Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The authors attempted to assert the usefulness of LN diagnosis through MRI in metastatic esophageal cancer. But, according to the last paragraph, they are emphasizing the importance of LN CT over MRI subjected to esophageal cancer. 1. It is unclear what developments in MRI radiomics are being discussed. 2. There was unclear clinical evidence that MRI is superior to CT for diagnosing lymph nodes in esophageal cancer patients.

Answer:
1. It is unclear what developments in MRI radiomics are being discussed.

Development of MRI radiomics in tumor research

Although most of the current radiomic studies of ESCC are based on CT and PET, with the advancement of MRI techniques such as DWI, DCE-MRI, and IVIM, and the availability of high-quality imaging sequences such as the related StarVIBE and T2_BLADE, MRI has excellent soft-tissue resolution and is more conducive to the mutual discrimination between lesions, lymph nodes, and vascular structures. MRI findings such as the size, morphology, and shape of cancer foci are important for their identification in the study of tumor subtypes [52, 53]. In some studies, it has been found that some specific MRI sequences can better detect lesions and aid in treatment selection [53]. The ROI generated from MRI images can be analyzed by imaging histology to extract superior imaging features. These features can be combined with clinically relevant patient information to generate high-quality CDSS to guide treatment planning.
ROI analysis of the primary tumor lesion not only yields key information about the relevant pathology but also has value for the prognostic analysis of patient survival. Shin et al. applied an MRI radiomic model to assess the pathological remission response in rectal cancer patients receiving neoadjuvant radiotherapy and found that the diagnostic value was superior to visual assessment by an experienced radiologist [54]. Meanwhile, Li et al. extracted radiomic features from T2-weighted MRI images and combined them with clinical data for deep machine learning, which stably predicted the survival of glioma patients and helped to preoperatively assess the extent of macrophage infiltration in glioma tumors [55].

Although there is increasing interest in MRI radiomics in various areas of oncology across studies, most of the studies have focused almost exclusively on the histological and radiomic features associated with the primary tumor. It is well-known that histopathological data of the primary tumor, such as lymph-vascular invasion, histological grading, and tumor markers, are important factors used to guide or determine clinical treatment decisions. Meanwhile, when MRI radiomics is focused on the diagnosis of preoperative lymph node status, its high-quality diagnostic results can further guide treatment decisions in the clinical setting. In a study by Domiziana et al., they found 3T MRI radiomics combined with histological data could predict preoperative lymph node metastasis in breast cancer patients and guide treatment planning. The results suggest that accurate prediction of lymph node status can avoid invasive surgery, such as lymph node dissection or biopsy [56]. Similar conclusions were reached in studies on the prediction of preoperative lymph node status in breast cancer, suggesting that the influential features of MRI radiomics are important for the determination of lymph node status [57-59].

It is worth noting that while the image features derived solely from the ROI of cancer foci can be used to analyze the status of lymph nodes, the CDSS obtained from both the ROI of lymph nodes and cancer foci is more clinically valuable when combined for imaging histological analysis. In Li et al.'s study, they combined the ROIs of both primary colon cancer lesions and lymph node lesions for imaging histological analysis, and their findings were even more convincing because they required the analysis of both cancer lesion features and lymph node features in their derived nomogram features [60].

While various high-quality MRI sequences have been studied, the analysis of optimal imaging sequences is still rare. Qu et al. selected 9 radiographic features based on the T2-TSE-BLADE and Star-VIBE enhancement sequences in MRI images to create radiographic features that are significantly associated with LN metastasis in 181 patients with pathologically confirmed lymph node metastasis. They found that the model based on this sequence effectively distinguished between metastatic and non-metastatic lymph nodes [44].

It is important to note that MRI examinations typically have a long examination time, and tumors that originate in the chest may be affected by the patient's respiratory movements, making artifacts unavoidable. While imaging histology can help reduce the impact of artifacts, it may also be beneficial to minimize examination time and extract established imaging histological features from optimal sequences to improve CDSS quality.

