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Neuroendocrine Tumors of the Gallbladder: Clinical Features, Diagnosis and Treatment

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Abstract

Aim and Background: The unique heterogeneous tumor originating from the neuroendocrine cells and the peptide-capable neurons is defined as the Gallbladder Neuroendocrine Neoplasm (GB-NEN). GB-NEN accounts for only 0.5% of all Neuroendocrine Tumors (NETs) and 2.1% of all gallbladder tumors. The aim of this study is to present an up-to-date review of clinical features, diagnosis, and treatment of neuroendocrine tumors of the gallbladder.

Methods: A systematic literature search was performed using leading medical journal citation databases (including PubMed, Wiley Online Library and Springer Link Science) in order to identify all pertinent studies published.

Results: At present, the pathogenesis of GB-NEN is not clear, and furthermore, the typical clinical manifestations are lacking specificity, particularly as seen in the laboratory examinations. Additionally, the imaging examination provides difficulty in distinguishing GB-NEN from other gallbladder diseases. Even though treatment, like chemo radiotherapy helps to prolong progression-free survival, surgery is the best option. Since the disease is rarely seen in clinical practice, only a few studies are available for review.

Conclusion: GB-NEN is a relatively rare gallbladder lesion and is often reported as a case study. Therefore, early detection, correct diagnosis and reasonable treatment of such tumors will aid in prolonging the quality of life of patients.

Keywords: Neuroendocrine tumor; Gallbladder; Pathological classification; Clinical features; Diagnosis

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Abbreviations

GB-NEN: Gall Bladder Neuro Endocrine Neoplasm; NETs: Neuroendocrine Tumors; NEN: Neuroendocrine Neoplasm; SEER: Surveillance Epidemiology and End Result; EGFR: Epidermal Growth Factor Receptor; VEGF: Vascular Endothelial Growth Factor; NET: Neuroendocrine Tumor; NEC: Neuroendocrine Carcinoma; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ERC: Endoscopic Retrograde Cholangiography; NSE: Neuron-Specific Enolase; Syn: Synapse Protein; CHG-A: Pheochromin-A; PGP 9.5: Protein Gene Product 9.5; 5-HIAA: 5-Hydroxyindole-Acetic Acid; VEGF-R: Vascular Endothelial Growth Factor Receptor; PDGF-R: Platelet-Derived Growth Factor Receptor; RCT: Randomized Control Trial; SSTR: Somatostatin Receptor; MSKCC: Sloan/Kettering Memorial Cancer Research Center

Introduction

Neuroendocrine and gastrointestinal neuroendocrine cells originate from the ectoderm neural crest and the endoderm, respectively. These cells possess biochemical functions such as uptake of amine precursors and decarboxylation, secretion of bioactive peptide hormones and nerve mediators. The diffuse endocrine system provides the distribution hub of human neuroendocrine cells. Neuroendocrine Neoplasm (NEN) is a type of heterogeneous neoplasm that originates from neuroendocrine cells and peptidergic neurons. It is a type of diffuse neuroendocrine cell tumor and originates from neural crest Kulchisky cells (silver-addicted cells) [1]. NEN was first reported and identified as a carcinoid by Oberndorfer in 1907. To date, there are relatively few testes on GB-NEN. Patients reported gallbladder occupation such as gallbladder polyps and gallbladder stones, ultimately leading to clinical misdiagnosis. The occurrence of the GB-NEN disease is very low and hence the etiology, pathogenesis, standard treatment plan and prognosis of this type of tumor lacks

the multi-center research data support generated from large sample sizes. As there is no unified standard for identification and treatment, the author has performed a systematic review of the current clinical characteristics, diagnosis and treatment progress of GB-NEN to provide a better understanding.

