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The Value of Multiple Imaging Methods in Primary Gastric Lymphoma

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Abstract

Primary gastric lymphoma (PGL) is the most common type of extranodal lymphoma that originates from the lymphatic tissue within the gastric submucosa. In the past two decades, the treatment of PGL has been overturned from surgery to non-surgical individualized treatment, and its treatment and prognosis are different from those of other malignant lesions in the stomach, so early diagnosis, accurate staging, and timely monitoring of outcome are extremely important. Unlike intra-nodal lymphoma, PGL can be evaluated by endoscopy, endoscopic ultrasound and gastric ultrasound, in addition to conventional imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT), which are specific to the gastrointestinal tract. This article introduces the application of various imaging modalities in the management of primary gastric lymphoma.

Keywords

Primary Gastric Lymphoma, Endoscopy, CT, PET/CT, Ultrasound

1. Introduction

Primary gastric lymphoma (PGL), the most common extra-lymph node lymphoma, is a malignant tumor originating in the intramucosal lymphatic tissue of the stomach with a low incidence, accounting for only 5% of primary gastric tumors [1]. Most PGLs are non-Hodgkin lymphoma (NHL), accounting for 30% - 40% of all NHL and 60% - 70% of the primary gastrointestinal lymphoma, Hodgkin's lymphoma with a primary origin in the stomach is rare [2]. PGL usually originates from B lymphocytes, but T cell origin is rare. The main histologic type is diffuse large B-cell lymphoma (DLBCL) and mucosa-associated

lymphoid tissue (MALT) lymphoma, while other types of lymphoma are rare [3] [4]. In recent years, due to the development of diagnostic techniques, the incidence of PGL has been on the rise significantly. 5 However, its insidious onset and lack of specificity in early gastrointestinal symptoms and endoscopic manifestations make it difficult to distinguish from other digestive tract diseases, and easy to be missed and misdiagnosed [5] [6].

The traditional view that surgery is the primary means of curing PGL has been challenged by the increased understanding of helicobacter pylori (HP)infection and the pathogenesis of the disease, as well as by the increasing research on PGL treatment. Studies have shown that the occurrence of PGL, especially gastric MALT lymphoma, is closely related to HP infection and that HP eradication is effective in the treatment of gastric lymphoma [7] [8]. The remission rate of early gastric MALT lymphoma after HP eradication therapy alone is as high as about 80%, making HP eradication therapy the treatment of choice for early MALT lymphoma, and for some DLBCL, the remission rate of HP eradication therapy can also reach 50% [9] [10]. Meanwhile, numerous studies have proved that conservative therapy for PGLs can achieve the same or better results than surgical treatment [11] [12]. In addition surgical treatment of PGL increases the incidence of recent complications such as perioperative bleeding, perforation and obstruction and late postoperative complications such as malabsorption syndrome, marginal ulcers and alkaline reflux gastritis, resulting in a serious decline in the quality of survival of patients undergoing PGL surgery [13]. PGL treatment has now shifted from a surgical focus to multimodality including HP eradication therapy, radiotherapy, chemotherapy and immunotherapy comprehensive treatment [14]. Surgical treatment is only used for serious complications such as uncontrollable bleeding and perforation of the gastrointestinal tract [15].

PGLs are a highly heterogeneous group of diseases with widely varying treatment efficacy across different histological types and disease stages, and do not currently form a uniform treatment pattern [16]. Therefore, the evaluation of the efficacy using various imaging techniques during treatment is important for timely adjustment of treatment options, improving patient survival, and early detection of recurrence. Not identical to lymph node lymphoma, in addition to imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) that are routinely used for efficacy assessment, PGL can be monitored by gastrointestinal specific imaging methods such as endoscopy, endoscopic ultrasound and gastric filling ultrasound. This article will review the application of various imaging techniques in gastric lymphoma.

