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Progress of Imaging Histology in the Diagnosis and TNM Staging of Gastric Cancer

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Abstract

Gastric cancer is one of the most common malignant tumours with complex dynamic heterogeneity and aggressiveness, and the information that can be evaluated by traditional imaging is limited and subjective. With the development of machine learning, radiomics can combine medical imaging with genomics and proteomics to discover latent information, a feature that makes it a beneficial aid to assist physicians in clinical decision making and is used in all areas of gastric cancer diagnosis and treatment. In this paper, we describe the workflow of radiomics and the research progress in gastric cancer diagnosis.

Keywords

Gastric Cancer, Radiomics, Diagnosis, Staging

1. Introduction

Gastric cancer (GC) is one of the most common cancers in the world, ranking fifth in global incidence and fourth in mortality, with more than one million new cases and about seventy-seven million deaths in 2020, according to statistics [1]. There are no obvious clinical symptoms in the early stage of gastric cancer, and when the patient develops symptoms related to gastric cancer, such as weight loss, indigestion, vomiting and anaemia, the disease is often in the middle or late stage and is difficult to be cured [2]. Currently, the auxiliary tests that can detect gastric cancer include CT, MRI, PET/CT, ultrasound, and so on. Computed tomography (CT) is the first choice for gastric cancer, and the overall diagnostic accuracy for T-stage is between 77.1% and 88.9%, but the differentiation between T3 and T4 stages is poor, and there is a lack of consensus diagnostic standard [3] [4]; Endoscopic ultrasound (EUS) is suitable for identifying early gastric

cancer with an overall T-staging accuracy of 75% and a Kappa value of 0.52, but high-frequency ultrasound has a limited depth of penetration, and studies on total T-staging in the West and in Asia have reported a wide variation in accuracy (41% - 92.1%) [5] [6] [7] [8] [9]. Positron emission tomography/computed tomography (PET/CT) can be used to complete staging by detecting the involved lymph nodes or metastases [10], but its application needs to take into account its histological features, and hypodifferentiated indolent tumors often do not show abnormalities on imaging [11]. Although traditional imaging techniques are advancing, they are still limited to the subjective diagnostic assessment of the superficial layers of images, while the emerging imaging histology can utilize the deep image features that are difficult to capture by the naked eye and collaboratively analyze multidimensional information, which can provide an efficient adjunct to clinical precision medicine and deepen the decision support system in many aspects such as staging, T-staging, lymph node metastasis and occult peritoneal metastasis prediction of gastric cancer. In this paper, we review the methodological process of imaging histology and the research progress in gastric cancer.

2. Overview of Imaging Histology and Workflow

1) Overview of imaging histology

Radiomics is an emerging technique that was introduced by Gillies *et al.* [12] in 2010 and further refined by Lambin *et al.* [13] in 2012. The term "Radiomics" means "the extraction of quantitative features from medical images" and emphasizes the systematic and holistic character of the study. The development of radiomics is based on the hypothesis that tumor imaging features reflect underlying molecular gene expression patterns, and the development and application of bioinformatics methods to develop and apply bioinformatics approaches to the imaging features and genomic data, as a result of the multiple nonlinear interactions of tumors at the genetic, transcriptional, protein, metabolic, and physiological-anatomical levels, and the spatial and temporal heterogeneity generated by such complex dynamic systems that make subsequent targeted treatment extremely difficult. Combining imaging features with genomic data for research. It was also referred to as "imaging genomics" in the early days because the original purpose was to mine imaging data to detect correlations with genomic patterns. In addition to research in the field of basic research, as an innovative decision support tool with CAD system as the cornerstone [14] in the direction of image analysis [15], it can extend from a single explicit definitive judgment to hypothesis testing, explore high-throughput latent features in biomedical images, convert high-dimensional data for mining pathophysiological information [16], and help clinics to assist in differential diagnosis of diseases.