GB-NEN: Epidemiology

The incidence of NEN is 115/100,000 and relatively rare in clinical practice [2]. Therefore, NEN accounts for only 1.25% of all malignant tumors, whereas the gastrointestinal tract presents the highest tumor prevalence, accounting for 66% of cases. The prevalence follows a pattern in the gastrointestinal tract of high to low from the appendix, to the small intestine, rectum, and finally the colon. However, the occurrence of NEN is very rare in the stomach and other regions of the gastrointestinal system. The organ with the next highest prevalence of NEN, in terms of area, is the lung with 31% [3]. Other organs seen to be affected are the ovaries, pancreas, and testicles, yet the occurrence noted in the liver and gallbladder is extremely rare [4]. Among the many gastrointestinal carcinoid, extrahepatic biliary carcinoid account for only 0.5% to 2.0% while liver metastases remain common [5,6]. Surveillance Epidemiology and End Result (SEER) research data indicates that GB-NEN accounts for only 0.5% of all NETs and 2.1% of all gallbladder tumors [7]. There are a few reports available regarding GB-NEN and even fewer on Cholecysto neuroendocrine carcinoma. From the data complied, there were three groups of large data reported that included two groups from Korea with 6 and 12 cases, respectively. The third group was from China with 10 cases [8,9]. Additionally, several pieces of literature found in China represent detailed case reports.

GB-NEN: Cause

In an effort to define the root cause of GB-NEN, investigation of the cellular nature of the disease is important. The presence of neuroendocrine cells on the gallbladder mucosa remains minimal, if any exist in this space [10-12]. Identifying their etiology may be as follows: (1) those undifferentiated gallbladder stem cells separate into neuroendocrine cells; (2) the gallbladder stones result in chronic inflammation of the gallbladder mucosa leading to pathological metaplasia, namely intestinal epithelium or gastric metaplasia. At a later stage, this inflammation produces neuroendocrine cells at the lesion site, and eventually GB-NEN; (3) there are certain circumstances under which the gallbladder adenocarcinoma changes to take on neuroendocrine functionality, resulting in chronic inflammation of gallbladder stones, as well as the gallbladder tissue, further increasing the risk factor for gallbladder adenocarcinoma [13-15].

GB-NEN: Molecular Mechanism

Despite the limited understanding with regard to the pathogenesis of GB-NEN, significant progress has been made in the area of those important pathways of NEN, both at the molecular and biological level. Results of this progress establish the foundation and generate the need for follow-up studies of new diagnostic and treatment strategies for the disease. For instance, as confirmed in two foreign studies, activation of the Epidermal Growth Factor Receptor (EGFR) up-regulates the expression of a downstream effector molecule, protein kinase B and extracellular signal-regulated kinase. Simultaneously, the target protein of rapamycin in human cells regulates the growth, proliferation and motor activity of the cells. The expression levels of this protein and the proliferation index of the cells are positively correlated. High expression of the above three molecules results in a poor prognosis of disease [16,17]. Scoazec18 described that angiogenesis plays an important role in the NEN pathogenesis. Due to the high expression of NEN in the Vascular Endothelial Growth Factor (VEGF) and its receptor, it is possible to inhibit the VEGF expression, thereby treating NEN and prolonging the survival period. Sun Hongze explained that death domain related proteins affect the prognosis by targeting telomerase activity and chromosome stability. However, there is no specific mechanism available to provide technically sound evidence.

GB-NEN: Pathological Classification

Classifying the types of GB-NEN distinguishes three pathological types including carcinoid or typical carcinoid (low malignancy), atypical carcinoid (moderate malignancy) and small cell carcinoma (high malignancy). These classifications are primarily based on the histopathological structure, cell morphology and degree of differentiation, in combination with mitotic, necrotic and biological behavior. Morphologically, most of the neuroendocrine tumor (NET) cells are small, cone-shaped, and polygonal with no clear cell boundaries [19]. While, cell granular chromatin has small nucleoli, tumor cell morphology is relatively consistent, and rich in interstitial blood vessels [20]. The well-differentiated NETs include G1 and G2, yet the poorly differentiated NET (G3) is defined as a Neuroendocrine Carcinoma (NEC). The NEC is further classified based on the tumor cell size as either large or small. G1 contains both the NEC and adenocarcinoma tumors and therefore identified as a mixed gland neuroendocrine carcinoma. The extrahepatic bile ducts and the ampulla region remain more common in a GB-NEC representing high malignancy, poor prognosis and little to no pathological differentiation. The occurrence of early metastasis is mainly identified through the local infiltration and lymph node metastasis. Lymph node, liver, lung, and peritoneum are the most common metastasis sites of small cells GB-NEC. American cancer institute research data reported the statistics of 41 cases of gallbladder NEC of pathological grade from 1973 to 2005. The data demonstrated that the pathological grade had high, medium and low/no differentiation accounting for 2.4%, 7.3%, and 89.7%, respectively [7]. Adenocarcinoma was the most common histological finding in gallbladder malignancy, followed by undifferentiated carcinoma, and squamous cell carcinoma/ squamous adenocarcinoma all accounting for 80 to 90%, 10%, and 5% of cases, respectively. Overall, the occurrence of NEC is extremely rare. The analysis carried out by Han Yue included a total of 1,898 cases of gallbladder carcinoma. The following distribution among the 1,898 cases was reported as such: adenocarcinoma (1764/1898, 92.9%), squamous cell carcinoma (76/1898, 4.0%), adenosquamous carcinoma (17/1898, 0.9%), adenoma malignant transformation (32/1898, 1.7%), inflammatory malignant transformation (3/1898, 0.2%), malignant polyp malignant transformation (4/1898, 0.2%), malignant lymphoma (1/1898, 0.05%), and carcinoid carcinoma (1/1898, 0.05%).