2. Clinical Characteristics of PGL

PGL tends to occur in people over 50 years old. The incidence rate of men is 2 - 3 times that of women [17]. PGL more often involves the gastric antrum and body [18]. Many studies have described potential risk factors related to the pa-

thogenesis of PGL, including infection with Helicobacter pylori, HIV, Epstein-Barr virus, and hepatitis B virus [19] [20] [21] [22]. The initial symptoms of PGL often lack specificity, similar to gastritis, peptic ulcer disease, or gastric dysfunction. 55% - 60% of patients may have no significant physical examination abnormalities [23]. The most common symptoms are abdominal pain, nausea, vomiting, abdominal distension, and indigestion. Symptoms such as gastrointestinal bleeding, perforation, or intestinal obstruction are not common [24]. These nonspecific symptoms lead to delayed diagnosis, which may be delayed for several years in some cases. High levels of lactate dehydrogenase (LDH) and b-2 microglobulin have been reported to be associated with poor prognosis. In addition, the expression of some molecules and genes, such as cyclooxygenase-2 (COX-2), *MYC*, *Bcl-2* and *Bcl-6*, may affect the prognosis of PGL [25] [26].

3. Endoscopy

Endoscopy combined with biopsy is the gold standard for the diagnosis of PGL [27]. Endoscopy itself cannot identify or distinguish between gastric lymphoma and more common gastric cancer, often displaying nonspecific gastritis or peptic ulcer, with uncommon mass lesions, including mucosal edema, fragility, patchy redness, irregular patchy gray or white particles, contact bleeding, superficial irregular erosion, and ulcers [28] [29]. Although these findings are not specific to PGL, endoscopy can initially diagnose and obtain multiple gastric biopsy specimens for subsequent diagnosis. Biopsy specimens should undergo histological, immunohistochemical, and genetic examinations to make a diagnosis. In addition, it is necessary to detect the presence of helicobacter pylori in the tissue samples obtained. Due to the multifocal distribution of PGL lesions and the infiltration of submucosa, it is difficult to identify the lesions by conventional endoscopic examination alone. Multiple and multipoint biopsies, as well as multiple sampling methods such as massive biopsy, snare biopsy, and tunnel biopsy, are required to improve the accuracy of PGL diagnosis [30].

Endoscopic ultrasound (EUS) can clearly display the hierarchical structure of the gastric wall on the image, thereby displaying the depth, scope, nature, and surrounding lymph node involvement of the lesion. It is a valuable technique for assessing the extent and aggressiveness of the lesion, making up for the shortcomings of gastroscopy. At the same time, it is superior to CT scanning in detecting false negative cases [31]. Endoscopic ultrasound guided fine needle aspiration (EUS FNA) not only improves the diagnostic efficiency of endoscopic biopsy, but also has a wide puncture range and low requirements for lesion size. It also reduces the risk of perforation and bleeding caused by deep excavation biopsy, with high safety [32] [33]. Effective staging is crucial for the selection of PGL treatment options and even for the evaluation of prognosis. EUS has a high sensitivity for detecting lymph node metastasis and thickening of gastric mucosa and wall, so it is one of the best tools for the partial stage of PGL [34]. In addition, new ultrasound techniques such as elastography and contrast-enhanced ul-

trasound can also improve the accuracy of N staging [35] [36]. However, in the follow-up after treatment, EUS has certain limitations, that is, EUS often overestimates residual lesions and cannot distinguish between tumor infiltration and inflammatory response after treatment [37].

The development of endoscopic technology provides a new means for the diagnosis of PGL. Enlarged endoscopy and narrow band imaging (NBI) technology can clearly display the microscopic structures and microvessels of gastric mucosa, which is helpful for disease diagnosis and guiding targeted biopsy. Secondly, the disappearance of abnormal blood vessels in the combination of magnifying endoscopy and NBI technology can also be used to evaluate the efficacy in later follow-up, even taking precedence over the biopsy results [38] [39]. Confocal endoscopy (CLE) is an in vivo histological technique that can achieve the effect of optical biopsy, avoiding the complications of repeated endoscopic examinations and multiple biopsies. It has shown great advantages in the diagnosis and differential diagnosis of gastric lymphoma and can be used as an alternative to conventional biopsy [40] [41]. The ultra high magnification function of cell endoscopy can observe tumors at the cellular level, just like in vivo pathological examination of tumors, achieving real-time observation of living tissue structures similar to in vitro microscopy. This technology is expected to replace biopsy pathology to reduce the damage and risk of biopsy [42].

