EDITORIAL
693 Early gastric cancer: A challenge in Western countries

MINIREVIEWS
704 Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis?
Choe JW, Lee HY, Rim CH

ORIGINAL ARTICLE
Retrospective Study
715 Clinical online nomogram for predicting prognosis in recurrent hepatolithiasis after biliary surgery: A multicenter, retrospective study

Observational Study
732 Effect of Bifidobacterium longum 35624 on disease severity and quality of life in patients with irritable bowel syndrome
Sabaté JM, Iglicki F

SYSTEMATIC REVIEWS
745 Stereotactic radiotherapy and the potential role of magnetic resonance-guided adaptive techniques for pancreatic cancer
Ermongkonchai T, Khor R, Muralidharan V, Tebbutt N, Lim K, Kataiba N, Ng SP

CASE REPORT
755 Crohn’s disease-related ‘gastrocnemius myalgia syndrome’ successfully treated with infliximab: A case report
Catherine J, Kadhim H, Lambot F, Lieffrinckx C, Meurant V, Otero Sanchez L

LETTER TO THE EDITOR
763 Gallbladder biliary lithotripsy: A new rationale applied to old treatment
Dioscoridi L, Mutignani M

766 Gastrointestinal microbiome and Helicobacter pylori: Eradicate, leave it as it is, or take a personalized benefit-risk approach?
Sitkin S, Lazebnik L, Avalueva E, Kononova S, Vakhitov T
ABOUT COVER
Editorial Board Member of World Journal of Gastroenterology, Madhusudana Girija Sanal, MBBS, PhD, Academic Fellow, Assistant Professor, Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi 110070, Delhi, India. sanalmg@gmail.com

AIMS AND SCOPE
The primary aim of World Journal of Gastroenterology (WJG, World J Gastroenterol) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING
The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG’s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Lin-YuTong Wang; Production Department Director: Xiang Li; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
February 21, 2022

COPYRIGHT
© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/gerinfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/gerinfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2022 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com  https://www.wjgnet.com
Early gastric cancer: A challenge in Western countries

Maria Michela Chiarello, Valeria Fico, Gilda Pepe, Giuseppe Tropeano, Neill James Adams, Gaia Altieri, Giuseppe Brisinda

María Michela Chiarello, Department of Surgery, Azienda Sanitaria Provinciale di Crotone, Ospedale San Giovanni di Dio, Crotone 88900, Italy

Valeria Fico, Gilda Pepe, Giuseppe Tropeano, Gaia Altieri, Emergency Surgery and Trauma Center, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome 00168, Italy

Neill James Adams, Health Sciences, Clinical Microbiology Unit, Magna Grecia University, Catanzaro 88100, Italy

Giuseppe Brisinda, Department of Medical and Surgical Sciences, Catholic School of Medicine, Rome 00168, Italy

Giuseppe Brisinda, Department of Surgery, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome 00168, Italy

Corresponding author: Giuseppe Brisinda, MD, Department of Surgery, Fondazione Policlinico Universitario A Gemelli IRCCS, Largo A Gemelli 8, Rome 00168, Italy. gbrisin@tin.it

Abstract

Early gastric cancer (EGC) is an invasive carcinoma involving only the stomach mucosa or submucosa, independently of lymph node status. EGC represents over 50% of cases in Japan and in South Korea, whereas it accounts only for approximately 20% of all newly diagnosed gastric cancers in Western countries. The main classification systems of EGC are the Vienna histopathologic classification and the Paris endoscopic classification of polypoid and non-polypoid lesions. A careful endoscopic assessment is fundamental to establish the best treatment of EGC. Generally, EGCs are curable if the lesion is completely removed by endoscopic resection or surgery. Some types of EGC can be resected endoscopically; for others the most appropriate treatment is surgical resection and D2 lymphadenectomy, especially in Western countries. The favorable oncological prognosis, the extended lymphadenectomy and the reconstruction of the intestinal continuity that excludes the duodenum make the prophylactic cholecystectomy mandatory to avoid the onset of biliary complications.

Key Words: Early gastric cancer; Diagnosis; Treatment; Endoscopic resection; Surgery; Lymph nodes metastases

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Early gastric cancer (EGC) is an invasive stomach cancer confined to the mucosal or submucosal lining and represents approximately 20% of gastric cancers in Western countries. A correct classification allows the most appropriate treatment. Some types of EGC are adequately treated by endoscopic mucosal resection, whilst others need gastrectomy. In Western countries, due to a higher incidence of the diffuse histotype and the less widespread advanced endoscopic procedures, surgical resection and D2 lymphadenectomy are regarded as the “gold standard” treatment.

INTRODUCTION

In its initial stages, gastric cancer tends to spread in the lamina propria, infiltrating the muscularis mucosae and the submucosal layer of the gastric wall[1-4]. The Japanese Society for Gastroenterological Endoscopy’s definition of early gastric cancer (EGC) is an invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastases (LNM). Thanks to rigorous screening programs in the Asian countries, up to 50% of patients treated for a gastric cancer have EGC [5,6]. Such a high incidence is not found in European countries, where advanced gastric cancer is prevalent.

The difference in incidence between Asian and Western countries may be due to a wide use of magnifying upper endoscopy with high-resolution images and chromoendoscopy in Japan and South Korea.

A correct classification and an accurate diagnosis are fundamental to plan the most effective treatment[7-10]. Some forms of EGC can be treated by endoscopic resection; in other forms surgical treatment is mandatory[10-14].

EGC carries an excellent prognosis if the lesion is completely removed by endoscopic resection or surgery[15-17]. Most of the Japanese studies have reported 5-year and 10-year survival rates of more than 90% for the patients with EGC. In the Western studies, 5-year survival rates are variable, ranging from 68% to 92%. EGCs recur in at least 1.9% of cases after resection with time intervals ranging from 4 mo to more than 10 years. Important risk factors for the recurrence are the presence of submucosal invasion, LNM and undifferentiated histology.

CLASSIFICATION

The most common classification is the TNM, which relates information about the primitive lesion (T), node involvement (N) and distant metastases (M) thus providing information about the diffusion of the disease.

The macroscopic classification of EGC, as defined by the Japanese Gastric Cancer Association (JGCA), identifies different subtypes: type 0-I (protruding-polypoid tumors); type 0-IIa (superficial elevated tumors); type 0-IIb (tumors without elevation or depression); type 0-IIc (slightly depressed tumors); and type 0-III (excavated tumors), referring to the morphological features of the lesion on the mucosal surface[18].

The Vienna classification (Table 1) is a histologic classification. While the TNM defines EGC as a cancer invading no more deeply than the submucosa, irrespective of LNM, the Vienna classification is the most exhaustive[19,20]. In particular, the intramucosal EGC is classified in 3 categories, while the submucosal EGC in 2, according to the depth of infiltration. This distinction is not present in the TNM system and is fundamental for the treatment planning. In fact, it allows the option for an endoscopic therapy [endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)] or surgery if mandatory.

The Paris classification of polypoid and non-polypoid lesions including flat lesions is useful to evaluate possible endoscopic treatments. This classification was created for the superficial colon neoplasms, undoubtedly the most frequent in the Western World and with some small changes was adopted to the superficial gastric neoplasms. One of the changes is the thickness of the wall layer, as in the submucosa, are thinner in the stomach.
Chiarello MM et al. Early gastric cancer in Western world

**Table 1 Vienna classification**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative for dysplasia/neoplasia</td>
<td>No treatment</td>
</tr>
<tr>
<td>2</td>
<td>Indefinite for dysplasia/neoplasia</td>
<td>Follow-up, recheck</td>
</tr>
<tr>
<td>3</td>
<td>Non-invasive, low-grade dysplasia</td>
<td>Follow-up</td>
</tr>
<tr>
<td>4</td>
<td>Non-invasive, high-grade dysplasia</td>
<td>Endoscopic resection, surgery</td>
</tr>
<tr>
<td>4.1</td>
<td>High-grade adenoma/dysplasia</td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td>Non-invasive carcinoma (CIS)</td>
<td></td>
</tr>
<tr>
<td>4.3</td>
<td>Suspicious of invasive carcinoma</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Invasive neoplasia</td>
<td>Surgery (recently ESD)</td>
</tr>
<tr>
<td>5.1</td>
<td>Intramucosal carcinoma</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Mucosa only</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>Mucosa with preservation of muscularis mucosae</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>Not further than muscularis mucosae</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>Submucosal carcinoma or beyond</td>
<td></td>
</tr>
<tr>
<td>sm1</td>
<td>Invasion of muscularis mucosae &lt; 0.5 µm</td>
<td></td>
</tr>
<tr>
<td>sm2</td>
<td>Invasion of muscularis mucosae &gt; 0.5 µm</td>
<td></td>
</tr>
</tbody>
</table>

CIS: Cancer in situ; ESD: Endoscopic submucosal dissection.

**DIAGNOSIS**

A correct endoscopic diagnosis is fundamental in EGC[21]. The Japanese Society for Gastroenterological Endoscopy suggests that the length of the endoscopy, the accurate stomach wall distension and the further removal of mucous from the stomach lining are proportional to diagnostic accuracy and lesion detection rate[22]. As far as the length of the procedure is concerned, the most appropriate protocol is the Systematic Screening Stomach, which requires careful vision of the gastric lumen and acquisition of 22 pictures (12 in anterograde vision and 10 in retro vision) with a global length of the exam not inferior to 12 min[22]. Sedation is advised, while trans-nasal endoscopy is not.

Regarding diagnostic accuracy, the use of traditional or virtual cromo-endoscopy is advised to look for the “minimal changes” of the Japanese authors to evaluate the size and morphology of the lesion and the glandular and vascular pattern. Lesions should be described according to the Paris classification (Type 0I protruding, Type 0-IIa elevated, Type 0-IIb flat, Type 0-IIc depressed, Type 0-III excavated)[23].

**TREATMENT**

Endoscopic resection must be taken into account when the risk of LNMs is low or when the location and size of the tumor allows a safe “en-bloc” complete resection[24,25]. Selected EGCs can be treated with EMR or ESD with good results in Western patients[26-28]. Absolute indications for endoscopic resection, according to the Japanese gastric cancer treatment guidelines, are: cT1a differentiated-type adenocarcinoma without ulcerative findings or cT1a differentiated-type adenocarcinoma with ulcerative findings and a diameter 3 cm. Endoscopic resection for cT1a undifferentiated carcinoma without ulcerative findings and with a diameter 2 cm is considered an expanded indication. Therefore, endoscopic resection should be considered for elderly patients with a high operative risk (relative indication)[18,29].

According to JGCA guidelines (Table 2), en-bloc endoscopic resection for differentiated pT1a cancer without ulcerative findings (UL0), negative horizontal margin (HM0), negative vertical margin (VM0) and no lymphovascular infiltration (Ly0, V0) or en-bloc endoscopic resection for pT1a cancer with ulcerative findings, tumor size 3 cm, HM0, VM0, Ly0 and V0 are classified as endoscopic curability A. However, the resection is classified as endoscopic curability B for undifferentiated pT1a cancer resected en-bloc, tumor size 2 cm, without ulcerative findings, HM0, VM0, Ly0 and V0 or for en-bloc resected pT1b differentiated cancer, with a depth of infiltration < 500 µm, tumor size 3 cm, HM0, VM0, Ly0 and V0. When the resection fulfills criteria to be classified as endoscopic curability A or endoscopic curability B, but the cancer was not resected en-bloc or has positive horizontal margin, it is classified as
endoscopic curability C-1. All other resections are classified as endoscopic curability C-2.

Both endoscopic curability A and endoscopic curability B are considered to have low risk of LNMs and do not require additional surgery, so the patient can go to follow-up. Endoscopic curability C-1 has a low risk of LNMs but should be aware of residual or local recurrence, so the patient could be treated with another ESD, surgical resection, close observation or endoscopic coagulation. After an endoscopic resection classified as endoscopic curability C-2, gastrectomy with lymphadenectomy should be considered the standard-of-care[18].

The results of endoscopic treatment (EMR and ESD) have been compared to traditional surgical treatment in patients with EGC in several meta-analyses[30]. Overall survival after EMR or ESD is not significantly different when compared to surgical resection (hazard ratio: 0.995, 95% confidence interval: 0.836-1.185; P = 0.9). As for recurrence free survival, it has been proved that the recurrence risk after EMR is significantly higher compared to surgical resection (hazard ratio: 3.946, 95% confidence interval: 1.233-12.632, P = 0.02)[30]. However, it has been noted that in adequately selected patients endoscopic resection offers results that are similar to those of traditional surgery[31]. In patients who underwent EMR/ESD, strict endoscopic surveillance is mandatory, given the higher risk of endoluminal recurrence.

Complications of EMR or ESD for EGC include pain, bleeding and perforation[32]. Pain after resection is typically mild. Bleeding occurs in up to 8% of patients undergoing endoscopic treatment. Immediate bleeding appears more common with EMR/ESD of tumors located in the upper third of the stomach. Perforation occurs in 4% of the patients during ESD[15].

An innovative procedure called laparoscopic endoscopic cooperative surgery (LECS) that combines the strongest points of interventional endoscopy and laparoscopic surgery for the removal of gastric wall tumors was developed by Hiki et al[33]. In the original procedure of LECS, the stomach wall is opened for resection of the tumor, and the lumen is exposed to intraperitoneal space. LECS involves precutting around the tumor with an endoscope and artificial perforation of the gastric wall. Next, excision of the tumor with laparoscopy and repair of the gastric wall with a stapler are performed[34, 35].

The indications for LECS are currently limited to lesions that are normally managed by ESD but are technically challenging to resect via ESD because of the presence of ulcers, or if the tumor size is more than 30 mm in diameter[36].

When a LECS procedure and sentinel node biopsy were combined, an extremely minimally invasive procedure that is adequate for radical oncological resection of EGC is achieved. Sentinel node navigation surgery is an ideal surgical option for preservation of most parts of the stomach and consequent maintenance of normal gastric function to improve quality of life in patients with EGC. Although many previous studies and clinical trials have demonstrated the safety and feasibility of the sentinel node concept in gastric cancer, the clinical application of sentinel node navigation surgery is debatable. Several issues regarding technical standardization and oncological safety need to be resolved. Recently several studies to resolve these problems are being actively performed, and sentinel node navigation surgery might be an important surgical option in the treatment of gastric cancer in the future.

Other techniques (Table 3) have been developed to avoid spread of the tumor to the peritoneum[37-39]. When performed by expert teams they show a lot of promise and achieve solid oncologic results[40, 41]. Use and standardization of these minimally invasive surgical procedures contributes to reduction of unnecessary gastrectomy for gastric submucosal tumors[42]. Most of the clinical experiences are Japanese, and the small number of treated cases does not allow a comparison with the longest used endoscopic and surgical techniques. More research and clinical trials about LECS for EGC are expected. Furthermore, surgeons need to select one of these minimally invasive procedures according to the characteristics of the tumor, the localization of the tumor in the stomach, the personal surgical experience and the technological characteristics of the health institution.

In the case of EGC without the above features, total or partial gastrectomy with a free margin of at least 2 cm is the treatment of choice. Adequate lymphadenectomy offers a high chance of curing patients

### Table 2 Criteria for endoscopic mucosal resection, endoscopic submucosal dissection and surgery

| Mucosal cancer | No ulcer | Ulcer present | | Submucosal cancer | SM1 | SM2 |
|----------------|----------|--------------| | SM2 | Submucosal invasion ≥ 500 µm | |
| Size ≤ 20 | > 20 | ≤ 30 | > 30 | ≤ 30 | Any size |
| Differentiated | Y | G | G | R | R |
| Undifferentiated | Gray | R | R | R | R |

Y: Yellow is guideline criteria for endoscopic mucosal resection; G: Green is guideline criteria for endoscopic submucosal dissection; R: Red is surgery; Gray: Expanded indication for endoscopic submucosal dissection; SM1: Submucosal invasion < 500 µm; SM2: Submucosal invasion ≥ 500 µm.
Similar to NEWS, this procedure has also been developed to avoid cancer cell spillage. The concept of LAER is contrary to that of EAWR. The procedure involves opening of the gastric wall under the direct view of an endoscope, tagging the tumor with a laparoscopic suture and performing wedge resection with a laparoscopic stapler. The procedure is performed to remove tumors with a laparoscope after localization by an intraoperative endoscope. EAWR is difficult to implement in sites where strictures may occur, such as near the pylorus and the gastroesophageal junction. The procedure was developed so that EFTR could be performed without spillage. The advantages are that the stomach can be preserved. However, the main procedure is ESD, which requires a skilled endoscopist. If the tumor invades deeper than the muscle layer of the wall of the stomach, full-thickness resection with an endoscope is performed and a laparoscope is used for repair.

The procedure involves opening of the gastric wall under the direct view of an endoscope, tagging the tumor with a laparoscopic suture and performing wedge resection with a laparoscopic stapler. This procedure is the same as LAER with laparoscopic perigastric lymph node dissection. This procedure is also mandatory when there is a lack of training in complex endoscopic procedures. In hospitals with a low volume of advanced endoscopic procedures, gastrectomy remains the gold standard for treatment of EGC.

In EGC lymphatic invasion is early and is linked to the distribution of the lymphatic vessels in the mucosa and submucosa, which form a rich plexus located just above, inside and below the muscularis mucosae. Infiltration of the mucosa (EGC T1a) is sufficient to cause LNMs. Submucosal infiltration (EGC T1b) entails a higher incidence of LNMs. In addition, the risk is higher in cases where the submucosal invasion has destroyed the muscularis mucosae (5.3% of intramucosal cancer and in 19.6%-64.3% of submucosal neoplasms).

