorithms, and least absolute shrinkage and selection operator (LASSO) regression, display superior predictive efficacy. Further comparison and research are warranted to select a suitable generalisable clinical model.

**Tumour Immune Microenvironment (TIME)**

Tumours at primary or metastatic sites include, in addition to cancer cells, different subpopulations of immune cells, which together constitute a suppressive local ecosystem of tumour microenvironment. In this ecosystem, the immune component of the tumour is called the TIME. TIME contains a variety of immune cells, immune molecules, and various stromal components that interact internally with each other, which usually represses tumour immunity and thus promotes tumour growth, metastasis, and the development of tumour drug resistance (Fu et al. 2021; Luker 2021). Accordingly, overcoming immunosuppression of the tumour microenvironment, that is, immune-targeted therapy, has emerged as one of the most promising complementary therapeutic modalities.

Immunotherapy for tumours refers to a form of cancer treatment that harnesses the patient's immune system to recognise and eliminate tumour cells by enhancing antitumour immune responses and counteracting tumour immune-evasion mechanisms. Programmed cell death protein 1 (PD-1) is an important immune checkpoint expressed on T cells. Its interaction with programmed death-ligand 1 (PD-L1) can inhibit T-cell activation and effector function, thereby contributing to tumour immune evasion (Juneja et al. 2017; Xiong et al. 2019). PD-1/PD-L1 inhibitors have become an important treatment option for advanced tumours and can restore or enhance antitumour T-cell responses by blocking inhibitory PD-1/PD-L1 signalling (Nishino et al. 2019). Immune checkpoint inhibitors have also demonstrated clinical activity in EC (Yang et al. 2020). Moreover, immune cells, including cluster of differentiation 4-positive (CD4+) T helper lymphocytes (Th), cluster of differentiation 8-positive (CD8+) cytotoxic T lymphocytes, and other tumour-infiltrating lymphocytes (TILs), play important roles in antitumour immunity and have been investigated as prognostic markers in EC (Liu et al. 2023). CD8+ TILs represent a major effector population in antitumour immunity, and their abundance may reflect pre-existing immune activity and be associated with the response to immunotherapy in EC (Han et al. 2020; Kuo et al. 2020). When pre-existing CD8+ T-cell infiltration is limited, responses to PD-1/PD-L1 blockade may also be attenuated, because tumour cells can suppress antigen-specific CD8+ T-cell activity through PD-L1/PD-1-mediated inhibitory signalling (Tumeh et al. 2014; Zhou 2021).

Therefore, the combination of PD-L1 expression and tumour-infiltrating cell status has the potential to serve as a predictive biomarker for EC patients (Yan et al. 2019). Comprehensive assessment of PD-L1 and $CD8^+$ TIL levels within tumours can better reflect the whole status of TIME and classify it into four types accordingly (Ock et al. 2016; Teng et al. 2015). The identification of TIME subgroups may improve patient stratification and contribute to the prediction of immunotherapy response and prognosis in EC. However, non-invasive selection methods are lacking in clinical practice so far. Zhou (2021) conducted a clinical trial on 18F-FDG PET/CT-based radiomics and NSCLC, which validated the correlation between radiomic features and immune markers and demonstrated the possibility that PET/CT-based radiomics could predict tumour immune phenotypes, providing preliminary clinical evidence for identifying a potentially dominant population for neoadjuvant immunotherapy through radiomics and immunology.

The interactions among components of the TIME, including immune cells, cytokines, and surface molecules, are closely associated with the development, progression, and metastasis of EC and may provide potential targets for immunotherapy (Liu et al. 2023). However, current studies have focused mainly on the relationship between im-

mune characteristics, treatment response, and prognosis, whereas relatively few studies have specifically addressed the identification of patients who are most likely to benefit from neoadjuvant immunotherapy. Meanwhile, emerging high-throughput and spatially resolved technologies, including probe-based in situ imaging, spatial transcriptomics, and proteomics, are increasingly being used to characterise the spatial organisation of the TIME and may help clarify its association with prognosis and immunotherapy response (Fu et al. 2021). Nevertheless, these approaches may increase the time and cost of pretreatment assessment, and some may involve invasive procedures. Therefore, non-invasive imaging approaches capable of reflecting selected immune characteristics may complement tissue-based assessment, facilitate patient stratification, and support more personalised treatment strategies in EC.