4. CT and MRI

CT is a commonly used technique in the diagnosis and treatment of PGL, which helps to clearly diagnose and determine the extent of the lesion. It is often manifested as significant thickening of the gastric wall, extensive lateral infiltration of tumors along the submucosa (*i.e.*, along the gastric wall), and sometimes the affected gastric wall includes most of the stomach. Although such extensive gastric wall involvement, gastric outlet obstruction, or perigastric fat invasion are not common in PGL, Extensive retroperitoneal and local lymph node enlargement can often be seen [43]. CT can assess adjacent structures, lymph node involvement, and localized stages, but its value in diagnosing lymphoma with mild gastric wall thickening or limited to the mucosa is limited [44]. With the development of new technologies, imageomics and texture analysis based on CT images improves the differential diagnostic value of CT by quantifying the imageomics and texture features of tumors that cannot be distinguished by the human eye, and is expected to provide beneficial means for clinical auxiliary diagnosis [45] [46].

MRI can also be used to evaluate PGL. Relevant imaging features include irregular thickening of mucosal folds, irregular submucosal infiltration, annular stenosis, exogenous tumor growth, mesenteric masses, and mesenteric/retroperitoneal lymphadenopathy [47]. Compared to conventional MRI techniques, Diffusion Weighted Imaging (DWI) is increasingly used for abdominal imaging. DWI is a non radiative whole-body MRI technique that can indirectly and quantitatively assess cell density based on limitations on the movement of water in the extra-

cellular space compressed by surrounding tumor cells. Therefore, DWI is considered a highly sensitive technique capable of assessing cell death [48]. The changes in DWI images and apparent diffusion coefficient (ADC) values in tumor areas reflect information such as tissue structure and organ functional status, which can not only provide evidence for the diagnosis of diseases earlier, but also be used for monitoring the efficacy after treatment [49] [50].

5. PET/CT and PET/MRI

18F fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in the diagnosis, staging, and efficacy evaluation of PGL [51]. However, in MALT lymphoma, due to its inert behavior and disease, small tumor volume FDG-PET may exhibit false negative results [52]. Therefore, new promising PET tracers, such as 18F-fluorothymidine (18 f-flt) and 68Ga-Pentixafor (68 Ga), may be significantly beneficial for the diagnosis and evaluation of PGL [53-58]. At the same time, PET/CT can also more accurately detect the recurrence of lymphoma after treatment. For some patients who cannot be clearly diagnosed by structural imaging, functional PET imaging may provide some important diagnostic information [59].

Positron emission tomography/magnetic resonance imaging (PET/MRI) scanning may improve the evaluation of MALT lymphoma through the combination of PET and DWI. Some studies have shown that the performance of PET/MRI is not weaker than that of PET/CT, and in terms of radiation dose, the radiation dose of PET/MRI is much lower than that of PET/CT [60] [61]. However, at present, PET/MRI has not been widely used. On the one hand, due to the long examination time, PET/MRI scanning time is usually 2-3 times that of PET/CT; On the other hand, PET/MRI has a significantly higher cost in scanner acquisition and maintenance [62].

6. Ultrasound

Based on the fact that intraluminal gas is a major obstacle to gastrointestinal visualization, traditional transabdominal ultrasound is not suitable for evaluating the gastrointestinal tract [63] [64]. However, transabdominal ultrasound using oral contrast agents can not only empty the gas in the stomach, but also create a uniform high echo background in the gastric cavity, clearly depicting the 5-layer structure of the gastric wall, thereby optimizing morphological evaluation, while also ensuring sufficient intragastric residence time for detailed examination [65] [66] [67]. Currently, oral contrast agent ultrasound has been widely used in the detection of gastrointestinal diseases in China. Some studies have demonstrated the efficacy of oral contrast agents in evaluating digestive system diseases [68] [69]. In addition, research has shown that for elderly or children, due to poor tolerance to gastroscopy and many contraindications, the use of gastroscopy is limited, and transabdominal ultrasound with oral contrast agents has comparable diagnostic capabilities to gastroscopy, which can be an effective means of di-

agnosis [70].