As already known, tumor grading and vascular-lymphatic invasion were found to be significant risk factors. A study on 517 patients with EGC found that LNMs are present in 22% of cases (114 patients), directly related to an ulcerated lesion of more than 2 cm diameter. Furthermore, the risk of LNMs is higher in males ($P = 0.03$), elderly patients ($P = 0.01$), in the presence of depressed tumor ($P = 0.01$) and with submucosal invasion ($P = 0.03$). Further risk factors include tumor localization in the body ($P = 0.04$) or at the angles ($P = 0.02$). In these areas, the submucosa is thinner, and the lymphatic vessels are more widespread in the lamina propria of the mucosa.

Similar results have been documented in a recent paper, where age, gender, tumor size, type of differentiation, Lauren classification and lympho-vascular and perineural invasion showed a significant correlation with the rate of LNMs in EGC by univariate and multivariate analyses in 1033 patients who underwent radical gastrectomy with lymphadenectomy. Patients with T1b gastric cancer had an older age, a higher proportion of proximal lesions, larger tumor size, more frequent vascular lymphatic invasion, perineural invasion and more LNMs than patients with T1a gastric cancer.

In a series of 5265 Japanese patients that underwent gastrectomy and lymphadenectomy, 3016 lesions were intramucosal EGCs, and 2249 were infiltrating the submucosa. LNMs were present in 65 (2.2%) of patients with intramucosal EGC and in 402 (17.9%) of those with penetrating EGC. The authors with EGC. The lymph nodes of the stomach are classified into stations numbered as in Table 4. The regional stations are the lymph node stations 1-12 and LN station 14v (Figure 1A). The remnant stations are considered as distant stations, and metastases to these nodes are classified as M1. The JGCA defined the extent of systematic lymphadenectomy according to the type (total or distal) of gastrectomy indicated (Table 5). Surgical treatment is also mandatory when there is a lack of training in complex endoscopic procedures. In hospitals with a low volume of advanced endoscopic procedures, gastrectomy remains the gold standard for treatment of EGC.

In EGC lymphatic invasion is early and is linked to the distribution of the lymphatic vessels in the mucosa and submucosa, which form a rich plexus located just above, inside and below the muscularis mucosae. Infiltration of the mucosa (EGC T1a) is sufficient to cause LNMs. Submucosal infiltration (EGC T1b) entails a higher incidence of LNMs. In addition, the risk is higher in cases where the submucosal invasion has destroyed the muscularis mucosae (5.3% of intramucosal cancer and in 19.6%-64.3% of submucosal neoplasms).

As already known, tumor grading and vascular-lymphatic invasion were found to be significant risk factors. A study on 517 patients with EGC found that LNMs are present in 22% of cases (114 patients), directly related to an ulcerated lesion of more than 2 cm diameter. Furthermore, the risk of LNMs is higher in males ($P = 0.03$), elderly patients ($P = 0.01$), in the presence of depressed tumor ($P = 0.01$) and with submucosal invasion ($P = 0.03$). Further risk factors include tumor localization in the body ($P = 0.04$) or at the angles ($P = 0.02$). In these areas, the submucosa is thinner, and the lymphatic vessels are more widespread in the lamina propria of the mucosa.

Similar results have been documented in a recent paper, where age, gender, tumor size, type of differentiation, Lauren classification and lympho-vascular and perineural invasion showed a significant correlation with the rate of LNMs in EGC by univariate and multivariate analyses in 1033 patients who underwent radical gastrectomy with lymphadenectomy. Patients with T1b gastric cancer had an older age, a higher proportion of proximal lesions, larger tumor size, more frequent vascular lymphatic invasion, perineural invasion and more LNMs than patients with T1a gastric cancer.

In a series of 5265 Japanese patients that underwent gastrectomy and lymphadenectomy, 3016 lesions were intramucosal EGCs, and 2249 were infiltrating the submucosa. LNMs were present in 65 (2.2%) of the patients with intramucosal EGC and in 402 (17.9%) of those with penetrating EGC. The authors

---

**Table 3 Laparoscopic endoscopic cooperative procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic endoscopic cooperative surgery</td>
<td>Endoscopic dissection of the mucosal or submucosal layers with laparoscopic seromuscular resection.</td>
</tr>
<tr>
<td>Endoscope-assisted laparoscopic wedge resection</td>
<td>The procedure is performed to remove tumors with a laparoscope after localization by an intraoperative endoscope. EAWR is difficult to implement in sites where strictures may occur, such as near the pylorus and the gastroesophageal junction.</td>
</tr>
<tr>
<td>Laparoscopy-assisted endoscopic resection</td>
<td>The concept of LAER is contrary to that of EAWR. The procedure is an ESD procedure assisted by laparoscopy.</td>
</tr>
<tr>
<td>Endoscope-assisted laparoscopic transgastric resection</td>
<td>The procedure involves opening of the gastric wall under the direct view of an endoscope, tagging the tumor with a laparoscopic suture and performing wedge resection with a laparoscopic stapler.</td>
</tr>
<tr>
<td>Laparoscopic intragastric surgery</td>
<td>Procedure can be used in laparoscopic surgery performed within the stomach. The incision in the wall of the stomach is minimized and laparoscopic trocars are inserted into the gastric lumen.</td>
</tr>
<tr>
<td>Single-incision intragastric resection</td>
<td>This is a single-port laparoscopic surgery.</td>
</tr>
<tr>
<td>Endoscopic submucosal dissection with laparoscopic lymph node dissection</td>
<td>This procedure is the same as LAER with laparoscopic perigastric lymph node dissection. The advantage is that the stomach can be preserved. However, the main procedure is ESD, which requires a skilled endoscopist.</td>
</tr>
<tr>
<td>Single-incision endoscopic submucosal dissection with laparoscopic lymph node dissection</td>
<td>The procedure is similar to SI-IGR, where sentinel node navigation surgery with unilateral perigastric laparoscopic lymph node dissection is performed with a single-port. Then ESD is performed through a single-port.</td>
</tr>
<tr>
<td>Laparoscopic-assisted endoscopic full-thickness resection</td>
<td>If the tumor invades deeper than the muscle layer of the wall of the stomach, full-thickness resection with an endoscope is performed and a laparoscope is used for repair.</td>
</tr>
<tr>
<td>Non-exposed wall-inversion surgery</td>
<td>The procedure was developed so that EFTR could be performed without spillage. The disadvantages are that the procedure time is long, as it involves ESD and endoscopic closure, and it is difficult to apply to the pyloric area and gastroesophageal junction.</td>
</tr>
<tr>
<td>Clean no-exposure technique</td>
<td>Similar to NEWS, this procedure has also been developed to avoid cancer cell spillage. Clean-NET can be applied to EGCs in most locations, except for pyloric area and gastroesophageal junction.</td>
</tr>
</tbody>
</table>
Table 4 Anatomical definitions of lymph node stations

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery</td>
</tr>
<tr>
<td>2</td>
<td>Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery</td>
</tr>
<tr>
<td>3a</td>
<td>Lesser curvature LNs along the branches of the left gastric artery; 3b: Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery</td>
</tr>
<tr>
<td>4</td>
<td>(1) 4a: Left greater curvature LNs along the short gastric arteries (perigastric area); (2) 4b: Left greater curvature LNs along the left gastroepiploic artery (perigastric area); and (3) 4d: Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery</td>
</tr>
<tr>
<td>5</td>
<td>Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery</td>
</tr>
<tr>
<td>6</td>
<td>Infra- and paraesophageal LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatosplenic vein</td>
</tr>
<tr>
<td>7</td>
<td>LNs along the trunk of left gastric artery between its root and the origin of its ascending branch</td>
</tr>
<tr>
<td>8a</td>
<td>Anterosuperior LNs along the common hepatic artery; 8p: Posterior LNs along the common hepatic artery</td>
</tr>
<tr>
<td>9</td>
<td>Coeliac artery</td>
</tr>
<tr>
<td>10</td>
<td>Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch</td>
</tr>
<tr>
<td>11</td>
<td>(1) 11p: Proximal splenic artery LNs from its origin to midway between its origin and the pancreatic tail end; and (2) 11d: Distal splenic artery LNs from halfway between its origin and the pancreatic tail to the end of the pancreatic tail</td>
</tr>
<tr>
<td>12</td>
<td>(1) 12a: Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas; (2) 12b: Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas; and (3) 12p: Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas</td>
</tr>
<tr>
<td>13</td>
<td>LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla</td>
</tr>
<tr>
<td>14</td>
<td>LNs along the superior mesenteric vein</td>
</tr>
<tr>
<td>15</td>
<td>LNs along the middle colic vessels</td>
</tr>
<tr>
<td>16</td>
<td>(1) 16a1: Paraaortic LNs in the diaphragmatic aortic hiatus; (2) 16a2: Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein; (3) 16b1: Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery; and (4) 16b2: Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation</td>
</tr>
<tr>
<td>17</td>
<td>LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath</td>
</tr>
<tr>
<td>18</td>
<td>LNs along the inferior border of the pancreatic body</td>
</tr>
<tr>
<td>19</td>
<td>Infra- and paraesophageal LNs predominantly along the subphrenic artery</td>
</tr>
<tr>
<td>20</td>
<td>Paraesophageal LNs in the diaphragmatic esophageal hiatus</td>
</tr>
</tbody>
</table>

LNs: Lymph nodes.

Table 5 Extent of systematic lymphadenectomy according to the type (total or distal) of gastrectomy indicated

<table>
<thead>
<tr>
<th>Lymphadenectomy</th>
<th>Gastrectomy</th>
<th>Total</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Lymph node stations from N. 1 to 7</td>
<td>Lymph node stations N. 1, 3, 4a, 4d, 5, 6 and 7</td>
<td></td>
</tr>
<tr>
<td>D1+</td>
<td>D1 stations plus stations N. 8a, 9 and 11p</td>
<td>D1 stations plus stations N. 8a and 9</td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td>D1 stations plus stations N. 8a, 9, 10, 11p, 11d and 12a</td>
<td>D1 stations plus stations N. 8a, 9, 11p and 12a</td>
<td></td>
</tr>
</tbody>
</table>

documented that in the intramucosal cancer, the risk of LNMs is higher in depressed or ulcerated lesions, in lesions bigger than 30 mm, in those with an undifferentiated type or in those with vascular and lymphatic invasion. In submucosal EGCs a higher incidence of LNMs was documented in submucosal invasion ≥ 500 µm (23.7%) compared to submucosal invasion < 500 µm (8.8%, P < 0.0001), when there was vascular lymphatic invasion (36.6% vs 9.8% if no infiltration, P < 0.0001), in case of elevated EGC (24.8%) compared to depressed type (17.1%, P = 0.0003) and in tumors larger than 30 mm (P <0.0001). Moreover, extra-gastric LNMs (level II) were found in 10% of the cases, in the absence of involvement of the peri-gastric lymph nodes.
To optimize lymphadenectomy, the sentinel node search has been proposed. Said procedure is now standardized in breast cancer surgery but still experimental in the case of EGC[52,53]. Two endoscopically administered tracers are used sequentially: the 99Tc radioisotope (at least 3 h before the intervention) and the blue isosulphan dye (during the intervention). Since skip LNM are frequent (about 20% of cases in EGCs), a negative sentinel node does not exclude the possibility that subsequent lymph node stations are involved in the disease. The usefulness of the sentinel lymph node would therefore not consist in excluding LNMs, as initially proposed, but in identifying the lymphatic drainage basin that must be removed. Thus, the sentinel lymph node would therefore become an aid to identify the relationship between gastric anatomy and gastric lymphatic drainage.

LNM strongly affects the prognosis[14,54]. This is a topic of not negligible importance because EGC is believed to be a curable albeit malignant disease. In T1a EGCs, the 10-year survival rates are about 100% in patients undergoing gastric resection and extended (D2) lymphadenectomy[55]. Five-year and ten-year survival in these patients was 2%-3% higher than in those with limited (D1) lymphadenectomy. In the case of submucosal EGC, the 10-year survival rate was about 100% in patients undergoing gastric resection and extended lymphadenectomy. Five-year and ten-year survival was 10% higher in these patients than in those with limited lymphadenectomy. Looking at the postoperative lymph node positive (pN+) patient group, 10-year survival was 87% if extended lymphadenectomy was performed, and 55% if lymphadenectomy was limited.

In patients with a radical resection, when a D2 lymphadenectomy (Figure 1B) was performed and the duodenum was excluded in the intestinal reconstruction, cholecystectomy, considered by some to be a non-essential measure, is gastric continuity, with preservation of the duodenal transit or excluding the duodenum, is an independent risk factor for both the development of cholelithiasis ($P = 0.018$) and cholecystitis and cholangitis ($P = 0.006$). It has been also confirmed that in patients who develop cholelithiasis, the incidence of cholecystitis and cholangitis is particularly high when the duodenal transit was excluded (31.3%) compared to those with duodenal transit maintained (7.4%).
CONCLUSION

In agreement with the JGCA treatment guidelines, D1 lymphadenectomy can be sufficient to treat EGCs not suitable for endoscopic treatment when the regional nodes are clinically free from disease. It is important to point out, however, that a relevant percentage of EGCs in Western countries are of the diffuse type and therefore associated with a high risk of LNM, especially when the submucosa is invaded. Moreover, in Western countries, endoscopic resections are not very common, and preoperative diagnosis of lymph node status has some limitations, despite advancements in radiological techniques. Considering these limitations, D2 lymphadenectomy in EGCs not susceptible to radical endoscopic treatment is the surgical treatment of choice. In this area, based on a good prognosis and intestinal reconstruction that excludes the duodenum from gastrointestinal transit, we believe that prophylactic cholecystectomy is necessary.

FOOTNOTES

Author contributions: Chiarello MM and Brisinda G conceived the original idea; Fico V, Pepe G, Altieri G and Tropeano G performed a comprehensive review of all available literature and synthesized the data; Chiarello MM, Fico V, Adams NJ and Brisinda G wrote the manuscript; Chiarello MM, Fico V, Pepe G, Altieri G, Tropeano G and Brisinda G contributed to the study design, manuscript structure and performed a final critical appraisal of the manuscript; Chiarello MM, Fico V, Pepe G, Tropeano G, Adams NJ, Altieri G and Brisinda G read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Italy

ORCID number: Maria Michela Chiarello 0000-0003-3455-0062; Valeria Fico 0000-0003-1619-4164; Gilda Pepe 0000-0001-9852-6243; Giuseppe Tropeano 0000-0001-9006-5040; Neill James Adams 0000-0002-2813-8648; Gaia Altieri 0000-0002-0324-2430; Giuseppe Brisinda 0000-0001-8820-9471;

S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

REFERENCES


Abe N, Takeuchi H, Ooki A, Nagaog M, Masaki T, Mori T, Sugiyama M. Recent developments in gastric endoscopic


Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis?

Jung Wan Choe, Hye Yoon Lee, Chai Hong Rim

**Abstract**

Portal invasion of hepatocellular carcinoma (HCC) occurs in 12.5%-40% of patients diagnosed with cancer and yields poor clinical outcomes. Since it is a common cause of inoperability, sorafenib was regarded as the standard treatment for HCC in the Barcelona Clinic of Liver Cancer guidelines. However, the median survival of the Asian population was only approximately 6 mo, and the tumor response rate was less than moderate (<5%). Various locoregional modalities were performed, including external beam radiotherapy (EBRT), transarterial chemoembolization, hepatic arterial infusion chemotherapy, and surgery, alone or in combination. Among them, EBRT is a noninvasive method and can safely treat tumors involving the major vessels. Palliative EBRT has been commonly performed, especially in East Asian countries, where locally invasive HCC is highly prevalent. Although surgery is not commonly indicated, pioneering studies have demonstrated encouraging results in recent decades. Furthermore, the combination of neo- or adjuvant EBRT and surgery has been recently used and has significantly improved the outcomes of HCC patients, as reported in a few randomized studies. Regarding systemic modality, a combination of novel immunotherapy and vascular endothelial growth factor inhibitor showed results superior to that of sorafenib as a first-line agent. Future clinical trials investigating the combined use of these novel agents, surgery, and EBRT are expected to improve the prognosis of HCC with portal invasion.

**Key Words:** Surgery; Hepatocellular carcinoma; Radiotherapy; Systemic treatment
Core Tip: The prognosis of hepatocellular carcinoma with portal vein involvement is poor, and there had been few available local modalities. However, with the development of radiotherapy techniques, the 1-year survival rate has been reported to be close to 45%-50% after palliation. Recently, a surgical approach has also been attempted showing encouraging results. Furthermore, the combination of surgery and radiation therapy showed effective results in studies including randomized studies. The combination of these two modalities is expected to increase efficacy of treating hepatocellular carcinoma with portal invasion.

INTRODUCTION

Portal invasion of hepatocellular carcinoma (HCC) is a known clinical factor associated with poor prognosis. Portal vein invasion might cause portal hypertension, which can lead to decreased liver function and enlarge the gastrointestinal varices[1]. In addition, portal tumor thrombosis acts as a tumor deposit that can induce intra- and extrahepatic metastases[2,3]. Without active treatment, the survival period of HCC patients with portal invasion is usually less than 4 mo[4-6]. Portal invasion occurs in 12.5%-40% of all HCC patients in the clinical setting[7-11]. According to the 16th National Survey for Primary Liver Cancer conducted in Japan, portal involvement was found in 16% (808/5130) of patients who underwent hepatic resection[12]. In our previous study using data from the Nationwide Liver Cancer Registry, 2553 of 10743 patients (approximately 10% randomly extracted patient records from all administrative districts of South Korea), or about a quarter, had portal vein involvement at the time of diagnosis[13].