In oncology patients, accurately diagnosing lymph node status is critical for determining appropriate treatment options. While existing MRI radiomics studies have demonstrated its effectiveness in determining lymph node status, studies targeting focal radiomic features that link tumor features with lymph node status remain relatively uncommon. Analyzing various MRI sequences to identify sequences that yield high-quality imaging histological features may be an important area for future research.

Radiomics has garnered significant attention from researchers worldwide for its non-invasive, quantitative, and low-cost approach in diagnosing tissue characteristics, tumor staging, and treatment response. The current focus of radiomics research for esophageal cancer is on evaluating patient response and survival prognosis after different treatments. While predicting preoperative lymph node status using radiomics remains relatively rare, the numerous studies exploring various aspects of radiomics in esophageal cancer offer optimism for future research into using radiomics more widely to evaluate lymph nodes.

2. There was unclear clinical evidence that MRI is superior to CT for diagnosing lymph nodes in esophageal cancer patients.

It is common to use CT scans as a non-invasive method to assess metastatic infiltration of esophageal cancer lymph nodes. In CT diagnosis, intra-thoracic lymph nodes with a short diameter greater than 10 mm are considered metastatic lymph nodes. However, some studies have demonstrated that only a small percentage of metastatic lymph nodes in esophageal cancer have a short diameter greater than 10 mm [33, 34].

Additionally, a related study found that although the sensitivity of CT was 59% in detecting lymph nodes larger than 10 mm in the conventional lymph node region of esophageal cancer, the diagnostic value of lymph nodes with metastasis was still not sufficient [35]. Measuring the long and short axis diameters of lymph nodes in each region of esophageal cancer in CT images and calculating the axis ratio can improve the sensitivity of CT detection of lymph node metastasis in esophageal cancer. However, the sensitivity, specificity and accuracy of this approach are still insufficient to provide high-quality clinical decision support systems [36].

Recently, the StarVIBE sequence on MRI has been utilized in cases where patients are unable to hold their breath and has gradually been incorporated into studies on esophageal cancer [43,12]. Qu et al conducted a study where MRI was shown to better predict lymph node status in patients with preoperative esophageal cancer by extracting the region of interest (ROI) of esophageal cancer lesions [44]. This method demonstrated significantly improved diagnostic accuracy over CT and could facilitate better treatment planning for esophageal cancer. Therefore, MRI shows promise in aiding lymph node assessment in esophageal cancer patients, particularly when CT scans yield inconclusive results. Nevertheless, more research is required to confirm its effectiveness in clinical practice.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: It would be great to talk about radiomics pipeline, with overview of the various steps involved. The majority of references cited in the review were published before 2018, with a few exceptions. Need more recent citations. The review does not address the numerous potential pitfalls associated with the radiomic approach. These pitfalls include a lack of standardization and robustness of the descriptors, overfitting of methods when many variables are considered, insufficient validation in external cohorts or confirmatory studies, and the use of small patient cohorts.

Answer:

1.talk about radiomics pipeline, with overview of the various steps involved
Delineating the region of interest (ROI) or volume of interest (VOI) is a critical first step in any radiomics method. However, manual and semi-automatic segmentation methods often introduce observer bias and can be time-consuming. Moreover, the reproducibility and stability of radiomics features can be affected by inter- and intra-observer variation in ROI/VOI delineation. Therefore, studies using manual or semi-automatic segmentation with manual correction should evaluate the internal and external reproducibility of derived radiomics features. To ensure the reproducibility of results, it is also advisable to exclude irreproducible features from further analysis. Automating the segmentation process using deep learning techniques has also shown promise in improving the reproducibility and efficiency of ROI/VOI delineation in radiomics studies.
The second step in image processing is a crucial intermediary step between image segmentation and

feature extraction. Its aim is to standardize the images for radiomics feature extraction in terms of pixel spacing, grayscale intensities, and binning of the gray histogram, among other factors. The reliability of test-retest of the extracted radiomics features is dependent on the image processing settings used in this step. Therefore, it is essential to carefully select and optimize the image processing settings to ensure the robustness and reproducibility of radiomics features. Additionally, the pyRadiomics package, which is one of the most widely used packages for radiomics analysis, enables various image processing steps to be defined through a parameter file in YAML or JSON structured text format. This file can then be loaded into 3D Slicer or integrated into a Python framework to facilitate feature calculation.