## DISCUSSION

### Correlation of Radiomics with Tumour Immune Microenvironment Features

Radiomic features are correlated with tumour microenvironment features including immune cells, long non-coding ribonucleic acids (RNAs), and methylation site types, implying a certain potential biological basis for radiomics such as MRI (Yu et al. 2021). For instance, 18F-FDG PET imaging can monitor the distribution of glucose to characterise the status of glucose metabolism in tumour tissues and tumour-associated immune cells, which illustrates the association of glucose metabolism with the expression of tumour immune markers (Kaira et al. 2018; Scharping and Delgoffe 2016). Moreover, different radiomic scores correspond to different immunophenotypes and immune cell compositions, indicating an association between radiomics and histopathology (Wang et al. 2022). A prior study elucidated good predictive performance of radiomic label scores and composite models for tumour microenvironment immune type I (TMIT-I) tumours (Zhou 2021). Although this finding was obtained based on NSCLC, it also provides a basis for predicting tumour immunity types in EC patients with radiomics.

The association between radiomic features and immune characteristics has also been examined in previous studies. For example, Feng et al. (2023) found that CT-based radiomics was associated with the prediction of humoral immunodeficiency. The research by Han et al. (2021) also unraveled that radiomics could be used to predict immune scores. Wen et al. (2020) extracted eight features from CT images to construct a radiomics model and combined them with clinical models to build a combined model, which elevated the predictive efficacy of identifying $CD8^+$ TIL expression. Yoon et al. (2020) observed that radiomics could identify T helper 2 (Th2) cell features in the immune system. Another study revealed that the combined PET/CT radiomics-clinical model might be a clinically practical method for noninvasive detection of the immune status of NSCLC (Tong et al. 2022). Although this evidence was derived from NSCLC, it supports the broader concept that radiomic features may serve as non-invasive surrogates for selected characteristics of the tumour immune microenvironment. However, evidence supporting this application specifically in EC remains limited.

Radiomics extracts quantitative features from medical images that are not readily appreciable by visual inspection and may capture aspects of underlying tumour heterogeneity and biology, including imaging characteristics associated with immune-cell infiltration and immune-related protein expression. In particular, PD-L1 expression and CD8+ TIL levels have been associated with several radiomic characteristics, including metabolic and texture features (Zhou 2021).

The study of Zhou (2021) on the PET/CT-based radiomics exhibited that gray-level run-length matrix long-run high gray-level emphasis (GLRLM_LRHGE) was the optimal texture feature for predicting PD-L1 expression and can reflect the association between regions with high PD-L1 expression and high metabolic distribution on PET images and that neighbourhood gray-level difference matrix contrast (NGLDM_Contrast) had a strong correlation with $CD8^+$ TILs. Taken together, these earlier studies suggest that radiomic characteristics may provide indirect information on components of the TIME; however, associations between imaging features and individual immune markers should not be interpreted as direct measurements of the immune microenvironment.

More recent evidence has moved the field from indirect associations with immune phenotypes towards direct prediction of response to neoadjuvant chemoimmunotherapy in ESCC. Zhu et al.

(2025) developed a multicentre model in 271 patients by combining sub-regional radiomics with deep-learning features and reported areas under the receiver operating characteristic curve ranging from 0.793 to 0.910 across different cohorts. Chen et al. (2026) subsequently evaluated 251 patients from two centres and showed that fusion of radiomic and deep-transfer-learning features achieved areas under the curve of 0.85 and 0.84 in the external testing cohort for two-dimensional and two-and-a-half-dimensional models, respectively. More recently, Yang et al. (2026) conducted a prospective multicentre study involving 215 patients and demonstrated that a combined intratumoral and peritumoral habitat-radiomics model achieved an area under the curve of 0.93 in the external test cohort. Compared with earlier evidence derived largely from other tumour types, these studies provide more direct support for the use of imaging-based phenotyping to stratify patients with ESCC before neoadjuvant chemoimmunotherapy (Chen et al. 2026; Yang et al. 2026; Zhu et al. 2025).