To date, there is no standard treatment for HCC with portal invasion; hence, various systemic and locoregional modalities have been used. Since portal invasion is a component of the Barcelona Clinic of Liver Cancer (BCLC) stage C, the European Association for the Study of the Liver (EASL)[14] and American Association for the Study of Liver Diseases (AASLD) guidelines[15], which were published in 2018, support the use of sorafenib for the treatment of HCC with this stage. Although sorafenib was the only modality that achieved an overall survival (OS) benefit, as reported in a phase 3 randomized study conducted within a period of 15 years, the tumor response rate was not satisfactory (less than 5%), and the median OS was only 6 mo after treatment as shown in an Asian population study[16]. In addition, it should not be overlooked that approximately 95% of the enrolled patients were in Child-Pugh class A in this study, even though a significant portion of the HCC patients with PVT have a liver function of Child-Pugh class B or C[17]; data on the use of sorafenib in these patients is limited. A randomized phase 3 trial was done comparing sorafenib vs best supportive care alone in Child-Pugh class B patients, and the results are expected to provide further guidance[18]. A recent study investigated the use of regorafenib for the HCC patients who have failed to improve on sorafenib; the median OS of 10.6 mo was achieved in patients who received regorafenib, which was better than the OS of 7.8 mo for those receiving the placebo[19]. Although several studies on the expansion of indications for systemic and rescue therapies are in progress, satisfactory results have not yet been obtained.

Therefore, various locoregional modalities have been used to improve the patient outcomes. Despite that the AASLD guidelines endorsed treatment recommendations of BCLC system previously[20], in its updated version in 2018, it is mentioned that systemic therapy for HCC with macrovascular invasion is recommended but not over locoregional treatments[15]. The preferred option of locoregional modality was not suggested, although recent studies regarding transarterial chemoembolization (TACE), external beam radiotherapy (EBRT), and hepatic arterial infusion chemotherapy (HAIC) were referenced, because evidence is limited to suggest relative superiority among those modalities.

The application of locoregional treatment for HCC with portal invasion varies regionally, and treatment strategies also differ between Eastern and Western countries[21]. In Asian countries, hepatitis B virus-related HCCs comprise the majority of diagnosed diseases. These diseases are mainly caused by insertion mutation of viral oncoproteins and tend to progress rapidly and invasively, whereas liver function can be relatively preserved. In Western countries, the common causes of HCC include alcohol consumption or fatty liver of other causes. These diseases are associated with somatic alterations and chromosomal instability accumulated due to cirrhosis progression; they tend to be less progressive and have higher differentiation, but the liver function is commonly damaged due to persistent cirrhosis[22]. Therefore, the active locoregional treatments including TACE, surgery, EBRT, and HAIC are more rigorously attempted in Asia than in Western countries[21]. For instance, the surgical approach is preferentially recommended for portal invasion cases that do not invade the main branch, as indicated.

Citation: Choe JW, Lee HY, Rim CH. Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis? World J Gastroenterol 2022; 28(7): 704-714
URL: https://www.wjgnet.com/1007-9327/full/v28/i7/704.htm
in the recent Chinese expert consensus guidelines[23], although the vast majority of international guidelines did not suggest surgery as the preferred option for those cases[24,25]. Based on the Korean Liver Cancer Study Group guidelines, the combination of TACE and EBRT was suggested as the best option for HCC patients without extrahepatic metastases but with major vessel invasion[26].

Various locoregional modalities have been used independently or in combination to treat HCC with portal invasion. In particular, despite the fact that surgery is not generally recommended for portal invasive cases, recent studies have achieved favorable oncologic results by reducing the extent of tumors through EBRT and surgery. In this review, we aimed to discuss the role of locoregional modalities in the treatment of HCC with portal invasion, focusing on the recent results of surgery and EBRT as individual treatments and as a combination therapy.

### PALLIATING PORTAL INVASION WITH EXTERNAL RADIOThERAPY

In the early 1990s, before the generalization of a planning system using computed tomography, EBRT was known to have a limited role in HCC. EBRT had been “technically radioresistant” during the era of two-dimensional radiotherapy, of which the treatment was planned and performed under plain radiographic guidance. Since EBRT relies on bony and organ shadows available on plain films, radiation therapy inevitably encompasses a significant portion of the normal liver. Due to the possibility of hepatic radiotoxicity, only doses lower than 30 Gy could be administered, which is not sufficient to control the tumor[24,27].

Although the risk of radiation-induced liver disease steeply increased after delivering 30 Gy of irradiation to the entire liver, CT-based planning has enabled the safe delivery of high doses of over 50 Gy. The application of a more updated technology, such as intensity-modulated radiotherapy (a special type of EBRT that increases the conformality of the radiation target by actively modulating the dose intensity, portal shape, and beam movements), enabled the irradiation of advanced intrahepatic tumors while saving the necessary portion of the normal liver (Figure 1). Furthermore, despite the fact that tumor vascular invasion makes the application of local modalities difficult, EBRT is feasible because the major blood vessels can withstand more than approximately 100 Gy (in conventional fraction) and the target dose can be delivered regardless of the location of tumor[28]. Indeed, the HCC cells are radiosensitive and highly proliferative tumor cells with an alpha/beta ratio of approximately 15, which is similar to that of head and neck cancer (a radiosensitive cancer commonly treated with chemotherapy or radiotherapy)[29,30]. Previous studies using radiation therapy for locally advanced HCCs, which recruited patients from the 90s to the 2000s, have shown that HCC responds well to high doses of radiation. In a previous study including 158 unresectable HCC patients (about 50% of patients had portal invasion), Park et al[31] reported that the tumor response rates in patients who received irradiation doses of < 40 Gy, 40-50 Gy, or > 50 Gy increased to 29.2%, 68.6%, and 77.1%, respectively. Similarly, our previous study reported that as a result of prescribing a median total EBRT dose of 61.2 Gy, a high tumor response rate of 62.2% was reported in 45 HCC patients with portal vein thrombosis (PVT)[32].

Various studies have reported the use of EBRT in HCC patients with portal invasion in recent decades. In order to integrate the data from several studies, we performed a meta-analysis of 26 studies and 2,111 HCC patients treated with EBRT[33]. The pooled 1- and 2-year OS rates were 43.8% [95% confidence interval (CI): 37.6%-50.2%] and 22.3% (17.7%-27.6%) in patients who underwent three-dimensional conformal radiotherapy (3DCRT), and 48.5% (39.4%-57.8%) and 26.8% (19.0%-36.3%) in patients who underwent stereotactic body radiotherapy (SBRT). The pooled tumor response rates were 51.5% (95%CI: 45.7%-57.0%) and 70.7% (95% CI: 63.7%-76.8%) in patients who underwent 3DCRT and SBRT, respectively. Severe gastrointestinal or hepatic complications rarely occurred and were either not reported in most studies or were documented in less than 5%-10% of treated patients. Various locoregional modalities have been applied for the treatment of unresectable HCCs, and TACE is the most common modality performed in combination with EBRT. Huo et al[34] reported that the combination of TACE and RT had higher survival benefit [odds ratio (OR): 1.36, 95% CI: 1.19-1.54 for 1-year OS] and complete response rate (OR: 2.73, 95% CI: 1.95-3.81) than TACE alone for unresectable HCCs. They also pointed out that the benefits of OS progressively increased (ORs: 1.55, 1.91, 3.01, and 3.98 for 2-, 3-, 4-, and 5-year OS, respectively). In a recent randomized trial, Yoon et al[35] reported that the combination of TACE and EBRT improved the OS (median: 55 wk vs 43 wk, P = 0.04) and progression-free survival (median: 31 wk vs 11.7 wk, P < 0.001) of HCC patients with major vascular invasion compared with sorafenib. Recently, our team performed a study using nationwide data from all administrative districts of South Korea[13]. Strict propensity matching was performed, and data of 444 HCC patients with portal invasion (222 who underwent local treatment including EBRT and 222 who did not undergo active oncologic treatment) were analyzed. Local treatment, including radiotherapy, had significant benefits on the OS (median: 8 mo vs 2 mo, P < 0.001) and cancer-specific survival. Table 1 summarizes the key results of the cited studies.

In addition, particle therapy (e.g., proton or heavy ion therapy) can provide additional benefits compared to conventional EBRT, which uses X-rays in treating locally advanced HCC. Particle therapy
Table 1 Summary of key studies according to the treatment method

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiotherapy studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rim et al [33], 2018</td>
<td>Meta-analysis of observational studies</td>
<td>2111 with PVT</td>
<td>Pooled 1- and 2-yr OS: 43.8% and 22.3%, respectively (3DCRT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled 1- and 2-year OS: 48.5% and 26.8%, respectively (SBRT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3 complications less than 5% to 10%</td>
</tr>
<tr>
<td>Huo et al [34], 2015</td>
<td>Comparative meta-analysis</td>
<td>2577 underwent TACE or RTx</td>
<td>TACE and RT had OS benefit compared with TACE alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR: 1.55, 1.91, 3.01, and 3.98 for 2-, 3-, 4-, and 5-yr OS rates, respectively</td>
</tr>
<tr>
<td>Yoon et al [35], 2018</td>
<td>Randomized trial</td>
<td>90 with major vascular invasion</td>
<td>TACE and RT had survival benefit compared with sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS 55 wk vs 43 wk, P = 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median PFS 31 wk vs 11.7 wk, P = 0.001</td>
</tr>
<tr>
<td>Yoon et al [36], 2018</td>
<td>Observational study using national database</td>
<td>444 propensity-matched patients with PVT</td>
<td>Grade 3 complications less than 5% to 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TACE and RT had survival benefit compared with no oncologic treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS: 8 mo vs 2 mo, P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median CSS: 8 mo vs 2 mo, P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS and CSS benefit persist in the CPC A and CPC B subgroups</td>
</tr>
<tr>
<td><strong>Surgery studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kokudo et al [41], 2016</td>
<td>Observational study using national database</td>
<td>2116 propensity-matched patients with PVT</td>
<td>Surgery had benefit compared with non-surgery</td>
</tr>
<tr>
<td>Wang et al [42], 2016</td>
<td>Retrospective study</td>
<td>1580 with PVT underwent (1) surgery, (2) TACE, (3) TACE with sorafenib, or (4) TACE with RTx</td>
<td>Median OS:</td>
</tr>
<tr>
<td>Shen et al [43], 2010</td>
<td>Retrospective study</td>
<td>406 with PVT underwent surgery</td>
<td>Surgery showed better outcomes in Cheng’s type I and type II (1-yr OS: 52% and 38%, respectively) PVT than type III and IV (1-yr OS: 25% and 18%, respectively)</td>
</tr>
<tr>
<td>Cheng et al [44], 2006</td>
<td>Retrospective study</td>
<td>438 with PVT underwent surgery</td>
<td>Surgery yielded satisfactory results in Cheng’s type I and II (1-yr OS: 58.7% and 39.9%, respectively), not in type III and IV (1-yr OS: 39.5% and 20.4%, respectively)</td>
</tr>
<tr>
<td><strong>Combined surgery and radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chong et al [46], 2018</td>
<td>Retrospective study</td>
<td>26 underwent surgery following CCRT vs 18 underwent surgery alone</td>
<td>Surgery following CCRT had benefit on surgery alone</td>
</tr>
<tr>
<td>Sun et al [47], 2019</td>
<td>Randomized trial</td>
<td>26 underwent surgery with adjuvant IMRT vs 26 surgery alone</td>
<td>Adjuvant IMRT significantly improved clinical outcomes</td>
</tr>
<tr>
<td>Wei et al [49], 2019</td>
<td>Randomized trial</td>
<td>82 neoadjuvant RT vs 82 surgery alone</td>
<td>1- and 2-yr OS: 75.2% and 27.4%, respectively (neoadjuvant RT)</td>
</tr>
<tr>
<td>Li et al [50], 2016</td>
<td>Comparative study</td>
<td>45 neoadjuvant RT vs 50 surgery alone</td>
<td>Neoadjuvant RT decreased the rates of HCC recurrence [49% vs 88.7%, respectively (P &lt; 0.001)] and increased overall survival [1-yr OS: 69% vs 35.6%, respectively (P &lt; 0.01)]</td>
</tr>
</tbody>
</table>

PVT: Portal vein thrombosis; OS: Overall survival; 3DCRT: 3-dimensional conformal radiotherapy; SBRT: Stereotactic body radiotherapy; TACE: Transarterial chemoembolization; RTx: Radiotherapy; PFS: Progression-free survival; CSS: Cause-specific survival; CPC: Child-Pugh class; CCRT: 3-dimensional conformal radiotherapy.
Concurrent chemoradiotherapy; DSS: Disease-specific survival; IMRT: Intensity-modulated radiotherapy.

**Figure 1** A case of a locally advanced hepatocellular carcinoma with portal thrombosis treated with radiotherapy. A: Multiple tumors noted in right lobe and segment 4, with a large tumor in segment 8, and involving right portal vein thrombosis; B: A dose-distribution of external radiotherapy plan. We prescribed 53 Gy/20F to gross tumor volume (red color wash in upper-left figure) with at least 42 Gy/20F were delivered to clinical target volume (green color wash in upper-left figure). Quantitative dose-histogram for specific organs is generated (upper-right figure). We planned to save at least 70% of normal liver to be irradiated less than 30 Gy; C: One year after radiotherapy and three times of transarterial chemoembolization, tumors were remitted without active enhancing lesions. Liver function was maintained at Child-Pugh score A. GTV: Gross tumor volume; CTV: Clinical target volume.

is most similar to conventional EBRT in terms of the overall principle of causing cancer cell death. However, dose escalation and complication reduction could be achieved based on the physical characteristic called Bragg peak (e.g., the phenomenon that energy deposits almost disappear after radiation passes through the body and progresses to a certain depth)[36]. Sanford et al.[37] reported the benefit of proton therapy as compared to conventional EBRT for 133 unresectable HCC patients based on survival (median OS; 31 mo vs 14 mo, HR = 0.47, P = 0.008) and liver toxicities (odds ratio: 0.26, P = 0.03). Cheng et al.[38] also reported the benefit of proton therapy as compared to conventional EBRT based on survival (HR 0.56, P = 0.032) and radiation-induced liver disease (11.8% vs 36.4%, P = 0.004), using a propensity-matched cohort. The current hurdle for using particle therapy is its accessibility; currently, there are about 110 particle therapy centers in operation worldwide, but most of them are in major developed countries such as the US, Japan, and Germany[39]. The financial burden of treatment due to
the high cost of equipment is also a problem to be resolved. However, the efficiency of EBRT could be greatly improved once these difficulties are gradually resolved.

In summary, EBRT can be used for the treatment of HCC by delivering a high dose of radiation and has technical advances. It is an effective palliative modality for HCC with portal invasion and is commonly performed along with TACE.

**SURGICAL RESECTION OF HCC WITH PORTAL INVASION**

Previously, surgery was not commonly performed in HCC patients with portal invasion because of the short life expectancy and therapeutic risks. Neither the EASL nor the AASLD guidelines suggest the performance of surgical resection as treatment for HCC with portal invasion[14,15]. However, East Asian countries, including China and Japan, have recently been actively performing surgery for portal invasion[40].

Kokudo et al[41] performed a key study to evaluate the efficacy of surgical resection in HCC patients with portal invasion using the nationwide data from Japan. Among 6474 HCC patients with PVT, approximately 2100 patients with Child-Pugh A liver function were matched using propensity scores (liver resection group vs. non-liver resection group). The liver resection group showed significantly longer survival (median: 2.45 years vs 1.57 years, \( P < 0.001 \)). However, the OS benefit was not significant in the subgroup with Vp4 PVT (\( P = 0.242 \)). Figure 2 shows an illustration of the two common classifications of PVT. Furthermore, R2 resection was performed in 60.5% of patients, and the 90-day mortality was 8.2% in the Vp4 PVT group. The authors recommended liver resection as the first-line of treatment for HCC with PVT in the first-order branch. Another large series conducted by four Chinese centers[42] which included 1572 HCC patients with PVT, reported similar results. The median survival times of the surgical group were 15.9 and 12.5 mo for PVT of type I and II in Cheng’s classification, which were much better than those of their nonsurgical counterparts. However, for patients with Cheng’s type III PVT, the TACE and RT group showed higher survival rate than the surgery group (8.9 mo vs 6.0 mo). Therefore, authors suggested that surgery should be considered for type I and II PVT, but TACE and RT should be recommended for type III PVT (PVT in the main trunk or contralateral branches). Other series from East Asian countries reported the feasibility of surgical resection in HCC patients with branch thrombosis, but this modality may lead to poor outcomes and increase the surgical risks in those with main PVT[43,44].

Based on the above studies, consensus guidelines in East Asia recommend the use of surgery for the treatment of HCC with portal invasion. The recent treatment guidelines of the Japan Society of Hepatology[45] suggested four possible options for HCC with major vessel invasion: three locoregional modalities including TACE, surgical resection, hepatic arterial infusion chemotherapy, and molecular-targeted therapy. They stated that it is difficult to provide a universal ranking for the four modalities; therefore, the four modalities are recommended in parallel. On the contrary, the Chinese Expert guidelines for HCC with PVT recommend surgical resection as a preferred option for patients with Child-Pugh A, PVT type I and II based on Cheng’s classification (branch PVT), and good performance. Type III PVT cases are recommended to undergo surgery after downstaging via EBRT or TACE[23].

In summary, surgical treatment is being actively performed for HCC with PVT, especially in East Asia. Although surgical resection is a considerable modality for HCC with branch PVT (types I and II based on Cheng’s classification; Vp1-3 based on the Japanese classification), this modality can lead to poor outcomes and increase the risk for perioperative complications when used in patients with main PVT. Table 1 summarizes the key studies related to this topic.