2) Imaging histology workflow

a) Medical image acquisition:

Effective images should provide a complete overview of the region of interest while ensuring as much clarity as possible to improve the accuracy of subsequent

data analysis. While radiological images such as CT, PET/CT and MRI are modal acquisitions, ultrasound images are difficult to normalize due to the need to tailor gain and depth [17], which led Nicolaides to create a standardization method for ultrasound images. G M Biasi *et al.* showed that such standards, developed by analyzing images, can be applied to images of different regions of interest [18] with high inter- and intra-observer reproducibility [19]. It has also been demonstrated that differences in ultrasound equipment do not affect the overall results of imaging histology analysis, but there are no specific studies that have assessed the variability of radiomic features according to equipment type and machine settings [20].

b) Region of interest (ROI) division:

ROI segmentation determines which region will be analyzed further to extract data. Due to the blurred boundary of some tumors and the influence of attenuation, scatter and shadow in CT images, there is some controversy about the variability of ROI segmentation and the lack of relevant norms for tumor segmentation, and the academic community has not yet reached a consensus on the necessity of exploring the realism of boundary segmentation [21] [22] [23], so it is generally believed that the higher the reproducibility of image segmentation, the more reliable the results. ROI outlining mainly includes manual, semi-automatic and automatic segmentation methods. Manual segmentation is the most widely used method with the highest accuracy, but there are disadvantages such as low segmentation efficiency, high subjective variation and difficulty in handling large databases [24] [25] [26] [27]. Automatic and semi-automatic segmentation has been gradually developed to reduce the labor cost and improve the repeatability of tumor segmentation. It has been demonstrated that fully automatic segmentation based on random forest algorithm can be applied to images of different patients [28], but it is more difficult to identify lesions that are inhomogeneous and have little contrast with surrounding structures, and the current algorithm is not comprehensive enough to generalize. Semi-automatic segmentation combines the advantages and disadvantages of both by performing contour pattern search by region analysis followed by manual correction [29]. With the advancement of technology, the accuracy of semi-automatic and automatic contouring has gradually improved and is expected to become the mainstream in the future.

c) Feature extraction:

Extracting high-throughput features from the region of interest is the core of the concept of "radiomics", and currently the most used software includes 3D slicer and python-pyradiomics component, etc. The extracted features are the core of the concept of "radiomics". The extracted imaging features can be generally classified into "semantic features" and "agnostic features" [23]. "Semantic features" are features assessed subjectively using imaging vocabulary that can be combined with mRNA levels extracted from tumors to predict specific gene expression features [30], and "agnostic features" are quantitative features extracted

by mathematical algorithms, which can be subdivided into first-order, second-order and higher-order features. First-order features do not consider spatial relationships and only describe the distribution of signal intensity values of each voxel; second-order features describe the relationship between various contrasting voxels and are often summarized as texture features, which can objectively assess tumor heterogeneity by methods such as texture analysis (TA) grayscale co-occurrence matrix; higher-order features can be obtained by applying mathematical transformations or filters such as fractal analysis, Fourier transform, wavelet transform, etc. to the image to explore deeper latent information. The application of mathematical transformations or filters such as fractal analysis, fourier transform, wavelet transform, etc. can obtain higher-order features to explore deeper latent information [31] [32] [33] [34].

d) Feature screening and model building:

A large number of highly correlated features extracted are at risk of overfitting, and irrelevant features and redundant features need to be removed to reduce the effect of covariance [35] [36]. The filtering, packing and embedding methods are commonly used for feature selection [37]. The filtering method scores features according to their relevance and sets a threshold for filtering, e.g., minimum redundancy maximal relevance (mRMR); the packing method selects or excludes features according to their prediction effectiveness score. The filtering and packing methods do not involve model building, while the embedding method involves simultaneous feature selection and model building, as in the case of the most widely used LASSO regression in imaging [38]. In the part of model construction, it can be divided into supervised, unsupervised and semi-supervised learning according to whether labels are used. When supervised learning samples and sample label matching mappings appear, explicit label output is required [39], including deep neural network [40], random forest, logistic regression [41] and so on; unsupervised learning directly mining the original information. It is generally used for dimensionality reduction or clustering processing; semi-supervised learning guides unlabeled data with labeled data [42], which improves the disadvantages of supervised learning such as time-consuming, expensive, small amount of specimens and poor accuracy of unsupervised learning.

e) Evaluation and validation of the model:

The performance of predictive models is measured by different evaluation metrics [43]. Commonly used evaluation metrics are subject operating characteristic (ROC) curve analysis, calibration curves and decision curves (DCA), which can assess the accuracy, sensitivity and specificity of the model, measure the degree of agreement and clinical utility between real clinical outcomes and model predictions, and assist in clinical decision making [44] [45]. In terms of validation, leave-one-out cross-validation (LOOCV) is used to avoid the problem of internal data overfitting in internal validation and to judge the "generalization" ability of the model relatively objectively [46] [47] [48].