Nevertheless, imaging-based prediction should be interpreted in the context of the biological complexity of the TIME. Liu et al. (2025) integrated pathological images, CT radiomic features, and clinical information and obtained an area under the curve of 0.836 for PD-L1 prediction and 0.809 for immunotherapy-response prediction, suggesting that multimodal information may provide greater biological and clinical relevance than imaging features alone. At the cellular level, Wang et al. (2025) used single-cell RNA, T-cell receptor, and B-cell receptor sequencing to characterise the immune microenvironment during neoadjuvant immunochemotherapy. Their results linked treatment resistance to partial epithelial–mesenchymal-transition malignant cells, DES-positive myofibroblasts, FOLR2-positive macrophages, and terminally exhausted CD8-positive T cells, whereas RGS13-positive germinal-centre B cells were enriched in responders. These findings indicate that response to immunotherapy reflects interactions among multiple malignant, stromal, and immune-cell populations rather than being determined by PD-L1 expression or CD8-positive TILs alone (Liu et al. 2025; Wang et al. 2025).

Despite these advances, several barriers remain before such models can be incorporated into routine clinical decision-making. Many available studies are retrospective, and differences in imaging acquisition, tumour segmentation, radiomic feature extraction, machine-learning algorithms, treatment regimens, and definitions of pathological response limit direct comparison among models. Furthermore, most currently available cohorts consist predominantly of Chinese patients with ESCC, which may restrict generalisability to other populations and histological subtypes. The recent prospective multicentre evidence represents an important step forward, but additional independent and geographically diverse validation, methodological standardisation, model calibration, and prospective assessment of clinical utility are still required. Therefore, a clinically useful screening platform will probably need to integrate reproducible radiomic features with pathological, immune, and clinical variables rather than rely on radiomics or a single immune biomarker alone.

## CONCLUSION

Radiomics enables a noninvasive and comprehensive assessment of tumour heterogeneity, whereas tumour immune microenvironment features provide biologically relevant information regarding potential responses to immunotherapy. Integrating radiomic features with tumour immune microenvironment characteristics and other relevant clinical or pathological variables may improve the identification of patients with esophageal cancer who are most likely to benefit from neoadjuvant immunotherapy. Such a strategy may reduce unnecessary treatment, facilitate individualised therapeutic decision-making, and support the development of precision medicine. However, evidence regarding the combined application of radiomics and tumour immune microenvironment assessment in esophageal cancer remains limited, and a clinically validated screening platform has not yet been established.

## RECOMMENDATIONS

Future studies should develop standardised and reproducible models that integrate radiomic features, immune biomarkers, and relevant clinical characteristics. Prospective multicentre studies and independent external validation are required to evaluate model robustness, generalisability, and clinical utility. Further research should also focus on optimising image acquisition, feature extraction,

and patient-classification procedures and on assessing whether the proposed screening strategy can be effectively incorporated into routine clinical workflows. These efforts may facilitate the development of a practical, noninvasive platform for selecting patients for neoadjuvant immunotherapy.

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## AUTHOR CONTRIBUTIONS

Jue Yu contributed to the conception of the review, literature search and retrieval, organisation and interpretation of the relevant evidence, and preparation of the original manuscript. Zengwen Ma contributed to the study design, literature evaluation, synthesis of evidence concerning radiomics and the tumour immune microenvironment, and critical revision of the manuscript for important intellectual content. Xiaodong Du contributed to the conception and overall design of the review, supervision of the work, interpretation of the clinical implications, and critical review and final revision of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for the content of the work.

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