**PROMISING RESULTS OF SURGERY AND RADIOThERAPY AS COMBINATION TREATMENT**

In cancer treatment, the application of radiotherapy before and after surgical treatment to lower the recurrence and survival rates is a widely used method. Previously, patients with HCC with portal invasion were deemed to have a dismal prognosis; therefore, active treatment combining surgery and EBRT has not been widely accepted. However, several researchers have recently reported promising outcomes of neo- or adjuvant EBRT.

The multidisciplinary team of Yonsei University[46] reported their experience of trimodality treatment for HCC with portal invasion, which is neoadjuvant CCRT (HAIC plus EBRT) yielding downstaging and surgical resection. Patients who underwent trimodality treatment had a median disease-specific survival of 62 mo, while those who underwent resection alone had a median disease-specific survival of only 15 mo (\( P = 0.006 \)). Sun et al[47] from the Eastern Hepatobiliary Surgery Hospital performed a randomized study to investigate the benefit of adjuvant IMRT in HCC patients with PVT (adjuvant RT vs surgery alone). The adjuvant radiotherapy group showed significantly higher disease-free survival (DFS) (median: 9.1 mo vs 4.1 mo, \( P = 0.001 \)) and OS (median: 18.9 vs. 10.8 mo, \( P = 0.001 \)).
The most common complications after RT were fatigue or anorexia, and grade 3 gastrointestinal complications occurred in 2 of 26 patients (7.7%). Grade 4 or higher adverse effects have not been reported. Although OS difference was significant in subgroup analyses among patients with Cheng’s type I or II PVT (median 20.7 mo vs 11.7 mo, \( P = 0.008 \)), due to the limited number of patients (only 6 and 7 patients had Cheng’s type III or IV PVT, respectively, in both arms), the difference was not considered significant in the subgroup with PVT at main branch or trunk. Soin et al reported encouraging results that comparable survival was achieved in HCC patients with PVT after down-staging, including SBRT, and liver transplantation, to those without PVT who underwent transplantation (5-year OS 57% vs 65%, \( P = 0.06 \)). Wei et al performed a cornerstone study related to this topic, randomizing 164 patients into the neoadjuvant EBRT and surgery group and surgery groups. The 1- and 2-year OS rates in the neoadjuvant arm were 75.2% and 27.4%, whereas those in the surgery arm were 43.1% and 9.4%, respectively (\( P < 0.001 \)). EBRT improved the OS and DFS of patients with type II PVT (\( P = 0.01 \) and \( P = 0.016 \), respectively) and those with type III PVT (\( P < 0.001 \) and \( P = 0.002 \), respectively), according to Cheng’s classification. No significant difference was observed in the perioperative complications between the two groups, although a few more grade 3 or 4 complications were reported after RT (two cases of abdominal hemorrhage in the neoadjuvant EBRT arm and none in the surgery arm). In a previous non-randomized comparative study on HCC with main PVT (type III based on Cheng’s classification), Li et al investigated the benefit of neoadjuvant radiotherapy. The 1- and 2-year OS rates in the neoadjuvant group were 69% and 20.4%, whereas those in the surgery group were 35.6% and 0%, respectively (\( P < 0.01 \)). The recurrence rates were 49% and 88.7% at 6 mo in the neoadjuvant and surgery groups, respectively (\( P < 0.001 \)).

In summary, recent studies demonstrated that combining neo- or adjuvant EBRT and surgery could further improve the oncologic outcomes of HCC patients with portal invasion, possibly those with main PVT. Table 1 presents a list of related studies.

**FUTURE PERSPECTIVE AND SUMMARY**

Until the 2000s, there were limited practical treatment methods for HCC with portal invasion. Since the
mid-2000s, sorafenib, the first effective systemic agent for unresectable HCC, has been established. In recent decades, aside from TACE, which is the most commonly used locoregional modality, other methods including EBRT, TARE, HAIC, and surgery have also been attempted. Furthermore, the use of a novel systemic modality (atezolizumab-bevacizumab)[51] that surpassed sorafenib in terms of survival and tumor responses, which had been established as a standard systemic agent for 15 years, was reported in 2020. Atezolizumab-bevacizumab is a combination of anti PD-L1 (an immune checkpoint inhibitor) and anti-vascular endothelial growth factor (VEGF) (a tumor microenvironment-modulating agent). As the anti-VEGF therapy reverses the VEGF-mediated immune suppression and increases the T-cell infiltration in tumors, the efficacy of anti PD-L1 could be enhanced[51]. Radiation therapy also enhances the performance of tumor antigen presentation and T-cell infiltration in the tumors[52]. In addition, radiation itself induces the sensitization of tumor cells to immune-mediated cell death by upregulating FAS expression. Therefore, the combination of immune checkpoint inhibitors and radiation therapy could be a promising treatment for HCC due to its synergistic effect. In addition, advances in understanding tumor immunity have resulted in new emerging immunotherapies. For example, CD4+ CD25+ regulatory T cells have a well-established immunosuppressive role in the HCC microenvironment and express various chemokine receptors and surface molecules such as PD-1, CTLA4 and others[53]. They can potentially be direct or indirect targets for newly emerging immune checkpoint inhibitor immunotherapy. Future clinical studies investigating the efficacy and feasibility of novel immunotherapy in combination with EBRT are necessary.

CONCLUSION

Although HCC with portal invasion is considered to have a limited benefit from surgery, pioneering researchers have obtained promising outcomes, and recent studies have demonstrated that the addition of EBRT can further increase the treatment efficiency. If effective novel systemic agents, surgery, and EBRT are used in an appropriate combination, the prognosis of HCC with portal invasion can be significantly improved. In other words, we believe that the most potent anticancer modalities known to date, the tripartite collaboration of chemotherapy, surgery, and radiotherapy, commonly used in the treatment of other solid cancers, will be used as a new standard treatment for HCC with portal invasion in the near future. However, clinical trials are warranted to evaluate the efficacy of such collaborations.

FOOTNOTES

Author contributions: Rim CH contributed to conceptualization; Lee HY supervised the study; Choe JW and Rim CH wrote the original draft; Choe JW, Lee HY and Rim CH reviewed and edited the manuscript; All authors have read and agreed to the published version of the manuscript.

Supported by the National Research Fund of Korea, No. NRF-2021R1I1A2047475.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: South Korea

ORCID number: Jung Wan Choe 0000-0003-0634-5141; Hye Yoon Lee 0000-0001-9077-1412; Chai Hong Rim 0000-0001-7431-4588.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

REFERENCES

2 Addario L, Tritto G, Cavaglià E, Amodio F, Giannelli E, Di Costanzo GG. Preserved liver function, portal thrombosis and absence of oesophageal varices are risk factors for metastasis of hepatocellular carcinoma. Dig Liver Dis 2011; 43: 319-324
Surgery and RT for HCC with PVT


Cheng S Gastroenterology


50 Li N, Feng S, Xue J, Wei XB, Shi J, Guo WX, Lau WY, Wu MC, Cheng SQ, Meng Y. Hepatocellular carcinoma with main


Retrospective Study

Clinical online nomogram for predicting prognosis in recurrent hepatolithiasis after biliary surgery: A multicenter, retrospective study

Tian Pu, Jiang-Ming Chen, Zi-Han Li, Dong Jiang, Qi Guo, Ang-Qing Li, Ming Cai, Zi-Xiang Chen, Kun Xie, Yi-Jun Zhao, Cheng Wang, Hui Hou, Zheng Lu, Xiao-Ping Geng, Fu-Bao Liu

Tian Pu, Jiang-Ming Chen, Zi-Han Li, Dong Jiang, Qi Guo, Ang-Qing Li, Zi-Xiang Chen, Kun Xie, Yi-Jun Zhao, Xiao-Ping Geng, Fu-Bao Liu, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui Province, China

Ming Cai, Cheng Wang, Department of General Surgery, The First Affiliated Hospital of the University of Science and Technology of China, Hefei 230001, Anhui Province, China

Hui Hou, Department of General Surgery, The Second Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui Province, China

Zheng Lu, Department of General Surgery, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233030, Anhui Province, China

Corresponding author: Fu-Bao Liu, MD, PhD, Chief Doctor, Professor, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, No. 218, Jixi Road, Hefei 230022, Anhui Province, China. lancetlfb@126.com

Abstract

BACKGROUND

Methods for predicting the prognosis of patients undergoing surgery for recurrent hepatolithiasis after biliary surgery are currently lacking.

AIM

To establish a nomogram to predict the prognosis of patients with recurrent hepatolithiasis after biliary surgery.

METHODS

In this multicenter, retrospective study, data of consecutive patients in four large medical centers who underwent surgery for recurrent hepatolithiasis after biliary surgery were retrospectively analyzed. We constructed a nomogram to predict the prognosis of recurrent hepatolithiasis in a training cohort of 299 patients, following which we independently tested the nomogram in an external validation cohort of 142 patients. Finally, we used the concordance index (C-index), calibration, area under curve, decision curve analysis, clinical impact curves, and visual fit indices to evaluate the accuracy of the nomogram.
RESULTS
Multiple previous surgeries [2 surgeries: Odds ratio (95% confidence interval), 1.451 (0.719-2.932); 3 surgeries: 4.573 (2.015-10.378); ≥ 4 surgeries: 5.741 (1.039-3.717)], absence of immediate clearance [2.398 (1.304-4.409)], neutrophil-to-lymphocyte ratio ≥ 2.462 [1.915 (1.099-3.337)], and albumin-to-globulin ratio ≤ 1.5 [1.949 (1.056-3.595)] were found to be independent factors influencing the prognosis. The nomogram constructed on the basis of these variables showed good reliability in the training (C-index: 0.748) and validation (C-index: 0.743) cohorts. Compared with predictions using traditional classification models, those using our nomogram showed better agreement with actual observations in the calibration curve for the probability of endpoints and the receiver operating characteristic curve. Dichloroacetate and clinical impact curves showed a larger net benefit of the nomogram.

CONCLUSION
The nomogram developed in this study demonstrated superior performance and discriminative power compared to the three traditional classifications. It is easy to use, highly accurate, and shows excellent calibration.

Key Words: Gallstones; Reoperation; Risk factors; Nomogram; Prognosis; Model

INTRODUCTION
Hepatolithiasis is mostly prevalent in East and Southeast Asia, and the incidence in China is the highest in the world[1]. Although treatment strategies for hepatolithiasis have been improving, the overall treatment rate and prognosis remain poor because of the long course, complex pathological changes, high incidence of postoperative complications, and high recurrence rate. Sporadic cases of hepatolithiasis have been reported in Western countries, and with the increasing immigration from Asian countries, hepatolithiasis has become increasingly prevalent in the West[2-4]. The prevalence of this disease is 30%-50% in East Asia and 0.6%-1.3% in Western countries[5].

The treatment of hepatolithiasis involves pharmacologic, endoscopic, and surgical approaches. Surgery is the most effective treatment. However, the course of the disease varies, and stones can easily remain in the surgery and recur at a later date. Patients with recurrent hepatolithiasis who undergo multiple biliary surgeries often experience varying degrees of abdominal adhesions, causing greater difficulties and increasing the risks for surgery. Thus, surgeons should focus on improving the prognosis and quality of life of patients.

Recurrent hepatolithiasis is defined as hepatolithiasis with a history of biliary tract surgery for different reasons. Some classification systems for hepatolithiasis have been established, such as classification based on clinical manifestations[3]. Nakayama[6]’s classification based on the distribution of stones, Tsunoda et al[7]’s classification based on dilatation or stenosis, and the Chinese Classification model proposed by the Biliary Study Group of the Chinese Medical Association[8]. Despite their wide acceptance, these classification models are too complicated to implement in guiding clinical treatment. Thus, clinical classification of hepatolithiasis has practical significance in guiding treatment decisions and predicting patient prognoses. Nomograms are statistical tools that enable simultaneous consideration of various factors to facilitate visualization of prognosis. Moreover, nomograms offer many advantages, including personalized evaluation, user-friendliness, and ease of comprehension[9].
Considering the absence of a prediction model for the quality of life of patients with recurrent hepatolithiasis, this study aimed to establish a nomogram for predicting the prognosis of patients with recurrent hepatolithiasis after biliary surgery.

MATERIALS AND METHODS

Clinical and prognostic data of patients with recurrent hepatolithiasis who underwent surgery between January 2015 and December 2020 at the Departments of Hepatopancreatobiliary Surgery in four medical centers were retrospectively analyzed for evaluating patients’ quality of life. The patients from the First Affiliated Hospital of Anhui Medical University constituted the training cohort, while those from the Second Affiliated Hospital of Anhui Medical University, the First Affiliated Hospital of University of Science and Technology of China and the First Affiliated Hospital of Bengbu Medical College served as the validation cohort. All hospitals are high-volume surgical centers employing similar therapeutic approaches for hepatolithiasis.

The diagnosis of hepatolithiasis was confirmed by preoperative imaging examinations and intraoperative findings. Recurrent hepatolithiasis was diagnosed when the patient had a history of biliary surgery. These patients had already undergone at least one bile duct surgery for hepatolithiasis. Patients from the four centers were included if they met the following inclusion criteria: (1) A history of at least one biliary surgery; (2) Confirmation of stones by preoperative imaging examination; (3) Confirmation of intrahepatic cholangiolithiasis during the procedure; and (4) A preoperative liver function of Child-Pugh grade A or initial grade B that improved to grade A. The exclusion criteria were as follows: (1) Hepatolithiasis occurring within 6 mo after the last biliary tract surgery; (2) No history of surgical treatment; (3) History of abdominal surgery not involving the biliary tract system; (4) Malignant tumor on postoperative pathological evaluation; and (5) Patchy clinical or follow-up data. All clinical data were screened and collected in a computerized database by a specialized research assistant. This retrospective study was conducted in accordance with the declaration of Helsinki and was approved by the institutional ethics committees (Quick-PJ2021-08-19). All included patients or their relatives provided written informed consent before their data were analyzed.

Preoperative evaluation

Under the same preoperative evaluation protocol across all centers, the patients underwent blood tests, including routine blood counts and analysis of blood biochemistry, hemostatic function, immunological markers, and tumor markers. All patients underwent at least two imaging examinations, including ultrasound (US), computed tomography (CT), magnetic resonance imaging, or magnetic resonance cholangiopancreatography (MRCP), which provided information on the location of stones, biliary strictures, or liver atrophy. Definitive planning of the procedure was performed according to the findings of imaging studies. For patients with complex bilateral hepatolithiasis or those expected to undergo extensive liver resection, the ratio of the future remnant liver to total functional liver volume was calculated by volumetric CT scans or three-dimensional visualization techniques, and the indocyanine green 15-min retention rate was measured to evaluate the safety of surgeries.

Reoperative procedures

Patients who failed to reach Child-Pugh grade A before surgery underwent liver protection and supportive treatment. All surgeries were performed by experienced hepatobiliary surgeons. Patients with a history of repeated surgeries often have abdominal adhesions. After relieving the abdominal adhesions, a detailed surgical plan was created on the basis of the intraoperatively confirmed stone location, bile duct stenosis, liver atrophy, and function of the sphincter of Oddi (SO). The main surgical objective was to remove as many stones as possible and choose the appropriate method for biliary drainage. Routine intraoperative flexible choledochoscopy was performed after longitudinal incision of the common bile duct and removal of visible stones to determine the stone distribution and identify residual stones, which were directly extracted with a stone basket when needed. Then, SO function was evaluated, and the biliary drainage method was chosen based on SO function and the presence of residual stones; external T tube drainage was chosen for normal SO without residual stones, and cholangioenterostomy was chosen for SO laxity without residual stones. If residual stones could not be prevented, cholangioenterostomy and T-tube drainage were performed simultaneously[10]. Hepatectomy should be performed when bile duct stones are located within one liver lobe accompanied by atrophy or fibrosis, multiple liver abscesses secondary to bile duct infection, and suspected malignant masses. We applied the Pringle maneuver to occlude the blood inflow to the liver if necessary. Cholecystocholangiography was performed again after hepatic lobe resection to check for residual stones and to assess whether stones were cleared immediately. Bile acid was collected during the surgery and sent for bacterial culture and drug sensitivity testing in all patients.
Postoperative management
Standardized and meticulous postoperative patient management was performed in all patients at an early stage, including monitoring of vital signs, proper tissue perfusion, and nutritional support. Gastric acid secretion inhibitors and broad-spectrum antibiotics were administered immediately after the surgery, and antibiotics were adjusted according to the results of bile acid culture. Liver function tests were performed at 1, 3, and 7 d after the surgery. According to the Clavien-Dindo classification system, complications occurring within 90 d postoperatively were classified as grades I-V. Before discharge, all patients underwent abdominal CT examination again to further confirm whether the stone was removed immediately during the surgery. Patients who undergo external drainage of the T tube should undergo cholangiography or choledochoscopy after discharge to confirm or remove residual stones. In the present study, for patients with immediate stone residue, we usually performed choledochoscopy through the sinus of the T tube at 6-8 wk after the surgery; this was performed several times until the stone was removed or could not be removed by any means. For patients with immediate clearance, we performed T-tube cholangiography at 2 wk after surgery. In case a residual stone was observed, we performed choledo-choscopy as described above.

Follow-up
All patients underwent regular postoperative follow-up by the same team of surgeons in the hepatobiliary outpatient clinics or through telephone interviews at 2-3 mo after discharge. Follow-up evaluations included assessment of clinical symptoms and signs, routine blood tests, liver-function assessments, and US, CT, or MRCP to observe residual or recurrent stones. Postoperative residual stones were defined as stones that could not be removed by any method and were confirmed by US, CT, or MRCP 3 mo postoperatively[11]. Prognosis was evaluated according to the Terblanche criteria[12]. The patients were evaluated from 30 d to the end of the follow-up: (1) Grade I, no bile duct-related symptoms; (2) Grade II, occasional bile duct-related symptoms requiring no treatment; (3) Grade III, obvious bile duct-related symptoms requiring treatment; or (4) Grade IV, presence of anastomotic stricture or formation of bile duct stones requiring surgical intervention and causing disease-related cancer or death. Ter-blanche grades III and IV were considered to indicate a poor prognosis, which was the study endpoint.