GB-NEN: Clinical Manifestations

According to case reports, the occurrence of GB-NEN is higher among women, accounting for approximately 68% of cases identified. The age of onset is 60 years on average, and the majority of these patients do not have any manifestations of carcinoid syndrome. This case data is consistent with that stated in the literature through reports that gallbladder and extrahepatic bile duct NEC is a non-functional APUD tumor, with low or no function of endocrine particles in the tumor cells. However, early clinical manifestations,

other types of gallbladder cancer, abdominal distension pain, nausea, and other non-specific symptoms are more common. In order to distinguish from GB-NEC, symptoms specific to carcinoid syndrome include spasmodic abdominal pain, flushing, edema, wheezing, diarrhea, right heart valve disease, etc yet account for only 1.0% of those symptoms reported with NEC [13]. There are few studies that suggest NEC may be related to the entry of active hormones into the systemic circulation, as well as the absence of neuroendocrine cells in the normal gallbladder [21].

GB-NEN: Diagnosis

The diagnosis of GB-NEN before the surgical operation remains difficult. Currently, tumor markers and imaging examinations such as ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are commonly employed. Limitations in the current techniques hinder proper diagnosis. For instance, tumor markers that include CA19-9, CEA and CA125 are often negative. Ultrasound examination detects only the thickening of gallbladder walls, gallbladder swelling type lesions and a low echoic nodule (Figure 1). CT and MRI examination showed impressions indicating that GB-NEN typically presents a thickening of the cystic wall on one side, with the mass protruding into or out of the cavity (Figure 2). These scans also indicate the visible necrotic shadow in the larger lesion. In studies examining the results of CT and MRI scans, it was noted that after development, the lesion continued to strengthen in development over that of an adenocarcinoma [22]. Endoscopic Retrograde Cholangiography (ERC) revealed the defect of the tumor in the gallbladder (Figure 3). However, the presence of lymph node metastasis around the gallbladder and retroperitoneum is difficult to distinguish from the other gallbladder tumors. The imaging examination provides significant results only when detected at an early stage and provides evidence to aid in establishing a treatment plan. Diagnostic comparisons suggest immunohistochemical staining as the most effective tool. Immunohistochemistry is divided into two parts. First, neuroendocrine cell markers, such as Neuron-Specific Enolase (NSE), Synapse Protein (Syn), Pheochromin-A (CHG-A), IEU-7, Protein Gene Product 9.5 (PGP 9.5) and Rankine, are positive. The second is amines and amine hormones, such as adrenocorticotropic hormone, growth hormone, human chorionic gonadotropin, 5-hydroxytryptamine, vasoactive polypeptide, insulin, gastrin, somatostatin, pancreatic polypeptide, calcitonin, etc, can simultaneously express a variety of other hormones. Among all of them, the CHG-A, Syn and NSE have been reported to have the highest specificity [23]. Studies have shown that CHG-A is a substance released by secretory particles in neuroendocrine cells to represent its secretory characteristics. Evidence demonstrated that the serum CHG-A level in 60% to 80% of patients with NEC of the digestive system was higher than normal [24]. Therefore, the serum CHG-A test has the highest significance in the diagnosis of GB-NEN. Monier et al., [25] further suggested that the urine detection of 5-hydroxyindole-acetic acid (5-HIAA) can aid in the diagnosis of GB-NEN, however the positive rate reads low due to the insufficiency or non-secretion of 5-HIAA in some patients.