3. The Application of Imaging Histology in the Diagnosis and Treatment of Gastric Cancer

1) Application in the staging of gastric cancer

The Lauren classification system and the World Health Organization (WHO) classification system are the dominant histologic classification methods for gastric cancer. The Lauren classification of gastric cancer includes intestinal, diffuse and mixed types. Diffuse GC requires more resection and has a poor prognosis, while neoadjuvant chemotherapy (NAC) treatment is only sensitive to intestinal gastric cancer and has a relatively good prognosis. [49], preoperative precise identification of gastric cancer types facilitates decision-making and prognostic assessment. Gastroscopic biopsy is its gold standard, but the false-negative rate is high, and the concordance rate of Lauren's classification between biopsy and surgical samples is only 64.7%, so it is urgent to establish a diagnostic model with higher accuracy. In a study related to the differentiation of intestinal and diffuse gastric cancer, Wang [50] *et al.* compared three single-phase CT imaging histological models (arterial phase (AP), portal phase (PP) and delay phase (DP) with clinical models, and found that the imaging histological models were better than the clinical models, and the PP and DP models DING [51] *et al.* then took 539 PP images alone to compare the models located in the tumor and peri-tumor ROI areas and concluded that the peripheral ring model performed worse than the tumor model. The highest AUC values (0.75 - 0.90) were obtained for the imaging histology nomogram in both studies, showing good predictive performance and usefulness in clinical practice as a quality tool for individualized noninvasive prediction of Lauren's classification.

According to the WHO classification system, poorly differentiated gastric cancer includes hypofractionated adenocarcinoma, mucinous adenocarcinoma and signet-ring cell carcinoma (SRCC), and differentiated gastric cancer includes papillary adenocarcinoma and highly/medium differentiated tubular adenocarcinoma. The risk of lymph node metastasis is higher in poorly differentiated gastric cancer, and this factor is more influential in the selection of targeted neoadjuvant chemotherapy, and the determination of its type is useful in predicting lymph node metastasis to assist in clinical planning. In the field of CT-based imaging, investigators such as Xu [52] and Huang [53] have improved the predictive confidence by creating a nomogram combining selected features and CA125 to provide individual quantitative probabilities. Imaging histology of dual-energy spectral computed tomography (DESCT)-derived iodine-based material decomposition (IMD) images has also shown good performance, and SHI [54] *et al.* have developed imaging histology models for conventional multicolor (CP) images, iodine-based MD (IMD) images, and combined CP-IMD-clinical model to predict histological typing, and observed that the combined model outperformed other models in predicting the type of histological differentiation of GC with an AUC value of 0.912.

At the intersection of the two classification models, all WHO SRCC were classified as Lauren fusion type, but SRCC and non-SRCC in patients with fusion

gastric cancer actually have different biological behaviors [55], Chen [56] *et al.* retrospectively analyzed the CT images of 693 patients with gastric cancer. SVM model (Lauren Imagomics model) was established to identify fused GC, and another SVM model and SRCC normogram integrating image score and clinicopathological features were used to identify SRCC from fused GC. Nomogram has a higher AUC value (0.889) and accuracy than SVM model, and can be used as an effective preoperative identification method to guide preoperative clinical decision making.