Statistical analysis
Continuous variables are expressed as mean ± SD for normally distributed variables or median (interquartile range) for non-normally distributed variables, and appropriate statistical tests (the independent samples t-test or the Mann-Whitney U test) were used. Categorical variables are expressed as number (n) or proportion (%) and compared using the χ² test or Fisher’s exact test, as appropriate. Assigned cutoff values for continuous variables were derived from the Youden index[13]. Univariate logistic regression was used to determine the independent risk factors related to the prognosis of patients with recurrent hepatolithiasis after multiple biliary surgeries in the training cohort. Multivariate logistic regression was conducted using variables with clinical meaning or statistical significance in the univariate analyses. A nomogram for the prognosis of patients with recurrent hepatolithiasis after biliary surgery was created based on a multivariate logistic regression model. The performance of the nomogram was evaluated using the concordance index (C-index) and calibration plots with bootstrap samples. The C-index is a numerical measure of discriminative ability, and calibration plots are graphical evaluations of predictive ability that compare observed probabilities with nomogram-predicted probabilities. The area under the curve (AUC) of the receiver operating characteristic (ROC) curves and quality indices of models[14] in the training cohort and the external validation cohort were used to assess the predictive accuracy of the model in comparison with the three traditional classifications. The clinical usefulness of the nomogram was examined by determining the net benefit by using decision curve analysis (DCA)[15]. Clinical impact curves were also analyzed to demonstrate the predictive accuracy and clinical usefulness of the nomogram. The accuracy of the optimal cutoff value was assessed based on sensitivity, specificity, and predictive values. Statistical analyses were performed using R version 4.0.5, and SPSS version 23.0. Tests were 2-sided, and statistical significance was set at P < 0.05.

RESULTS
Baseline clinical characteristics and prognosis
Data of 943 consecutive patients who underwent surgical treatment for hepatolithiasis at the First Affiliated Hospital of Anhui Medical University between January 2015 and December 2020 were collected continuously. Among them, 363 patients (38.5%) with a history of biliary tract surgeries were classified as having recurrent hepatolithiasis. Of these 363 patients, 64 (17.6%) who did not fulfill the inclusion criteria were excluded: 28 were admitted to the hospital with a malignant tumor, 9 had a history of other abdominal surgery, 1 died in the perioperative period, 22 had incomplete clinical or
follow-up data, and 4 died of other causes after surgery. Ultimately, 299 (82.4%) patients were identified as the training cohort. Using the same criteria, 142 patients from the Second Affiliated Hospital of Anhui Medical University (57 cases), the First Affiliated Hospital of the University of Science and Technology of China (51 cases), and the First Affiliated Hospital of Bengbu Medical College (34 cases) were included in the external validation cohort. The two cohorts showed significant differences in the pre-, intra-, and postoperative clinical characteristics, as shown in Tables 1 and 2.

All patients had a history of multiple (1-6) biliary tract surgeries 1-55 years before this surgery. The training cohort included 199 (66.6%), 57 (19.1%), 33 (11.0%), and 10 (3.3%) patients who underwent 1, 2, 3, and ≥ 4 surgeries, respectively. In total, 167 (55.9%) patients had a history of cholecystectomy only, without hepatectomy or biliary drainage, while 61 (20.4%) and 42 (14.0%) patients had a history of hepatectomy and cholangioenterostomy, respectively. The validation cohort included 101 (71.1%), 29 (20.4%), 9 (6.3%), and 3 (2.1%) patients who underwent 1, 2, 3, and ≥ 4 surgeries, respectively; 167 (55.9%) patients had previously undergone only cholecystectomy, while 23 (16.2%) and 11 (7.7%) patients had a history of hepatectomy and cholangioenterostomy, respectively. Gall bladder removal was performed in the first (93.0%) or second (7.0%) surgeries for all patients. The appropriate surgical method was selected on the basis of preoperative evaluation and intraoperative conditions, and anastomosis reconstruction was performed depending on the presence of stenosis. In the training cohort, 229 (76.6%) and 283 (94.6%) patients achieved immediate and final clearance, respectively, and 129 (43.1%), 78 (26.1%), 66 (22.1%), and 26 (8.7%) patients showed Terblanche grades I-IV, respectively. In the validation cohort, 115 (81.0%) and 137 (96.5%) patients showed immediate and final clearance, respectively, and 53 (37.3%), 43 (30.3%), 34 (23.9%), and 12 (8.5%) patients showed Terblanche grades I-IV, respectively.

**Uni- and multivariate analysis in the training cohort**

The results of univariate and multivariate analyses of prognosis based on common variables, including demographic data, clinical symptoms, surgical histories, serologic data, and operative data, in the training cohort are listed in Table 3. The optimal cutoff values of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio were determined as described above. Factors that significantly affected prognosis in the univariate analysis were subjected to multivariate analysis, which demonstrated that more previous surgeries, bilateral hepatolithiasis, lack of immediate clearance, NLR ≥ 2.462, and albumin-to-globulin ratio (AGR) ≤ 1.5 were independent risk factors for a poor prognosis in patients with recurrent hepatolithiasis.

**Development and evaluation of the predictive model**

The independent risk factors associated with prognosis were then used to construct a nomogram for estimating the risk of poor prognosis (Figure 1). The nomogram demonstrated good predictive performance in estimating the risk of poor prognosis after reoperation for recurrent hepatolithiasis [C-index, 0.748; 95% confidence interval (CI): 0.687-0.810] in the training cohort and 0.743 (95% CI: 0.654-0.832) in the validation cohort. The constructed model was internally validated using the bootstrap validation method (n = 1000) to reduce the overfitting bias, and the calibration plots in the internal and external validations demonstrated good consistency between the observed and predicted probabilities. The predicted curves approximately overlapped with the reference curves, indicating good performance of the nomograms in both cohorts (Figure 2). The Brier score for overall performance, which assesses the difference between the observed and predicted values, was 0.175 (values closer to 0 indicated better predictive ability). The calibration slope, which assesses the agreement between the observed and predicted values, was 1.0 (values closer to 1 indicate better performance)[16]. An online calculator was developed, and the nomograms are freely available at https://ahmuptt.shinyapps.io/DynNomapp/ for prognosis.

**Comparison of the performance of the nomogram and traditional classifications models**

The discriminative performance of the three traditional classification models (Hepatolithiasis Research Group, Tsunoda classification, and Chinese Medical Association) were compared with that of the nomogram established in this study through ROC analyses (Figure 3). The AUC of the nomogram and the three classification models were 0.750, 0.544, 0.552, and 0.565 in the training cohort and 0.754, 0.608, 0.508, and 0.586 in the validation cohort, respectively. Thus, the nomogram showed better accuracy in predicting the prognosis for recurrent hepatolithiasis after reoperation. The optimal cutoff value of the nomogram total score was 77.5 in the ROC curve considering the maximum Youden index value, and the sensitivity and specificity for differentiating between good and poor prognoses were 62.0% and 79.2%, respectively. Using this cutoff value, patients with total nomogram scores of < 77.5 points or ≥ 77.5 points were classified as having a low or high risk of poor prognosis. In Figure 4, DCA graphically shows that the use of the nomogram to predict prognosis when the threshold probability ranged from 0.2 to 0.6 added more net benefit than the other three traditional classifications. The clinical impact curves of the nomogram indicated that the models had remarkable predictive power. Finally, in comparison with the other three traditional classifications, the fit indices of the nomogram are also visually reported in Figure 5.
## Table 1 Preoperative clinical characteristics of patients with recurrent hepatolithiasis after biliary surgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Training cohort</th>
<th>Validation cohort</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N = 299 )</td>
<td>( N = 142 )</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.785</td>
</tr>
<tr>
<td>Male</td>
<td>93 (31.1%)</td>
<td>46 (32.4%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>206 (68.9%)</td>
<td>96 (67.6%)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>153 (51.2%)</td>
<td>69 (48.6%)</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>146 (48.8%)</td>
<td>73 (51.4%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21.72 ± 2.87</td>
<td>22.19 ± 2.96</td>
<td>0.317</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td>0.204</td>
</tr>
<tr>
<td>No</td>
<td>39 (13.0%)</td>
<td>25 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>260 (87.0%)</td>
<td>117 (82.4%)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>0.162</td>
</tr>
<tr>
<td>No</td>
<td>175 (58.5%)</td>
<td>93 (65.5%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>124 (41.5%)</td>
<td>49 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
<td></td>
<td>0.060</td>
</tr>
<tr>
<td>No</td>
<td>227 (75.9%)</td>
<td>119 (83.8%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>72 (24.1%)</td>
<td>23 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>Number of previous surgeries</td>
<td></td>
<td></td>
<td>0.374</td>
</tr>
<tr>
<td>1</td>
<td>199 (66.6%)</td>
<td>101 (71.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57 (19.1%)</td>
<td>29 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 (11.0%)</td>
<td>9 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>10 (3.3%)</td>
<td>3 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Previous hepatectomy</td>
<td></td>
<td></td>
<td>0.293</td>
</tr>
<tr>
<td>No</td>
<td>238 (79.6%)</td>
<td>119 (83.8%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (20.4%)</td>
<td>23 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>Previous cholangioenterostomy</td>
<td></td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>No</td>
<td>257 (86.0%)</td>
<td>131 (92.3%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (14.0%)</td>
<td>11 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
<td>0.453</td>
</tr>
<tr>
<td>&lt; 2.462</td>
<td>188 (62.9%)</td>
<td>84 (59.2%)</td>
<td></td>
</tr>
<tr>
<td>≥ 2.462</td>
<td>111 (37.1%)</td>
<td>58 (40.8%)</td>
<td></td>
</tr>
<tr>
<td>&lt; PLR</td>
<td></td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>173.74</td>
<td>237 (79.3%)</td>
<td>114 (80.3%)</td>
<td></td>
</tr>
<tr>
<td>≥ 173.74</td>
<td>62 (20.7%)</td>
<td>28 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>AGR</td>
<td></td>
<td></td>
<td>0.430</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>104 (34.8%)</td>
<td>44 (31.0%)</td>
<td></td>
</tr>
<tr>
<td>≤ 1.5</td>
<td>195 (65.2%)</td>
<td>98 (69.0%)</td>
<td></td>
</tr>
<tr>
<td>TB (μmol/L)</td>
<td></td>
<td></td>
<td>0.262</td>
</tr>
<tr>
<td>&lt; 34.2</td>
<td>249 (83.3%)</td>
<td>112 (78.9%)</td>
<td></td>
</tr>
<tr>
<td>≥ 34.2</td>
<td>50 (16.7%)</td>
<td>30 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td></td>
<td></td>
<td>0.474</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>180 (60.2%)</td>
<td>90 (63.4%)</td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>119 (39.8%)</td>
<td>52 (36.6%)</td>
<td></td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>180 (60.2%)</td>
<td>99 (69.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>119 (39.8%)</td>
<td>43 (30.3%)</td>
<td></td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>146 (48.8%)</td>
<td>79 (55.6%)</td>
<td></td>
</tr>
<tr>
<td>≥ 150</td>
<td>153 (51.2%)</td>
<td>63 (44.4%)</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>271 (90.6%)</td>
<td>135 (95.1%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28 (9.4%)</td>
<td>7 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>CA19-9 (U/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 34</td>
<td>208 (69.6%)</td>
<td>104 (73.2%)</td>
<td></td>
</tr>
<tr>
<td>≥ 34</td>
<td>91 (30.4%)</td>
<td>38 (26.8%)</td>
<td></td>
</tr>
<tr>
<td>Hepatolithiasis research group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>19 (6.4%)</td>
<td>18 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>152 (50.8%)</td>
<td>67 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>100 (33.4%)</td>
<td>49 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>28 (9.4%)</td>
<td>8 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Tsunoda classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (5.7%)</td>
<td>19 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>166 (55.5%)</td>
<td>74 (52.1%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>100 (33.4%)</td>
<td>43 (30.3%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>16 (5.4%)</td>
<td>6 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Chinese medical association</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>238 (79.6%)</td>
<td>123 (86.6%)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>30 (10.0%)</td>
<td>8 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>25 (8.4%)</td>
<td>8 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>6 (2.0%)</td>
<td>3 (2.1%)</td>
<td></td>
</tr>
</tbody>
</table>


**DISCUSSION**

Our study indicated that for patients with recurrent hepatolithiasis following multiple biliary tract surgeries, multiple previous surgeries, bilateral hepatolithiasis, failure to clear the stones immediately, preoperative NLR ≥ 2.462, and preoperative AGR ≤ 1.5 were significant predictors. These factors combined the patients’ medical history, preoperative imaging and serological data, and intraoperative outcomes to comprehensively quantify the prognosis of patients in a concise and intuitive manner. Multiple validation methods also indicated that the model had sufficient statistical power to predict the prognosis. Moreover, considering the inconvenience of traditional nomograms for clinical use, an online version of the nomogram was built, which could be easily accessed using computers, smartphones, or other mobile devices, thereby greatly improving clinical practicability.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Training cohort</th>
<th>Validation cohort</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 299</td>
<td>N = 142</td>
<td></td>
</tr>
<tr>
<td>Operation duration (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>66 (22.1%)</td>
<td>38 (26.8%)</td>
<td>0.168</td>
</tr>
<tr>
<td>2-4</td>
<td>122 (40.8%)</td>
<td>64 (45.1%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4</td>
<td>111 (37.1%)</td>
<td>40 (28.2%)</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td></td>
<td></td>
<td>0.690</td>
</tr>
<tr>
<td>No</td>
<td>261 (87.3%)</td>
<td>122 (85.9%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (12.7%)</td>
<td>20 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Hepatic atrophy</td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>No</td>
<td>124 (41.5%)</td>
<td>72 (50.7%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>175 (58.5%)</td>
<td>70 (49.3%)</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic stenosis</td>
<td></td>
<td></td>
<td>0.182</td>
</tr>
<tr>
<td>No</td>
<td>238 (79.6%)</td>
<td>105 (73.9%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (20.4%)</td>
<td>37 (26.1%)</td>
<td></td>
</tr>
<tr>
<td>Extrahepatic stones</td>
<td></td>
<td></td>
<td>0.813</td>
</tr>
<tr>
<td>No</td>
<td>64 (21.4%)</td>
<td>29 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>235 (78.6%)</td>
<td>113 (79.6%)</td>
<td></td>
</tr>
<tr>
<td>Hepatectomy</td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>No</td>
<td>101 (33.8%)</td>
<td>60 (42.3%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>198 (66.2%)</td>
<td>82 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral hepatolithiasis</td>
<td></td>
<td></td>
<td>0.074</td>
</tr>
<tr>
<td>No</td>
<td>238 (79.6%)</td>
<td>123 (86.6%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (20.4%)</td>
<td>19 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Drainage mode</td>
<td></td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>External T tube drainage</td>
<td>205 (68.6%)</td>
<td>109 (76.8%)</td>
<td></td>
</tr>
<tr>
<td>Cholangioenterostomy</td>
<td>44 (14.7%)</td>
<td>19 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Combined drainage</td>
<td>50 (16.7%)</td>
<td>14 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Function of the SO</td>
<td></td>
<td></td>
<td>0.521</td>
</tr>
<tr>
<td>Normal</td>
<td>130 (43.5%)</td>
<td>72 (50.7%)</td>
<td></td>
</tr>
<tr>
<td>Dysfunction</td>
<td>62 (20.7%)</td>
<td>27 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Nonfunctional</td>
<td>83 (27.8%)</td>
<td>32 (22.5%)</td>
<td></td>
</tr>
<tr>
<td>Resected</td>
<td>24 (8.0%)</td>
<td>11 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Intraoperative bleeding (mL)</td>
<td></td>
<td></td>
<td>0.465</td>
</tr>
<tr>
<td>&lt; 400</td>
<td>285 (95.3%)</td>
<td>133 (93.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 400</td>
<td>14 (4.7%)</td>
<td>9 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td>0.112</td>
</tr>
<tr>
<td>No</td>
<td>258 (86.3%)</td>
<td>130 (91.5%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (13.7%)</td>
<td>12 (8.5%)</td>
<td></td>
</tr>
<tr>
<td>TB after operation (μmol/L)</td>
<td></td>
<td></td>
<td>0.131</td>
</tr>
<tr>
<td>&lt; 34.2</td>
<td>232 (77.6%)</td>
<td>119 (83.8%)</td>
<td></td>
</tr>
<tr>
<td>≥ 34.2</td>
<td>67 (22.4%)</td>
<td>23 (16.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Reoperation remains the preferred treatment for patients with recurrent hepatolithiasis. Satisfactory stone-clearance rates can be achieved through comprehensive preoperative evaluation, meticulous intraoperative exploration, and postoperative T-tube angiography with or without choledochoscopy. All patients in this study showed recurrent hepatolithiasis after biliary tract surgery. The immediate and final clearance rates were 78.0% and 95.2%, respectively, which were lower than those reported in previous studies that did not distinguish between primary and recurrent hepatolithiasis.[17-19].