GB-NEN: Differential Diagnosis

Examination of patients presenting with GB-NEN symptoms and markers can identify differential disorders such as cholestasis, gallbladder polyp, gallbladder adenomyosis, and gallbladder adenoma. Apart from the pathological immunohistochemical examinations, the contrast-enhanced ultrasonography also has certain differential significance. Case reports described that during contrast-enhanced ultrasonography, biliary sludge was not enhanced. The gallbladder polyp, however, was enhanced with grape-like fine pedicle and ultimately, the three-layer structure of gallbladder wall was clear. The entire angiography of gallbladder adenomyosis did not show any enhanced cystic echo and confirmed that the gallbladder intima and serosa were intact. Gallbladder adenoma resulted in delayed enhancement which is identifiable by "fast in and slow out" through the complete three-layer structure of gallbladder wall. Thus, contrast-enhanced ultrasonography can improve the appearance of gallbladder carcinoma and facilitate early differential diagnosis.

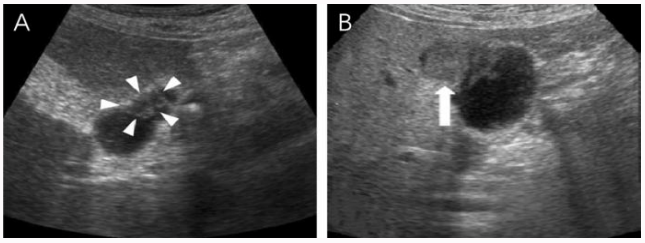
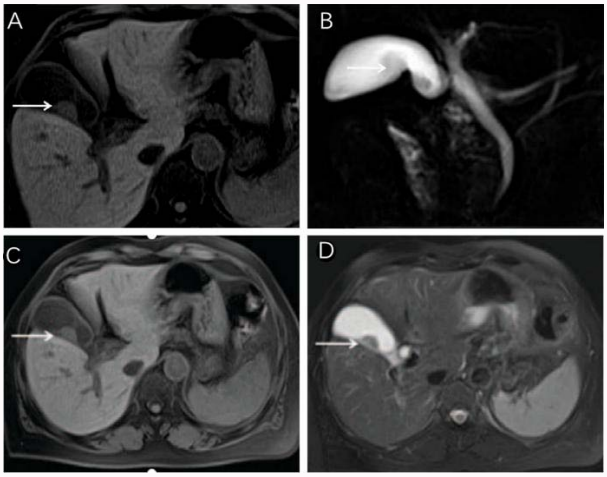


Figure 1: (A). Ultrasonography image shows a 0.8 cm low echoic nodule (arrowheads) in the neck of the gallbladder. (B). Ultrasonography image identifies a low echoic mass of 39 mm × 30 mm with clear boundaries to the liver from the fundus of the gallbladder (arrowheads).



Figures 2: (A-D) MRI image of gallbladder. The arrowheads depict a mass in the gallbladder. The arrow markings the broad base of GB-NET and the intact gallbladder wall.

GB-NEN: Treatment Options

Surgical treatment

Due to the complexity, gallbladder cancer must be treated surgically by experienced biliary tract physicians and pathologists. GB-NEC is characterized by extremely high malignancy, early lymphatic metastasis (the N2 lymph node metastasis rate is significantly higher, compared to the adenocarcinoma patients of the same period, $P<0.05$), and poor prognosis, when compared to all other types of gallbladder cancer. Radical resection is considered the most effective and preferred method for GB-NEC [26]. The purpose of a radical resection is to remove lesions, confirm a clear diagnosis, provide a basis for postoperative comprehensive treatment, and improve the quality of life. Surgical methods include simple, radical, and expanded radical cholecystectomy, whereby the choice of surgical type is often discussed between the medical professional and patient. The progress

made in recent years to expand the time period under which radical resection can be performed, including R0 resection for GB-NEC, has increased the overall long-term survival of patients. With these promising results, it is only expected that the expansion of the radical prostatectomy also should be attempted. Only under situations where the tumor invades the mucosa, submucosa or muscular is for GB-NET, is simple cholecystectomy feasible. In the case of late stage occurrence without distant metastasis, then cholecystectomy combined with local liver resection and lymph node clearance is an option for obtaining a good surgical margin [27]. At the same time, the study strongly recommends performing radical resection to the extent possible even when the liver metastases are limited. If radical resection is not feasible, then volume reduction surgery must be considered for an effective follow-up drug treatment to improve the quality of life.