2) Application in T-staging

Currently, the clinical staging of gastric cancer is mainly based on the American joint committee on cancer (AJCC) 8th edition [57]. Different stages of gastric cancer have different optimal treatment modalities, and accurate imaging staging of gastric cancer is an essential step in precision medicine and an important factor in assessing prognosis [58]. Various studies have demonstrated that imaging histology has higher accuracy than conventional imaging in distinguishing the depth of invasion of different tumor stages. In identifying T2 and T3/4 gastric cancer, Wang [59] analyzed AP and PP images of 244 patients with pathologically confirmed gastric cancer and used a random forest approach to build a classifier model, showing that the performance of the imaging histology model was better than the subjective score, and the accuracy of the AP model (75.3% - 84.1%) was slightly better than that of the PP model. While the distinguishing point between T3 and T4a is plasma membrane invasion, some recent studies found that spleen features and changes are highly correlated with the progression of gastric cancer staging, Pan [60] *et al.* established a gastric cancer serosal invasion prediction model based on the imaging tumor invasion score by identifying the imaging features of spleen, and the results showed that the accuracy index of the model was 0.884 for the differentiation between high-risk and low-risk groups, which was highly feasible in clinical application. At the same time, studies have shown that the nomogram combined with features extracted from the deep convolutional neural network can also achieve the same high accuracy (0.80 - 0.85) and the best calibration of the overall risk [61], effectively identifying the degree of serosal invasion of gastric cancer. pT4b in cT4 has a poor response to treatment, and to achieve R0 resection often requires extended radical gastrectomy or multi-organ resection with poor prognosis. Liu *et al.* [62] conducted a multicenter retrospective analysis of 704 gastric cancer patients with cT4 stage to evaluate the prediction potential of pT4b and patients without pT4b. The accuracy of Nomogram combined with clinical characteristics and rad score (0.812) was higher than that of clinical model (0.739), and the AUC value was 0.893. It is the best model among all prediction models, and has great clinical significance for the treatment of patients with stage cT4 gastric cancer.

3) Application in N-Staging

For early gastric cancer, surgery is its main treatment method, but it is just difficult to avoid the existence of many sequelae. If minimally invasive procedures such as endoscopic submucosal dissection and endoscopic mucosal resec-

tion can be chosen, the quality of life of patients can be improved, but endoscopic resection should only be used for tumorigenic lesions with low risk of lymph node metastasis. The standard treatment for advanced gastric cancer is radical gastrectomy plus lymph node dissection, but there has been a debate on the extent of lymph node dissection, and the applicability of its adjuvant treatment such as concurrent neoadjuvant chemotherapy is also related to the patient's LNM status [63]. Sentinel lymph node (SLN) biopsy is a powerful way to assess lymph node metastasis (LNM) in patients with gastric cancer, but its false-negative rate and safety are still controversial. In contrast, the accuracy of such noninvasive tests as conventional imaging examinations to assess LN staging is low, among which the accuracy of ultrasound endoscopy is 64% and that of CT is 61% - 64% [63] [64]. Radiomic features were found to be a robust and independent predictor of lymph node metastasis in gastric cancer. the imaging histological model based on ct by Wang *et al.* showed excellent discriminatory ability and improved the diagnostic accuracy of lymph node metastasis to 80% - 84%, which was better than conventional CT, but the model could only discriminate the negativity of lymph nodes and could not predict their detailed staging (N1-N3b) and anatomical location [65]. Sun *et al.*, on the other hand, were the first to combine radiomic features with clinically important factors in multivariate analysis, using deep learning of CT imaging histology nomograms in order to predict lymph node metastasis at each site. Decision curve analysis showed that the net benefit of columnar line graphs was superior to clinicopathologic features and could be a strong predictor of LNM status. No. 10 was the only site with poor predictive efficacy in this model [63]. Wang *et al.* then further constructed a venous ct-based radiomic column line plot for metastasis of No. 10 LNs in advanced proximal gastric cancer, and demonstrated for the first time that radiographic features (Rad-score) had good predictive power for pathological No. 10 LNs status with an AUC of 0.742 - 0.866 [65]. Previous studies were mostly for advanced gastric cancer, while GANG *et al.* established the first CT imaging histological model for predicting lymph node metastasis in early gastric cancer with an AUC of 0.89 - 0.91, which had good calibration and discrimination ability and performed significantly better than conventional contrast-enhanced CT [64]. LNM was present in 8.2% - 19.7% of early gastric cancers, with the highest incidence at station No. 3. Wang *et al.* by integrating No. 3 metastasis lymph node and primary tumor radiomic features, developed and validated a radiomic columnar map to predict preoperative LNM in patients with T1-2 gastric cancer, which showed an AUC 0.915 - 0.905 and a decision curve indicating its value for clinical application [66]. Unlike CECT imaging, 18F-fluorodeoxyglucose positron emission tomography-ct (18F-FDG-PET) reflects glucose metabolism in tumors, can detect disease in unenlarged lymph nodes, and may have higher specificity. Xue *et al.* developed and validated a binary prediction model based on 18FFDGPET/CT to predict preoperative LNMs (AUC = 82.2%), which showed superior performance in identifying LNMs and even detected some LNMs that were missing in conventional examinations, in-