In addition to requiring traumatic wounds, repeated surgeries impose an enormous psychological and economic burden on patients and their families. Moreover, considering the difficulty in guaranteeing the prognosis, patients will inevitably blame the surgeon, raising the possibility of doctor-patient conflict. Thus, accurate evaluation of the condition of patients with recurrent hepatolithiasis and provision of references for clinical efficacy are essential. However, the existing classification models for hepatolithiasis cannot describe the curative effect of prospective evaluation. In this study, we collected clinical and follow-up data of patients who underwent reoperation for recurrent hepatolithiasis at four large hepatobiliary centers and established and validated a nomogram model based on multicenter data. To the best of our know ledge, this is the first study to establish a predictive model for prognosis following multiple biliary tract surgeries in patients with recurrent hepatolithiasis after initial biliary surgery.

The nomogram clearly showed that the risk of a worse prognosis increased with the number of previous surgeries. The serious abdominal adhesions caused by repeated surgeries and the resultant disconnection and anastomosis of the tube will lead to complicated intraoperative conditions, making it difficult to excise the lesion and clear the stones accurately and increasing the possibility of a poor prognosis. Moreover, the nomogram showed that the model score for cases with three previous surgeries (67 points) was much higher than that for cases with two previous surgeries (33 points), suggesting that three previous surgeries significantly increased the possibility of a poor prognosis. Thus, in patients with an extended surgical history for the treatment of hepatolithiasis, a curative procedure and good quality of life are difficult to achieve, and such patients may experience prolonged disease in addition to the tremendous economic pressure caused by the repeated surgeries. Therefore, the benefits and disadvantages of repeat surgeries for patients should be weighed with care. We propose that conservative or non-open surgical treatment should be considered as the first choice of treatment, with conventional open surgery considered the second choice, for patients with a total nomogram score of > 77.5 or patients who meet the following criteria: (1) ≥ 3 previous surgeries; (2) No obvious bile duct stenosis on preoperative imaging examinations; (3) No suspicious malignant liver-occupying sites; and (4) No obvious jaundice or cholangitis.

In recent years, newer interventional therapies such as percutaneous transhepatic choledochoscopic lithotripsy (PTCSL) have been attempted by an increasing number of surgeons. Since its development in the 1970s[20], PTCSL has undergone major advancements and shows an ideal effect when combined with 3D visualization technology[21,22]. One study reported that PTCSL could be performed in patients with biliary strictures and yielded an optimal effect[23]. However, since most hepatobiliary surgeons have not gained expertise in this new technique, patients undergoing PTCSL were not included in this study for comparison. Through continuous learning, we hope to conduct prospective studies in the future to verify and enrich the pre-diction model of the nomogram in our study.
Table 3 Univariable and multivariable logistic regression analyses of the risk factors for a poor prognosis in patients with recurrent hepatolithiasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Sex: Female/Male</td>
<td>0.328</td>
<td>1.311 (0.762-2.257)</td>
</tr>
<tr>
<td>Age (yr): ≥ 60/ &lt; 60</td>
<td>0.603</td>
<td>1.139 (0.697-1.862)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.068</td>
<td>0.921 (0.843-1.006)</td>
</tr>
<tr>
<td>Abdominal pain: Yes/No</td>
<td>0.066</td>
<td>0.525 (0.264-1.043)</td>
</tr>
<tr>
<td>Fever: Yes/No</td>
<td>0.083</td>
<td>1.551 (0.945-2.547)</td>
</tr>
<tr>
<td>Jaundice: Yes/No</td>
<td>0.406</td>
<td>1.270 (0.724-2.230)</td>
</tr>
<tr>
<td>Previous operation times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 times/1 time</td>
<td>0.384</td>
<td>1.337 (0.695-2.571)</td>
</tr>
<tr>
<td>3 times/1 time</td>
<td>&lt; 0.001</td>
<td>4.840 (2.241-10.454)</td>
</tr>
<tr>
<td>≥ 4 times/1 time</td>
<td>0.005</td>
<td>7.340 (1.827-29.498)</td>
</tr>
<tr>
<td>Previous hepatectomy: Yes/No</td>
<td>0.026</td>
<td>1.936 (1.082-3.463)</td>
</tr>
<tr>
<td>Previous cholangioenterostomy: Yes/No</td>
<td>0.455</td>
<td>1.299 (0.654-2.577)</td>
</tr>
<tr>
<td>NLR: ≥ 2.462/ &lt; 2.462</td>
<td>0.001</td>
<td>2.334 (1.410-3.863)</td>
</tr>
<tr>
<td>PLR: ≥ 173.74/ &lt; 173.74</td>
<td>0.069</td>
<td>1.714 (0.959-3.065)</td>
</tr>
<tr>
<td>AGR: ≤ 1.5/ &gt; 1.5</td>
<td>0.002</td>
<td>2.459 (1.393-4.338)</td>
</tr>
<tr>
<td>TB (μmol/L): ≥ 34.2/&lt; 34.2</td>
<td>0.381</td>
<td>1.330 (0.703-2.518)</td>
</tr>
<tr>
<td>ALT (IU/L): ≥ 50/&lt; 50</td>
<td>0.664</td>
<td>1.117 (0.677-1.843)</td>
</tr>
<tr>
<td>AST (IU/L): ≥ 40/&lt; 40</td>
<td>0.169</td>
<td>1.418 (0.862-2.333)</td>
</tr>
<tr>
<td>ALP (IU/L): ≥ 200/&lt; 200</td>
<td>0.060</td>
<td>1.613 (0.981-2.654)</td>
</tr>
<tr>
<td>GGT (IU/L): ≥ 150/&lt; 150</td>
<td>0.464</td>
<td>1.202 (0.735-1.967)</td>
</tr>
<tr>
<td>HBsAg: Positive/ Negative</td>
<td>0.791</td>
<td>0.890 (0.377-2.103)</td>
</tr>
<tr>
<td>CA19-9 (U/mL): ≥ 34/&lt; 34</td>
<td>0.058</td>
<td>1.656 (0.984-2.787)</td>
</tr>
<tr>
<td>Operation duration (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4/≤ 2</td>
<td>0.803</td>
<td>1.085 (0.572-2.057)</td>
</tr>
<tr>
<td>&gt; 4/≤ 2</td>
<td>0.497</td>
<td>0.794 (0.408-1.545)</td>
</tr>
<tr>
<td>Liver cirrhosis: Yes/No</td>
<td>0.049</td>
<td>2.008 (1.004-4.016)</td>
</tr>
<tr>
<td>Hepatic atrophy: Yes/No</td>
<td>0.469</td>
<td>0.833 (0.507-1.368)</td>
</tr>
<tr>
<td>Intrahepatic stenosis: Yes/No</td>
<td>0.054</td>
<td>1.772 (0.989-3.176)</td>
</tr>
<tr>
<td>Extrahepatic stones: Yes/No</td>
<td>0.481</td>
<td>0.810 (0.450-1.456)</td>
</tr>
<tr>
<td>Hepatectomy: Yes/No</td>
<td>0.019</td>
<td>0.543 (0.326-0.904)</td>
</tr>
<tr>
<td>Bilateral hepatolithiasis: Yes/No</td>
<td>0.011</td>
<td>2.114 (1.183-3.775)</td>
</tr>
<tr>
<td>Drainage mode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangioenterostomy/External T tube drainage</td>
<td>0.292</td>
<td>0.663 (0.308-1.425)</td>
</tr>
<tr>
<td>Combined drainage/External T tube drainage</td>
<td>0.325</td>
<td>1.381 (0.726-2.629)</td>
</tr>
<tr>
<td>Function of the SO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfunction/Normal</td>
<td>0.760</td>
<td>1.110 (0.567-2.173)</td>
</tr>
<tr>
<td>Nonfunctional/Normal</td>
<td>0.051</td>
<td>1.791 (0.997-3.219)</td>
</tr>
<tr>
<td>Resected/Normal</td>
<td>0.845</td>
<td>0.905 (0.332-2.464)</td>
</tr>
<tr>
<td>Intraoperative bleeding (mL): ≥ 400/&lt; 400</td>
<td>0.682</td>
<td>1.264 (0.412-3.883)</td>
</tr>
</tbody>
</table>
Blood transfusion: Yes/No                           0.053  1.946 (0.993-3.815)
TB after operation (μmol/L): ≥ 34.2/< 34.2          0.908  1.035 (0.576-1.862)
Bile culture: Positive/Negative                      0.384  1.255 (0.753-2.093)
Clavien-Dindo classification: ≥ III/< III            0.541  1.430 (0.455-4.494)
Hospitalization expenses                            0.913  1.000 (1.000-1.000)
Immediate clearance: No/Yes                          < 0.001  3.271 (1.874-5.711) 0.005  2.398 (1.304-4.409)
Final clearance: No/Yes                              0.030  3.098 (1.117-8.595) 0.558  1.448 (0.420-4.996)

BMI: Body mass index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; AGR: Albumin-to-globulin ratio; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; HbsAg: Hepatitis B surface antigen; CA19-9: Carbohydrate antigen19-9; SO: Sphincter of Oddi; OR: Odds ratio; CI: Confidence interval.

The treatment of bilateral hepatolithiasis is more complicated and difficult than that of unilateral hepatolithiasis: Intraoperative lithotomy is more difficult, and the postoperative residual stone rate is higher[19]. Moreover, even if liver resection is performed, it is difficult to avoid residual stones on the opposite side of the liver, resulting in a higher probability of poor prognosis or recurrence. Many studies have confirmed these outcomes[18,19,24,25]. Hepatectomy on the severe side combined with choledochoscopic lithotripsy is a better treatment for bilateral hepatolithiasis with or without intrahepatic biliary strictures[18,19]. Due to the repeated stone stimulation and attacks of cholangitis, the affected hepatic segments are usually damaged, atrophied, or narrowed, while the unaffected hepatic segments may show compensatory hyperplasia. Anatomical hepatectomy is a crucial factor in the treatment of hepatolithiasis[18,26,27]. In addition, for bilateral hepatolithiasis, the use of three-dimensional reconstruction has been shown to improve the immediate clearance rate (96.1% vs 81%) and the final clearance rate (100% vs 90.5%)[28].

The nomogram also included two laboratory indicators, NLR and AGR. As common indicators of immune function and inflammation, NLR and AGR have been used to determine the prognosis of various benign and malignant diseases[29-32]. AGR reflects the degree of inflammation as well as the nutritional status of the human body, which can form a vicious cycle and promote disease development [33]. A reduction or inversion of AGR, which also appears in cirrhosis and chronic hepatitis, indicates serious liver damage. A previous study indicated that elevated NLR is an independent risk factor for secondary intrahepatic cholangiocarcinoma (ICC) after surgery for hepatolithiasis[34], but the association between elevated NLR and ICC remains to be elucidated. Inflammation and subtle
alterations in immune regulation may play important roles in this process[35]. We found that NLR and AGR independently affected the prognosis of patients with recurrent hepatolithiasis. Therefore, we included both in the nomogram and validated them in the validation group.

This study highlights the problem of concomitant ICC, which has been reported to occur in 2.5% of patients with intrahepatic stones[19]. To avoid the influence of malignant tumors on the prognosis of patients with hepatolithiasis during the follow-up period, patients in the training and validation groups who showed ICC at the time of hospitalization were excluded (7.7%). Moreover, cancer was regarded as one of the long-term complications of hepatolithiasis in the follow-up, and was classified as a follow-up endpoint (15 patients, 3.4%), in agreement with previous studies[19,25,34,36,37].

Our study has some limitations that merit discussion. First, although laparoscopic treatment of biliary tract stones has gradually attracted research attention, some studies have suggested that laparoscopic treatment of biliary tract stones in patients with a history of biliary tract surgery is feasible and has advantages[38,39]. In our study, only 35 and 19 patients in the training and validation groups, respectively, were completely operated by laparoscopy. We did not use laparoscopic surgery as a routine procedure because all patients included in this study had a history of biliary tract surgery, unlike the previous studies. During the actual surgeries, the abdominal cavity adhesions of patients with different surgical durations were very different. Conversely, a previous study reported that laparoscopic surgery and open surgery for patients with a history of biliary system surgery showed no statistically significant differences in the surgical duration, blood loss, the postoperative hospitalization
duration, postoperative complications, and the calculi clearance rate\cite{40}. Moreover, considering the majority of rural patients, economic affordability also needs to be considered. Thus, since many patients had undergone multiple biliary tract surgeries, we chose the most suitable surgical mode according to the individual patient characteristics.

Moreover, this was a retrospective study with inherent defects as a result of potential biases, and prospective validation is required to confirm the value of the findings. Since the aim of this study was to establish prognosis prediction in surgically treated recurrent hepatolithiasis patients, subsequent
treatment and prognosis of patients who progressed to ICC after reoperation were not analyzed further. Lastly, the present algorithm considered only patients who underwent surgery; therefore, a selection bias is likely.

CONCLUSION

In conclusion, our study is the first to develop and validate a novel online nomogram based on independent risk factors to dynamically predict the prognosis of patients with recurrent hepatolithiasis after reoperation. The nomogram is easy to use, highly accurate, and shows excellent calibration. The nomogram demonstrated superior performance and discriminative power compared to the three traditional classifications, which can help clinicians alert people at a higher risk of poor prognosis as early as possible and provide information for designing personalized clinical treatment of different patients.

ARTICLE HIGHLIGHTS

Research background
Hepatolithiasis is a refractory benign disease with high recurrence rate. Many patients have poor prognosis.

Research motivation
There have been no large studies of patients with hepatolithiasis, and there are no clear risk factors for prognosis in these patients.
**Research objectives**
We aimed to find the risk factors affecting the prognosis of these patients and establish a prediction model which is conducive to clinical surgical decision-making.

**Research methods**
We collected data of hepatolithiasis patients in four large medical centers, identified independent risk factors and established nomogram. And then we used the concordance index, calibration, area under curve, decision curve analysis, clinical impact curves, and visual fit indices to evaluate the accuracy of the nomogram.

**Research results**
Multiple previous surgeries, bilateral hepatolithiasis, absence of immediate clearance, neutrophil-to-lymphocyte ratio ≥ 2.462, and albumin-to-globulin ratio ≤ 1.5 were found to be independent factors influencing the prognosis. And our nomogram has a higher predictive value than traditional classifications.

**Research conclusions**
A nomogram for predicting the prognosis of patients with recurrent hepatolithiasis was established for the first time, and an online calculator was set up to help surgeons make clinical decisions.

**Research perspectives**
More medical centers included, more data collection, and application of “Artificial Intelligence”.

---

**ACKNOWLEDGEMENTS**

We would like to thank Prof. Faming Pan (Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University), who had full access to all the data in the present study, for ensuring the integrity and accuracy of the data analysis.

---

**FOOTNOTES**

**Author contributions:** Pu T, Chen JM, Li ZH, and Jiang D contributed to the data analysis and participated in drafting the article; Guo Q, Li AQ, and Cai M extracted the clinical data and calculated the clinical correlations; Chen ZX, Xie K and Zhao YJ interpreted the results and revised the manuscript; Liu FB, Hou H, Lu Z, Wang C, and Geng XP gave final approval of the version to be published; and all authors contributed to the design and interpretation of the study and to further drafts and approved the final version to be published.

**Supported by** the Key Research and Development Plan of Anhui Province, No. 1804h08020239.

**Institutional review board statement:** The study was reviewed and approved by the Institutional ethics committees of the First Affiliated Hospital of Anhui Medical University (Approval No: Quick-FJ2021-08-19).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Data sharing statement:** No additional data are available.

**STROBE statement:** We have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** China

**ORCID number:** Tian Pu 0000-0002-6961-0814; Jiang-Ming Chen 0000-0003-4683-5866; Zi-Han Li 0000-0003-0378-0252; Dong Jiang 0000-0003-3372-6062; Qi Guo 0000-0002-3808-0224; Ang-Qing Li 0000-0002-5156-1056; Ming Cai 0000-0003-0001-0316; Zi-Xiang Chen 0000-0002-5782-2625; Kun Xie 0000-0002-2491-4998; Yi-Jun Zhao 0000-0001-9082-8861; Cheng
REFERENCES


25. Chen DW, Tung-Ping Poon R, Liu CL, Fan ST, Wong J. Immediate and long-term outcomes of hepatocytectomy for


Observational Study

Effect of *Bifidobacterium longum* 35624 on disease severity and quality of life in patients with irritable bowel syndrome

Jean-Marc Sabaté, Franck Iglicki

**Abstract**

**BACKGROUND**

*Bifidobacterium longum* 35624 has shown efficacy in improving irritable bowel syndrome (IBS) symptoms compared with placebo in double-blind randomized studies. However, few data are available from real-life clinical practice or from studies that used Rome IV criteria to diagnose IBS.

**AIM**

To assess the effect of *B. longum* 35624 on IBS severity and quality of life in a real-life setting.

**METHODS**

From November 2018 to January 2020, 278 patients with IBS (according to Rome IV criteria) were enrolled in a prospective, open-label, multicenter observational study by private practice gastroenterologists to received one capsule of *B. longum* 35624 (10^9 colony-forming units) per day for 30 d. Participation in the study was independently proposed to patients during spontaneous consultations. Disease severity (assessed by the IBS severity scoring system) and patient quality of life (assessed by the IBS quality of life questionnaire) were compared between the inclusion visit (baseline) and the visit at the end of 30 d of treatment. The characteristics of patients were described at baseline. Continuous variables comparisons between inclusion and end-of-treatment visits were performed using the t-test and Kruskal-Wallis test. Categorical variables comparisons were performed using the χ² test.

**RESULTS**
A total of 233 patients, with a mean age of 51.4 years and composed of 71.2% women, were included in the study. Of these patients, 48.1% had moderate IBS and 46.4% had severe IBS. After a 30-d treatment period with one B. longum 35624 capsule per day, a significant decrease in IBS severity was observed compared to baseline (mean ± SD, IBS severity scoring system scores: 208 ± 104 vs 303 ± 81, P < 0.001) and 57% of patients moved to lower severity categories or achieved remission. The quality of life of patients was also improved by the treatment (IBS Quality of Life questionnaire score: 68.8 ± 20.9 vs 60.2 ± 20.5; P < 0.001) and 63.8% of patients were satisfied with the treatment.