Chemotherapy

Patients who are not medically fit for surgery must be given chemotherapy, a significant alternate treatment method. However, GB-NEC is highly invasive and develops early lymph node metastasis, hence surgery followed by radiotherapy and chemotherapy is recommended to help prolong the survival period of the patients. But, in the case of NEC with high differentiation and slow growth, the effect of chemotherapy has been seen to be limited. For rapidly growing tumors, chemotherapy response rates range from 20% to 60%. Based on the differing degrees of tumor differentiation, the most commonly used chemotherapy drugs include streptozotocin, 5-FU, Adriamycin, cisplatin, and etoposide. With the clinical incidence of GB-NEN very low, there are few related studies available which results in a lack of a unified standard chemotherapy program. Eligible studies have shown that oxaliplatin + gemcitabine are the most effective chemotherapy regimen for gallbladder cancer at present, but the Cholecysto NEC has a poor response to this treatment. Therefore, usage of chemotherapy drugs advocated for gastrointestinal and cholecystic NEC includes VP16, cisplatin, and Adriamycin. Related case reports state that post-operative use of gemcitabine, docetaxel, or cisplatin combined with cisplatin, sunitinib, docetaxel, respectively resulted in a longer survival time [28,29]. Inoue et al., [30] reported that after combined treatment with cisplatin and irinotecan, the tumor of a GB-NEC patient was significantly reduced, and the tumor-free survival period also significantly prolonged. In addition, it has been reported that the response rate to VP16 and cisplatin increased up to 50% to 56% in poorly differentiated and rapidly growing NEC [31]. In the cases investigated, alpha-interferon was widely used as adjuvant therapy for NEC, generally in the medium dose of 3 million U-6 million U, 3-7 times a week [31].

Molecular targeted therapy

At present, there is no molecular targeted drug therapy that has achieved acclaim. While there are limited drug therapies under review, few studies have reported progression of the disease coupled with an increased level of VEGF in the blood of patients with GB-NEN [32]. This indicates that VEGF-mediated neovascularization plays an important role in the occurrence, progression, metastasis, and recurrence of GB-NEN. Raymond et al., [33] and Yao et al., [34] confirmed in their studies that the targeted drug sunitinib extends the progression-free survival ($P<0.001$) and the overall survival rate ($P=0.02$) of pancreatic NEN patients through resisting the Vascular Endothelial Growth Factor Receptor (VEGF-R) and platelet-derived growth factor receptor (PDGF-R). However, to generate an effective treatment option, the mechanism by which sunitinib treats GB-NEN requires detailed analysis and study.

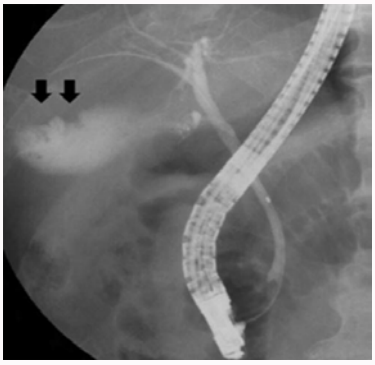


Figure 3: Endoscopic Retrograde Cholangiography (ERC) did not show abnormalities of the bile duct but pinpointed the defect of the tumor in the gallbladder (arrowhead).

Treatment with somatostatin analogs

Caplin et al., [35] conducted the Randomized Control Trial (RCT); the progression-free survival rate of NEN patients treated with a somatostatin analog (octreotide) was significantly higher compared to the placebo group ($P<0.05$). Igaz et al., [36] and Oberg et al., [37] confirmed the significance of somatostatin analogs (octreotide) in inhibiting tumor progression, improving symptoms and overall patient prognosis. Meanwhile, Oberg et al., [37] also described that with the emergence of long-acting prescriptions, patients can treat themselves through once monthly injections. It is to be noted that this treatment method is effective for patients with positive expression of Somatostatin Receptor (SSTR) GB-NEN.