dicating its potential to complement 18F-FDG PET/CT and optimize diagnostic performance. However, this study focused only on identifying the presence of LNMs and lacked judgment on the location of n-stage (N0 and N1-N3b) and metastatic lymph nodes [67].

4) Application in peritoneal transfer

Primary peritoneal metastasis (PM) occurs mainly in stage T4 and is associated with Lauren's staging, Borrmann's type, tumor location and size, ascites and serum tumor biomarkers, and is an independent influence on the prognosis of gastric cancer patients. The gold standard for its diagnosis is laparoscopy, but some patients cannot tolerate such invasive examinations, and the non-invasive CT diagnosis suffers from low sensitivity (28.3% - 50.9%) [68], which requires the development of diagnostic modalities with higher sensitivity and accuracy. Giorgio [69] and Liu [70] have both shown that large tumors have a higher risk of occult PM, with the difference that Giorgio suggested that high-gray voxel lesions distributed in a long homogeneous direction are more correlated with PM, while Liu suggested that the more heterogeneous the gray distribution, the greater the potential for peritoneal metastasis, the greater the potential for peritoneal metastasis. Huang [71] *et al.* analyzed 955 pT4 CT images and integrated cT, cN staging and four texture features to build an imaging histology nomogram with good predictive performance in the internal and external validation cohorts with auc of 0.870 and 0.815, respectively, which can fully reflect the disease status. Wang [72] *et al.* also developed a clinical model containing Lauren's typing, Borrmann type clinical model, and with specificity higher than 90%, the overall predictive value of the imaging histology model for primary peritoneal metastasis was higher than the clinical model, and the sensitivity could reach 82.1%, which was higher than the value of the study reported by Liu [70], and the effect of selecting different clinical markers on the performance of the clinical model needs further study.

DECT can quantify different densities in mixed materials by obtaining two different energy levels. Chen [73] compared the R IU model based on IU images, the R MIX model based on traditional CT mixed images and the combined image omics model, and the R IU model (AUC: 0.981) The prediction performance of PM is significantly better than other models, and the image omics based on iodine images has more possibilities than traditional methods. The sensitivity of PET/CT to detect PM is higher than that of CT, and the imaging omics based on PET/CT images also shows a similar trend. Xue [74] extracted the imaging features and metabolic parameters data from the preoperative 18F-FDG-PET images of 355 patients and compared it with the Ct-based model. PET/CT imaging has the best performance (AUC: 0.89) and has a higher predictive value than CT.

4. Conclusions

Imaging histology has high predictive value for lesions, and has the advantages of non-invasive, accurate, high sensitivity and reproducibility. It can analyze and evaluate the imaging images in multiple dimensions based on traditional imag-

ing examinations, and shows excellent predictive ability in the differential diagnosis of gastric tumors and gastric cancer staging. The current studies have the following problems: 1) There is no consensus standard for segmentation of ROI zones of tumors with blurred boundaries. 2) Most of the studies are single-center retrospective studies with limited sample size and lack of external validation. 3) Few imaging studies have so far included different ethnic groups, and future expansion of the database may lead to changes in model accuracy. 4) 3D images can contain more information than 2D images, 3D images provide higher dimensional detail and also depict surface information around the tumour [75], but studies based on 3D images are still relatively few. 5) Ultrasound-based studies in the field of gastric cancer imaging histology are currently scarce and need to be explored.

Prospective, multi-ethnic, multi-center, and multi-image examination methods for large-scale data information collection, standardized image preprocessing, generalization verification and application of automatic segmentation algorithms, and further feature analysis based on deep learning and neural networks may become important directions for gastric cancer imaging research. Imaging omics has the potential to reduce clinicians' subjective errors and assist clinical decision-making. It is expected to be widely used in future clinical diagnosis and treatment.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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