CONCLUSION
Thirty days of treatment with B. longum 35624 reduces disease severity and improves the quality of life of patients with IBS, particularly those with the most severe forms of IBS.

Key Words: Irritable bowel syndrome; Probiotics; Bifidobacterium longum; Quality of life; Severity of illness index; Abdominal pain

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Our observational study of 233 patients with moderate-to-severe irritable bowel syndrome demonstrated that 30 d of treatment with once-daily Bifidobacterium longum 35624 (a probiotic) resulted in a significant improvement in symptoms and disease severity for two thirds of the patients. Patient quality of life was also significantly improved, and the majority of patients expressed that they were satisfied with the treatment.

Citation: Sabaté JM, Iglicki F. Effect of Bifidobacterium longum 35624 on disease severity and quality of life in patients with irritable bowel syndrome. World J Gastroenterol 2022; 28(7): 732-744

INTRODUCTION
Irritable bowel syndrome (IBS) is a chronic functional bowel disorder, which combines abdominal pain and transit disorders and affects approximately 4% to 10% of the population, depending on whether the Rome III or Rome IV definition is used[1]. IBS may be responsible for impairment in quality of life, especially in the most severe forms, which represent approximately 25% of cases[2]. The pathophysiology of IBS is complex and multifactorial, involving both peripheral and central factors[3]. Several lines of evidence suggest that the intestinal microbiota plays a role in the pathophysiology of IBS, including the existence of post-infectious forms of IBS, and the difference in microbiota composition between patients with IBS and healthy individuals. Moreover, studies carried out in humans and in animal models have shown that strategies targeting the gut microbiota are effective in the treatment of IBS[4].

Probiotics are available over the counter and few have real recommendations from learned societies and/or claims substantiated by findings from properly conducted clinical trials. Few probiotics have shown efficacy in improving IBS symptoms relative to placebo in randomized double-blind studies[5], as it is the case with Bifidobacterium longum 35624 (formerly B. infantis) with two conclusive randomized clinical trials[6,7]. Studies of probiotics have been criticized for the criteria used to measure efficacy[8]. Few studies have thus far adopted the efficacy criteria for the assessment of treatments for IBS specified by the United States Food and Drug Administration or the European Medicines Agency (EMA)[9-11]. At a minimum, studies should demonstrate the ability of a probiotic to reduce disease severity, as is the case for fecal microbiota transplant studies[12], and to improve quality of life. However, in most clinical studies of probiotics, disease severity at baseline is often not reported, patients with mild or moderate forms of IBS are recruited and quality of life is not evaluated. The strengthening of the diagnostic criteria for IBS, with the deletion of the term “dis-comfort” and the modification of the frequency of abdominal pain that patients must present in the new version of the Rome criteria (the Rome IV criteria), had the effect of decreasing the incidence of the disease and increasing the percentage of severe forms among patients[13]. Few studies have assessed the efficacy of probiotics in the Rome IV era.

The aim of our study was to assess the effect of B. longum 35624 treatment on IBS severity and patients’ quality of life in real-life clinical practice.
MATERIALS AND METHODS

Study design and population
This was a prospective, open-label, multicenter study (FLORAVIE study). Patients over 18 years of age with IBS diagnosed according to the Rome IV criteria were enrolled from November 2018 to January 2020. Patients had to have had recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, associated with two or more of the following criteria: Pain related to defecation or associated with a change in frequency of stool or associated with a change in form (appearance) of stool. IBS diagnosis criteria had to be fulfilled for the last 3 mo with symptom onset at least 6 mo prior to diagnosis. Participation in the study was proposed by private gastroenterologists during spontaneous consultations with new or former patients consulting for their IBS. The gastroenterologist was free to prescribe or not B. longum 35624 according to his appreciation if he thought it was a good therapeutic option for the patient. Participating patients were seen in consultation at a second visit after 30 d of treatment.

This study was conducted according to the guidelines of the Declaration of Helsinki and the Guidelines for Good Clinical Practice (EMA/Committee for Medicinal Products for Human Use/International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use/135/1995) and approved by the North-west III Protection of Persons Committee of the University Hospital of Caen, France. Study conduct was in full accordance with French applicable laws and regulations, including but not limited to current International Council on Harmonisation-Good Clinical Practices. All participants received an information note and were informed about the objectives, methodology and purpose of the study, and those who agreed to participate were required to provide oral non-opposition prior to entry, according to France regulation. The study was registered on clinicaltrials.gov under study number NCT04662502. To ensure that the patient population was representative of the country, participants were recruited by gastroenterologists working in private practice (with a maximum of 12 patients per investigator) throughout France.

Eligible patients were included only if they met all the inclusion and none of the exclusion criteria. Previous treatment with B. longum 35624 was an exclusion criterion. The use of other probiotics was not allowed within 2 wk from inclusion. Recent antibiotic treatment or treatment modification that could have an impact on microbiota, gut motility or digestive symptoms were prohibited. Participants with a history of abdominal surgery (except for appendectomy, cholecystectomy, surgery for hemorrhoids or cesarean section) were excluded.

After obtaining the patient’s oral non-opposition to the study and verifying the inclusion and exclusion criteria, treatment with B. longum 35624 was initiated. Patients who were included in the study were to take one capsule per day containing 10⁹ colony-forming units of B. longum 35624 for 30 d. Patients were advised not to change their diet during the study. Clear instructions were provided to patients and gastroenterologists on how to complete and review the study questionnaires.

During the first visit, patients’ demographics (sex, age), medical history, medical conditions other than IBS and concomitant treatments, disease characteristics (mode of onset, disease duration, transit sub-type, treatments, associated conditions) and the effect of IBS on their personal, professional, and social life were collected. The effect of IBS on the patient’s personal, professional, and social life was assessed using a six-point Likert scale, ranging from “no impact” to “very severe impact”. Patients recorded their treatment intake in a daily diary. Stool consistency was assessed using the Bristol stool scale[14] at baseline and every 10 d throughout the study and recorded in the diary. The severity of IBS was determined using the IBS severity scoring system (IBS-SSS), which consists of five domains assessing the intensity and frequency of abdominal pain, intensity of abdominal distension, satisfaction with transit and quality of life. IBS-SSS scores range from 0 to 500, with scores < 75 indicating remission, scores between 75 and 174 indicating mild severity, scores between 175 and 299 indicating moderate severity, and scores between 300 and 500 indicating severe disease[15]. Quality of life was assessed using the IBS quality of life questionnaire (IBS-QOL), which consists of 34 questions exploring eight dimensions, including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationships, with scores ranging from 0 to 100, 100 indicating the best quality of life[16]. IBS-SSS and IBS-QOL questionnaires were administered at baseline before treatment and after 30 d of treatment with B. longum 35624 (second visit). Satisfaction with the treatment was assessed by gastroenterologists and by patients independently using a five-point Likert scale. Adherence to treatment was assessed by recording daily medication intake in the patient’s diary and based on the gastroenterologist’s records at the follow-up visit. Adverse events (AEs) occurring throughout the study were recorded, as were any events that could have interfered with B. longum 35624 treatment, including changes in diet.

The main outcomes were the proportion of patients who had a decrease of > 50 points in the IBS-SSS score and the proportion of patients who had an increase of > 10 points in the IBS-QOL score after a 30-d treatment with B. longum 35624. Secondary outcomes were the change in IBS-SSS and IBS-QOL scores, the proportion of patients who had a shift from one severity category to another, and the proportion of patients and gastroenterologists who were satisfied with the treatment.
Considering a variation in the IBS-QOL score of 15, the total number of patients to be assessed was determined to be 203 to obtain a level of precision of 10%. To maintain this level of precision considering that a certain number of patients (about 10%) would not be eligible for primary endpoint analysis (missing data), 220 patients had to be included in the study.

The safety population included all patients who received at least one dose of *B. longum* 35624. The evaluable population included all patients in the safety population with at least one post-baseline assessment who did not use any drugs that could have interfered with effect of *B. longum* 35624.

**Statistical methods and data analysis**

The statistical methods of this study were reviewed by a biomedical statistician from ICTA (International Clinical Trials Association, fontaine-les-Dijon, France). Statistical analyses were performed using SAS® software (version 9.2-SAS Institute, North Carolina, United States). Means and SD or medians and interquartile ranges (IQR) were calculated for continuous variables and comparisons were performed using the *t*-test and Kruskal-Wallis test. Frequencies were calculated for categorical variables and comparisons were performed using the *χ*² test. Comparisons of IBS-QOL or IBS-SSS scores at baseline vs at the end of treatment were performed using the Wilcoxon test. Correlations between variables were evaluated using the Pearson correlation coefficient. Missing data were not replaced.

**RESULTS**

This observational study was proposed to 129 gastroenterologists throughout France, of whom, 86 were interested in participating and 61 recruited patients. They were representative of the profession with 80% being male (vs 70% nationally) and distributed all over the territory, in 12 of the 13 French regions, to be representative of the national practice (Supplementary Figure 1).

From November 2018 to January 2020, 278 patients were enrolled in the study, of which 233 were included in the evaluable population. The detailed flowchart of the population is shown in Figure 1.

**Baseline data**

Patient baseline characteristics are presented in Table 1. The patient cohort consisted primarily of middle-aged women, most were non-smokers (87.7%) and did not consume alcohol (63.9%). Body mass index was classified as normal in 51.2% of patients, as overweight in 33.5%, as obese in 9.4%, and as underweight in 5.2%. Thirty-two percent of patients (n = 75) had at least one pre-existing condition, the most common of which were gastrointestinal conditions other than IBS (7.3%, n = 17; gastroesophageal reflux, hiatal hernia, colonic diverticulum, hemorrhoids), endocrine (5.2%, n = 12) and vascular disorders (5.2%, n = 12). In addition, 21.0% of patients received at least one concomitant treatment that was unlikely to interfere with study treatment. At baseline, thirty-seven patients (15.8%) had already been on a specific diet [low fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) diet, n = 7; gluten-free diet, n = 2; lactose-free diet, n = 4] for more than 1 mo, and did not change it during the study period.

IBS was triggered by an acute episode of gastroenteritis (post-infectious IBS) in nine patients (3.9%) and by a stressful event in 91 patients (34.8%), with sexual abuse reported in eight patients. No triggering factor for IBS was identified in 127 patients (54.5%). Median disease duration was 8.0 years (IQR: 3.0, 16.0). Diarrhea-predominant IBS (IBS-D) (38.2%) was the most common subtype, while IBS of unidentified subtype (IBS-U; 5.2%) was the least common; antispasmodics and transit modifiers had previously been prescribed respectively in 65.7% and 35.7% of IBS patients.

At baseline, the average IBS severity among the included patients was high (mean ± SD IBS-SSS score 303.0 ± 81.5), with the majority having either a severe or a moderate form of the disease, and fewer than 10% having mild disease severity or being in remission. IBS severity scores were different across transit pattern subtypes (Figure 2A) with constipation-predominant IBS (IBS-C) and IBS-D having the highest scores (326.8 ± 84.2 and 300.8 ± 81.2, respectively) compared to mixed IBS (IBS-M) and IBS-U (284.1 ± 77.9 and 277.8 ± 54.3, respectively).

Quality of life was impaired in most patients (mean ± SD IBS-QOL score 60.2 ± 20.5). Quality of life scores were comparable across transit pattern subtypes (Figure 2B) and were correlated with disease severity (*r* = −0.66, *P* < 0.0001), with higher IBS severity associated with lower the IBS-QOL scores (i.e., lower quality of life) (Figure 3). In 96% of cases, IBS impaired the patient’s personal, professional, and social life (low or mild in 26.0% of patients, moderate in 37.7%, and severe or very severe in 36.3% of patients).

**Follow-up data**

Duration of exposure to study treatment was 28.2 ± 3.4 d (mean ± SD). Patients’ adherence to treatment according to patients’ daily diary reports was excellent, with 94.1% adherence to capsule intake.

After 30 d of treatment, there was a significant reduction in IBS severity compared with baseline (mean ± SD overall IBS-SSS score: 208.1 ± 104.8 vs 303.2 ± 81.5, *P* < 0.001) (Figure 4A), and in all transit subtypes (Figure 2A). The evolution of IBS severity scores was similar and of the same magnitude in all

**Statistical methods and data analysis**

The statistical methods of this study were reviewed by a biomedical statistician from ICTA (International Clinical Trials Association, fontaine-les-Dijon, France). Statistical analyses were performed using SAS® software (version 9.2-SAS Institute, North Carolina, United States). Means and SD or medians and interquartile ranges (IQR) were calculated for continuous variables and comparisons were performed using the *t*-test and Kruskal-Wallis test. Frequencies were calculated for categorical variables and comparisons were performed using the *χ*² test. Comparisons of IBS-QOL or IBS-SSS scores at baseline vs at the end of treatment were performed using the Wilcoxon test. Correlations between variables were evaluated using the Pearson correlation coefficient. Missing data were not replaced.

**RESULTS**

This observational study was proposed to 129 gastroenterologists throughout France, of whom, 86 were interested in participating and 61 recruited patients. They were representative of the profession with 80% being male (vs 70% nationally) and distributed all over the territory, in 12 of the 13 French regions, to be representative of the national practice (Supplementary Figure 1).

From November 2018 to January 2020, 278 patients were enrolled in the study, of which 233 were included in the evaluable population. The detailed flowchart of the population is shown in Figure 1.

**Baseline data**

Patient baseline characteristics are presented in Table 1. The patient cohort consisted primarily of middle-aged women, most were non-smokers (87.7%) and did not consume alcohol (63.9%). Body mass index was classified as normal in 51.2% of patients, as overweight in 33.5%, as obese in 9.4%, and as underweight in 5.2%. Thirty-two percent of patients (n = 75) had at least one pre-existing condition, the most common of which were gastrointestinal conditions other than IBS (7.3%, n = 17; gastroesophageal reflux, hiatal hernia, colonic diverticulum, hemorrhoids), endocrine (5.2%, n = 12) and vascular disorders (5.2%, n = 12). In addition, 21.0% of patients received at least one concomitant treatment that was unlikely to interfere with study treatment. At baseline, thirty-seven patients (15.8%) had already been on a specific diet [low fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) diet, n = 7; gluten-free diet, n = 2; lactose-free diet, n = 4] for more than 1 mo, and did not change it during the study period.

IBS was triggered by an acute episode of gastroenteritis (post-infectious IBS) in nine patients (3.9%) and by a stressful event in 91 patients (34.8%), with sexual abuse reported in eight patients. No triggering factor for IBS was identified in 127 patients (54.5%). Median disease duration was 8.0 years (IQR: 3.0, 16.0). Diarrhea-predominant IBS (IBS-D) (38.2%) was the most common subtype, while IBS of unidentified subtype (IBS-U; 5.2%) was the least common; antispasmodics and transit modifiers had previously been prescribed respectively in 65.7% and 35.7% of IBS patients.

At baseline, the average IBS severity among the included patients was high (mean ± SD IBS-SSS score 303.0 ± 81.5), with the majority having either a severe or a moderate form of the disease, and fewer than 10% having mild disease severity or being in remission. IBS severity scores were different across transit pattern subtypes (Figure 2A) with constipation-predominant IBS (IBS-C) and IBS-D having the highest scores (326.8 ± 84.2 and 300.8 ± 81.2, respectively) compared to mixed IBS (IBS-M) and IBS-U (284.1 ± 77.9 and 277.8 ± 54.3, respectively).

Quality of life was impaired in most patients (mean ± SD IBS-QOL score 60.2 ± 20.5). Quality of life scores were comparable across transit pattern subtypes (Figure 2B) and were correlated with disease severity (*r* = −0.66, *P* < 0.0001), with higher IBS severity associated with lower the IBS-QOL scores (i.e., lower quality of life) (Figure 3). In 96% of cases, IBS impaired the patient’s personal, professional, and social life (low or mild in 26.0% of patients, moderate in 37.7%, and severe or very severe in 36.3% of patients).

**Follow-up data**

Duration of exposure to study treatment was 28.2 ± 3.4 d (mean ± SD). Patients’ adherence to treatment according to patients’ daily diary reports was excellent, with 94.1% adherence to capsule intake.

After 30 d of treatment, there was a significant reduction in IBS severity compared with baseline (mean ± SD overall IBS-SSS score: 208.1 ± 104.8 vs 303.2 ± 81.5, *P* < 0.001) (Figure 4A), and in all transit subtypes (Figure 2A). The evolution of IBS severity scores was similar and of the same magnitude in all
IBS subtypes ($P = 0.115$) (Table 2). Hence, after treatment, IBS severity scores were different across transit pattern subtypes (Figure 2A) with IBS-C having the highest scores compared to IBS-D, IBS-M and IBS-U.

Each of the five IBS-SSS domains was improved (Figure 5 and Supplementary Figure 2). In addition, the proportion of patients who reported experiencing symptoms every day over a period of 10 d was reduced by half after treatment, dropping from 76 patients (32.9%) to 34 patients (15.6%). Moreover, the number of pain-free patients over a 10-d period, which was low at baseline (0.4%; one patient), increased to 10.1% (22 patients) after 30 d of treatment.

A change towards categories of lower IBS severity or remission occurred in 56.7% of patients (Figure 6). A significant improvement in disease severity (> 50-point decrease in the IBS-SSS score) was observed in 65.7% of patients, with significant improvement noted in all transit subtypes.