After image segmentation and processing, the third step of radiomics feature extraction can finally be performed. Feature extraction involves the calculation of feature descriptors to quantify the gray-level features within the ROI/VOI. As many ways and formulas exist to calculate these features, it is recommended to follow the Image Biomarker Standardization Initiative (IBSI) guidelines [47].

The Image Biomarker Standardization Initiative (IBSI) guidelines provide a consensus for standardized feature calculations from a matrix of all radiomics features. Different types (i.e., matrices) of radiomics features exist, the most common being intensity-based (histogram) features, shape features, texture features, transform-based features, and radial features. In addition, different types of filters (e.g., wavelet or Gaussian filters) are usually applied in the feature extraction step. After feature selection/deviation is performed, subsequent statistical analysis and machine learning will be used to identify the important features that support image analysis. Dimensionality reduction is a multi-step process to exclude irreducible, redundant, and irrelevant features from the dataset. The first step involves excluding non-replicated features, as a feature that is subject to high intra- or inter-observer variability may be less likely to be useful. The second step is to select the most relevant variables for the corresponding task. Various methods that often rely on machine learning techniques can be used for this initial feature selection step, such as elimination filters, recursive feature elimination methods, or random forest algorithms. As these algorithms are often unable to account for covariance and correlation in the data, constructing correlation clusters is the logical next step in the dimensionality reduction workflow. In some cases, this step may be combined with the previous (second) step, as few machine learning techniques can handle correlations in the data. Correlation clustering allows the visualization of highly correlated features in the data and the selection of only one representative feature per correlation cluster.

The variable with the highest bio-clinical variability in the dataset should be selected, as it is likely to be the most representative of the variation within a given patient population. Once the dimensionality of the data has been reduced, the importance of the data visualization step increases. Therefore, reducing the number of features used to build statistical and machine learning models through a step called feature selection or dimensionality reduction is critical to generating valid and generalizable results. The last remaining, uncorrelated, and highly correlated features can be used to train models for the corresponding classification tasks, and the constructed radiomics models are evaluated according to the radiomics quality score (RQS). These key steps are the basis for ensuring that the imaging histology produces high-quality CDSS.

2.address the numerous potential pitfalls associated with the radiomic approach

It is important to note that while radiomics analysis can be performed on medical images from different modalities, integrating cross-modality approaches using the potential information extracted from MRI, CT, and PET can provide added value compared to evaluating each modality separately. However, the level of research sophistication still shows low stability and generalization ability, and specific study conditions and author selection still have a strong influence on the results. In addition, most radiomics studies are based on retrospective data, resulting in a low level of evidence, which requires prospective studies for validation in external cohorts or confirmatory studies, as well as using larger patient cohorts.

To increase the likelihood of clinically relevant and valuable radiographic studies, it is essential to ensure that the imaging histology study is of high quality, addresses actual clinical needs, and can be clinically implemented. Obtaining all relevant non-imaging data, such as demographics and bioinformatics, is also critical. Standardizing the acquired images before performing imaging omics analysis is essential to minimize the impact of different settings on modeling. Implementing these key steps can lead to valuable CDSS formation.

However, with the precise determination of lymph node status by various MRI techniques and the high-quality CDSS provided by radiomics findings, we believe that the combination of MRI techniques and radiomics studies in esophageal cancer lymph nodes may introduce new quantitative imaging markers in medical imaging. This may lead to significant breakthroughs in clinical studies, enabling preoperative personalized clinical characterization and precise treatment planning of esophageal cancer.