The application of contrast-enhanced ultrasound in solid organs such as the liver, kidney, and spleen has been widely used and recognized in many countries [71] [72] [73]. Dual contrast ultrasound combines oral and intravenous contrast agents to improve diagnostic performance. It provides a promising tool for distinguishing between benign and malignant lesions based on different enhancement characteristics and quantitative perfusion parameters of the lesions. Many early studies have demonstrated a positive correlation between tumor microvessel density and tumor invasion in malignant tumors [74] [75]. The positive correlation between tumor focal enhancement intensity and microvessel density has also been confirmed by research, and dual contrast ultrasound is expected to become a new noninvasive, convenient, and repeatable method for evaluating tumor neovascularization, thereby evaluating tumor angiogenesis and invasion in vivo [76] [77]. Moreover, studies have shown that contrast-enhanced ultrasound can effectively evaluate the early treatment response of patients with hepatocellular carcinoma and gastrointestinal stromal tumors after treatment with angiogenesis inhibitors [72] [73]. Therefore, contrast-enhanced ultrasound can predict tumor response to treatment early based on microvascular changes before morphological changes [78].

7. Summary

Most patients with primary gastric lymphoma do not require surgery and differ significantly from other gastric malignancies in terms of treatment options and prognosis. Therefore, it is still a topic of interest for researchers to provide more optimal diagnosis and treatment for patients with various imaging techniques. To summarize the full text, the characteristics of various imaging techniques are shown in Table 1. Most of the previous studies were on the use of a particular

Table 1. A comparison of the advantages and disadvantages of various imaging techniques.

Imaging Technology	Strengths	weaknesses
Endoscopy	Biopsy is the gold standard for diagnosis, Endoscopy can visually observe the lesions and take biopsies.	When the lesion grows in the submucosa, it is prone to false negatives, leading to missed diagnosis.
Endoscopic ultrasound	It can improve the accuracy of biopsy, and is the preferred method for local stage, which can be used for follow-up evaluation	Residual lesions are often overestimated in follow-up and in determining recurrence
CT	Evaluates not only gastric lesions but also perigastric lymph nodes and adjacent tissue and organ involvement	CT is usually unable to display lymphoma confined to the mucosa
MRI	Disease diagnosis and efficacy evaluation can be conducted through structural and functional information provided by DWI	Not suitable for patients with metal implants and claustrophobia
PET/CT	Combining the advantages of morphological and functional imaging, it is widely used in the diagnosis, staging, efficacy evaluation, and recurrence detection.	MALT lymphoma may exhibit false negative results, while physiological uptake and inflammation may exhibit false positive results

Continued

PET/MRI	Not inferior to PET/CT performance and far lower radiation levels than PET/CT	Failure to widely apply due to long inspection time and high use and maintenance costs
Transabdominal ultrasound	It is a convenient, non-invasive, radiation free diagnostic method and a reasonable method for patients who require continuous monitoring, especially for patients who are not suitable for endoscopic ultrasound, such as the elderly	The value of transabdominal ultrasound for gastric lymphoma is still not clear enough because there are few domestic and international studies.

imaging technique in gastric lymphoma. This article reviews the characteristics and shortcomings of various imaging techniques in order to improve clinical understanding of the various examination modalities and to facilitate combining the advantages of various imaging methods to make the best choice when used for different clinical purposes.

In future studies, further research and analysis should be conducted on the application of new techniques such as ultrasound endoscopy combined with elastography and ultrasonography in primary gastric lymphoma and the development and testing of new tracers for PET/CT. In addition, transabdominal ultrasound with a combination of oral and intravenous contrast agents can show both morphological and microperfusion features of the lesion, which has potential value in the diagnosis and evaluation of the efficacy of gastric lymphoma.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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