Radiotherapy and interventional therapy

The molecular mechanism behind the clinical effect of radioactive isotopes of peptide receptors and the somatostatin analogs are similar. The local radiotherapy inhibits tumor growth through the labeling of radioactive isotopes Y90 or Lu177, with good clinical tolerance [38]. Additionally, the adjuvant treatment of GB-NEN also includes interventional therapy, namely the radiofrequency ablation, seed implantation, arterial embolization, and laser hyperthermia. Among them, interventional embolization of the hepatic artery is found to be effective on hepatic metastasis. The embolization agents used include anhydrous ethanol or chemotherapy drugs, but the clinical effect and safety of the above treatment methods required further detailed study. In clinical practice, it is suggested to carry out targeted treatment following the relevant guidelines and comprehensive consideration of the specific conditions of patients.

GB-NEN: Prevention

NEC is a slow-growing malignant tumor, without any specific clinical manifestations [39]. Preoperative diagnosis most often depends on the typical oncoid syndrome. Since GB-NEN and oncoid syndrome are not associated, patients typically visit the doctor only during middle or late stage presentation with metastasis. Therefore, to increase the diagnosis rate, prevent the severity of GB-NEN and provide appropriate treatment it is advised to complete a routine examination for all patients with chronic cholecystitis and cholecystolithiasis. GB-NEN is further complicated with gallbladder stones [22]. Stimulation of gallbladder wall by stones and the occurrence of this disease are related [40]. Furthering the complexity,

GB-NEN is also associated with the small intestinal carcinoid, and hence regular examination is strongly recommended to decipher the correct prognosis. Both gastrointestinal and pulmonary carcinoid cancers result in calcification via dystrophic calcification and endocrine hormone stimulation [41]. However, no national or international cases of GB-NEN have reported calcification, providing some level of distinction.

GB-NEN: Prognosis

The prognosis of GB-NEN depends on the pathological type under investigation. Difficulty in defining the type of disease increases in identifying the typical carcinoid as follows: atypical carcinoid, low-differentiated adenocarcinoma, and small-cell carcinoma. Prognosis, in general, is acceptable for GB-NET, especially G1, as it has a low degree of clinical malignancy with no obvious early metastasis. However, due to the high malignancy and rapid progress of GB-NEC, lymph node and liver metastasis occurs at the time of diagnosis but has a poor prognosis in practice. Studies at home and abroad indicate that the lower Ki-67 index with smaller tumor volume leads to better prognosis. Conversely, the prognosis is worse when the tumor sizes vary, and the symptoms are more complex [42]. Based on the research data submitted by Sloan/Kettering Memorial Cancer Research Center (MSKCC) in New York, the median survival of 13 patients with GB-NEC was slightly shorter, compared to 435 patients with gallbladder cancer (9.8 months and 10.3 months, respectively) [13]. Liliana et al., [10] demonstrated that GB-NEC 1-, 2- and 3-year survival rates were lower, compared to the other types of gallbladder cancer (20% *vs.* 38%, 10% *vs.* 31%, 0 *vs.* 30.1%, respectively) during the same period.

Conclusion

We report that GB-NEN is a relatively rare gallbladder lesion, unique in its presentation and often relayed as a case study. Therefore, we believe that early detection, correct diagnosis and reasonable treatment of such tumors will help in extending the quality of life. At present, the origin of GB-NEN is still under investigation, the clinical manifestations are atypical and most laboratory and imaging examinations provide no specificity. The diagnosis inherently depends on pathological and immunohistochemical examinations such as Syn, NSE, and CHG-A. In terms of treatment options, surgical treatment is the best choice, and active multi-mode comprehensive treatment such as chemo radiotherapy, targeted therapy, and somatostatin analogs also significantly prolong the survival period. However, this review does have some shortcomings. Due to the low incidence and availability of relatively few studies, there is no uniform standard treatment identified for treating GB-NEN. Therefore, we suggest considering the specific conditions of patients to comprehensively integrate the advantages of various treatment methods for providing targeted treatment and to maximize the benefits of patients in clinical practice.

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