Compared with baseline, the overall quality of life was improved at the end of treatment in the entire patient population (mean ± SD IBS-QOL score 68.8 ± 20.9 vs 60.2 ± 20.5; $P < 0.001$) (Figure 4B) and in IBS-C, IBS-D and IBS-M subgroups ($P < 0.001$) without difference in absolute score evolution between transit pattern subgroups ($P = 0.658$) (Table 2 and Figure 2B). A clinically significant meaningful improvement in the overall IBS-QOL score (> 10-point increase) was observed in 36.9% of patients, and was more pronounced in patients with more severe disease at baseline (9.1% of patients with mild IBS, 28.6% of patients with moderate IBS, and 49.1% of patients with severe IBS). Each of the eight dimensions of IBS-QOL were improved at the end of treatment ($P < 0.001$, Supplementary Figure 3).

Over the course of the study, stool consistency tended to be normalized in all IBS transit subtypes (Figure 7) with a decrease in the percentage of patients reporting stool types 1–2 and 6–7 according to different transit patterns.

Approximately two-thirds of patients (63.8%) and gastroenterologists (63.8%) were satisfied with *B. longum* 35624 treatment at the end of the study.

**Safety**

During the study, 10 AEs possibly related to the use of *B. longum* 35624 were reported in 4.1% ($n = 10$) of patients in the safety population ($n = 244$ patients), including flatulence ($n = 3$), abdominal pain ($n = 2$), constipation ($n = 1$), abdominal distension ($n = 1$), upper abdominal pain ($n = 1$), gastrointestinal motor disorder ($n = 1$), and increased weight ($n = 1$).

**DISCUSSION**

While the new Rome criteria have decreased IBS prevalence and increased the percentage of patients...
Table 2 Absolute evolution of irritable bowel syndrome quality of life and irritable bowel syndrome severity scoring system after treatment (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>IBS-C, n = 71</th>
<th>IBS-D, n = 89</th>
<th>IBS-M, n = 61</th>
<th>IBS-U, n = 12</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-SSS scores</td>
<td>-89.5 ± 105.9</td>
<td>-107.4 ± 85.5</td>
<td>-91.7 ± 85.6</td>
<td>-66.0 ± 104.2</td>
<td>0.115 (NS)</td>
</tr>
<tr>
<td>absolute evolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-QOL scores</td>
<td>8.9 ± 14.1</td>
<td>10.4 ± 15.8</td>
<td>6.6 ± 14.8</td>
<td>4.7 ± 10.9</td>
<td>0.658 (NS)</td>
</tr>
<tr>
<td>absolute evolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Intergroup comparison was assessed with a Kruskal Wallis test.

C: Constipation; D: Diarrhea; IBS: Irritable bowel syndrome; IBS-QOL: Irritable bowel syndrome quality of life; IBS-SSS: Irritable bowel syndrome severity scoring system; M: Mixed; NS: Not significant; SD: Standard deviation; U: Unclassified.

Figure 1 Patient flow. C: Constipation; D: Diarrhea; IBS: Irritable bowel syndrome; M: Mixed; U: “Unclassified” (subtype not determined).

with severe disease, few studies have evaluated the efficacy of probiotics with this new paradigm. In our study conducted in patients with IBS according to Rome IV definition with different transit subtypes and levels of severity, a 30-d treatment regimen with \( B. \) longum 35624 reduced disease severity and improved quality of life, especially in patients with the most severe forms of IBS.

The significant reduction in disease severity that we found in approximately two-thirds of patients in this study after 30 d of \( B. \) longum 35624 treatment is consistent with the literature reporting that two-thirds of patients with IBS have dysbiosis, further supporting the link between IBS severity and dysbiosis[17]. It is also consistent with the results of two previous randomized studies of the same probiotic strain, including a large 4-wk study performed in 362 women with IBS[7] and a smaller 8-wk study performed in 80 patients with IBS[6]. The effect on digestive symptoms and disease severity reduction could be secondary to an effect on pro-inflammatory cytokines as it was show previously by O’Mahony et al[6]. with a normalisation of an interleukin (IL)-10/IL-12 cytokine ratio that was impaired at baseline[6]. In a recent study[18], at baseline, similar IBS-SSS global scores, IBS severity distribution and IBS subtype distribution were observed for patients with IBS according to Rome IV criteria. Interestingly, in our study, the improvement in overall IBS-SSS score was observed in all its component items (intensity and frequency of abdominal pain, distension and its intensity; satisfaction with bowel habits) and regardless of the IBS subtype (IBS-C, IBS-D, or IBS-M), as also described in the study by Whorwell et al[7]. Few studies of probiotics conducted in patients with IBS[19] have included a large...
Figure 2 Mean irritable bowel syndrome severity scoring system and Irritable bowel syndrome quality of life score at baseline and at the end of treatment by transit subtype. A: IBS-SSS; B: IBS-QOL. Error bars denote standard deviation. *P < 0.001 versus baseline. IBS: Irritable bowel syndrome; IBS-QOL: Irritable bowel syndrome quality of life; IBS-SSS: Irritable bowel syndrome severity scoring system; C: Constipation; D: Diarrhea; M: Mixed; NS: Not significant; U: Unclassified.

Figure 3 Irritable bowel syndrome quality of life score according to irritable bowel syndrome severity scoring system severity categories at baseline. IBS-QOL: Irritable bowel syndrome quality of life; IBS-SSS: Irritable bowel syndrome severity scoring system.

The proportion of patients with severe forms of the disease, as in our present study (approximately half of the patients), and in many such studies, disease severity was not monitored. For a population of patients who are not being treated at tertiary centers, such a level of disease severity may appear surprising; however, a similar level of IBS severity has been reported in patients treated by private gastroenterologists in France[20] using Rome II criteria. Moreover, the selection of patients according to Rome IV criteria tends to increase the proportion of patients with severe IBS[13]. It should be noted that the
Figure 4 Mean irritable bowel syndrome severity scoring system and irritable bowel syndrome quality of life score at baseline and at the end of treatment. A: Mean irritable bowel syndrome severity scoring system score at baseline and at the end of treatment; B: Mean irritable bowel syndrome quality of life score at baseline and at the end of treatment. Error bars denote standard deviation. *P < 0.001 vs baseline. IBS-QOL: Irritable bowel syndrome quality of life; IBS-SSS: Irritable bowel syndrome severity scoring system.

Figure 5 Irritable bowel syndrome severity scoring system scores by domain at baseline and after treatment with B. longum 35624. *P < 0.001 vs baseline. IBS-SSS: Irritable bowel syndrome severity scoring system.

The magnitude of reduction in disease severity observed in our study is uncommon. Further, during the present study, the majority of patients shifted to lower IBS severity categories, some moving from a severe to a mild form of the disease, which has been associated in the literature with a decrease in health care seeking and an improvement of quality of life. Quality of life is often impaired in patients with IBS, especially in those with severe disease. Therefore, the 2014 EMA “Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome” recommended the use of validated quality of life scales in order to better understand the real impact of a treatment on the disease. In the present study, overall quality of life measured by the IBS-QOL, a validated questionnaire, was significantly improved, as well as all its individual domains. Comparable levels of improvement in IBS-QOL scores (< 10 points at the group level vs placebo) were observed at 3 mo in the trials of drugs such as eluxadoline or linaclotide that have been approved for the treatment of IBS by health authorities in the United States or in Europe. However, in our real-life study a “clinically meaningful” improvement (> 10 points) was observed only in approximately one-third of patients (i.e., half as many as the number of patients who had a significant reduction in IBS severity). The link between disease severity and quality of life observed in
this study has been previously described in IBS using different quality-of-life instruments[2,24]. The fact that a decrease in severity did not translate into a similar improvement in the quality of life could be because certain behaviors that affect quality of life may require more than 1 mo, which was the duration of the present study, to change (e.g., self-confidence, attitude at work, relationships with others). A similar lag in improvement in the quality of life compared with IBS severity was also observed in a recent study of two other probiotic strains, *Lactobacillus acidophilus* DDS-1 and *B. lactis* UABla-12[11]. Interestingly, a clinically significant improvement in quality of life was observed in our patients with the highest severity of IBS at baseline, suggesting that *B. longum* 35624 has also therapeutic potential in patients with severe IBS. The absence of improvement of quality of life in the study conducted by Whorwell *et al.*[7] could be explained by the fact that their study probably included fewer patients with severe forms of IBS because it relied on the Rome II criteria for inclusion, and it has been shown that the Rome IV criteria, which are more stringent, increase the percentage of patients with severe forms of IBS[13]. Nevertheless, O’Mahony *et al.*[6] have observed a significant improvement in quality of life over placebo in an 8-wk study using the same probiotic strain as in our study[6].

Most of the published studies on probiotics do not target a specific IBS subtype. In our study, the effect of treatment with *B. longum* 35624 over a 30-d period was analyzed according to IBS subtypes. Treatment was effective on each IBS subtype (IBS-C, IBS-D and IBS-M) in terms of disease severity and quality of life. During treatment, we observed the normalization of stool consistency, with a decrease in the frequency of extreme stool types according to the Bristol stool scale (type 1-2 for IBS-C or type 6-7 for IBS-D) and an increase of normal stool type (type 3-5), as it was the case using the same strain in the study of Whorwell *et al.*[7].

We found that the incidence of AEs was low (5%), and that AEs were generally minor. This finding is in accordance with the results from a previous large randomized study of *B. longum* 35624[7], confirming its favorable tolerability profile. This observational study, were only data concerning the patients who took treatment with *B. longum* 35624 are available, had several limitations, namely the absence of a placebo or comparator group and the relatively short treatment duration. Strong placebo effect and a tendency for spontaneous improvement are sometimes described in studies of IBS[25]. For example, in their study, Martoni *et al.*[11] observed an average decrease of 30 points in the IBS-SSS score at 3 wk in the placebo group[11]. However, the magnitude of the reduction in severity, which is a relatively stable parameter[2], and the choice of the 50-point reduction in the IBS-SSS score as the threshold[15], which has been previously validated as a reliable indicator of improvement, provide some confidence in the robustness of our results. Even if short, the duration of the present study was sufficient to obtain positive results that are comparable to those of a large randomized study of *B. longum* 35624[7] and three recently published randomized studies of other probiotics[19,26,27]. It should also be noted that, to our knowledge, our study is one of the few[11] that simultaneously assessed severity and quality of life using validated instruments, and one of the few probiotic studies to include patients with IBS diagnosed using the Rome IV criteria. Stool analysis was not performed to correlate improvement of IBS patients’ symptoms with a qualitative or quantitative improvement of the intestinal microbiota, but this is rarely done in clinical
studies. Nevertheless, Charbonneau et al.\textsuperscript{[28]} using the same probiotic strain observed that after 4 and 8 wk of treatment, fecal levels of \textit{B. infantis} 35624 from IBS subjects who received the probiotic rose significantly compared with those from subjects who received placebo. While in some diseases there may be variations in the microbiota according to ethnicity, this factor could also have influenced the results. However, in France, the legislation does not allow the collection of ethnic data for this type of analysis.

**CONCLUSION**

This study conducted in IBS patients diagnosed according to the Rome IV criteria and who had different transit pattern subtypes and different levels of symptom severity showed that 30 d of treatment with \textit{B. longum} 35624, whose superiority to placebo has already been established, reduced IBS disease severity and improved patient quality of life in all subgroups of patients, and notably in those with the most severe form of IBS.

**ARTICLE HIGHLIGHTS**

**Research background**

Some probiotics have been shown efficacy on irritable bowel syndrome (IBS) symptoms.

**Research motivation**

However, little data is available on the effectiveness of probiotics on IBS severity and quality of life.
Research objectives
To assess in real life settings efficacy of treatment with *B. longum* 35624 on IBS severity and quality of life.

Research methods
To assess in an observational study on IBS patients defined according to Rome IV criteria, the effect of a 30 d of treatment with *B. longum* 35624 on the disease severity (IBS severity scoring system) and quality of life (IBS quality of life questionnaire).

Research results
After one month of treatment, the severity and quality of life improved in approximately two-thirds and one-third of patients respectively, especially in more severe patients with changes to lower severity categories in more than half of the patients. A gradual improvement in stool consistency was also observed in all transit sub-types.

Research conclusions
In IBS patients defined according to Rome IV criteria, a 30 d treatment with *B. longum* 35624 reduces the disease severity and improves the quality of life even in patients with severe disease that were excluded of most published studies.

Research perspectives
Future research should help to define predictors of good response to probiotic therapy and should study responses to prolonged therapy for this chronic disease.

ACKNOWLEDGEMENTS
Medical writing assistance in the preparation of this manuscript was provided by Georgii Filatov of Springer Healthcare Communications. Special thanks to the investigators of the study (last name, first name): Anacreon Nival Sophie; Audan Alain; Barbereau Didier; Bastid Christophe; Baudet Anne; Berry Pascal; Bion Eric; Blot Marie-Christine; Caumes Jean-Luc; Cazals Jean-Brice; Chambon Jacques; Chatrenet Philippe; Colonna Patrick; Constant Thierry; Courtial Philippe; D Abrigeon Gilles; Dalbies Pierre Adrien; Daude Mathieu; Delette Olivier; Dewaele François; Duchesne Charlene; Duval Gilles; Écuer Stephane; Escartin Michel-Pierre; Etienney Isabelle; Geros Christos; Gilbert Thierry; Gorez Etienne; Helbert Thierry; Higuero Thierry; Hubert Jean; Jeandroz Madec Véronique; Juin De Faucalet Dominique; Kéririzin Anne; Lame Charles; Levy Jonathan; Luneau Fabrice; Magiannan Philippe; Menat Jean Philippe; Necriaux Olivier; Plegat Serge; Poggi Jean-Pierre; Pospait Dan; Pujol Pascale; Regensberg Michel; Rémy André Jean; Renkes Pascal; Richard Mireille; Rigo François; Ronanbaum Alain; Rouillon Jean-Michel; Rouquie Patrick; Rudelli Alain; Samak Valérie; Schneider Philippe; Stancu Feier Laura; Texier Frédéric; Thevenot Aldine; Vove Jean Paul; Wittersheim Christian; Zalar Alberto.

FOOTNOTES
Author contributions: Sabaté JM and Iglicki F were responsible for conceptualization, methodology, writing—original draft preparation, and supervision of the study; Sabaté JM conducted the formal analysis and data curation; all authors have read and agreed to the published version of the manuscript.

Supported by Biocodex.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and the Guidelines for Good Clinical Practice (EMA/CHMP/ICH/135/1995), and approved by the Northwest III Protection of Persons Committee of the University Hospital of Caen (protocol code OBS 17-03; dated March 27, 2018 and approved on September 24, 2018).

Informed consent statement: An information sheet was provided to all patients, and oral non-opposition to the study was obtained from all patients involved in accordance with French regulation.

Conflict-of-interest statement: Sabaté JM and Iglicki F report personal fees from Biocodex during the conduct of the study. Sabaté JM also reports personal fees from Biocodex, Kyowa Kirin, Norgine, Mayoly Spindler, Arko Pharma, and Tillots Pharma outside the submitted work.

Data sharing statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.
**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** France

**ORCID number:** Jean-Marc Sabaté 0000-0001-5591-3489; Franck Iglicki 0000-0001-8815-8395.

**S-Editor:** Fan JR  
**L-Editor:** A  
**P-Editor:** Wu RR

---

**REFERENCES**


Stereotactic radiotherapy and the potential role of magnetic resonance-guided adaptive techniques for pancreatic cancer

Tai Ermongkonchai, Richard Khor, Vijayaragavan Muralidharan, Niall Tebbutt, Kelvin Lim, Numan Kutaiba, Sweet Ping Ng

**Abstract**

**BACKGROUND**

Pancreatic cancer is a malignancy with one of the poorest prognoses amongst all cancers. Patients with unresectable tumours either receive palliative care or undergo various chemoradiotherapy regimens. Conventional techniques are often associated with acute gastrointestinal toxicities, as adjacent critical structures such as the duodenum ultimately limits delivered doses. Stereotactic body radiotherapy (SBRT) is an advanced radiation technique that delivers highly ablative radiation split into several fractions, with a steep dose fall-off outside target volumes.

**AIM**

To discuss the latest data on SBRT and whether there is a role for magnetic resonance-guided techniques in multimodal management of locally advanced, unresectable pancreatic cancer.

**METHODS**

We conducted a search on multiple large databases to collate the latest records on radiotherapy techniques used to treat pancreatic cancer. Out of 1229 total records retrieved from our search, 36 studies were included in this review.

**RESULTS**
Studies indicate that SBRT is associated with improved clinical efficacy and toxicity profiles compared to conventional radiotherapy techniques. Further dose escalation to the tumour with SBRT is limited by the poor soft-tissue visualisation of computed tomography imaging during radiation planning and treatment delivery. Magnetic resonance-guided techniques have been introduced to improve imaging quality, enabling treatment plan adaptation and re-optimisation before delivering each fraction.

**CONCLUSION**

Therefore, SBRT may lead to improved survival outcomes and safer toxicity profiles compared to conventional techniques, and the addition of magnetic resonance-guided techniques potentially allows dose escalation and conversion of unresectable tumours to operable cases.

**Key Words:** Magnetic resonance imaging; Pancreatic cancer; Radiotherapy; Stereotactic; Adaptive techniques

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

---

**Core Tip:** Locally advanced pancreatic cancer has very poor outcomes. These cases are treated with chemoradiotherapy regimens, but conventional radiotherapy techniques often yield minimal survival benefit while accruing significant toxicities. Stereotactic body radiotherapy (SBRT) is an advanced technique that is associated with improved survival outcomes and reduced toxicities compared to its predecessors. The addition of Magnetic resonance-guided techniques to SBRT provides excellent imaging that enables intra-treatment plan adaptations. This provides the possibility of dose escalation, which may be the key to achieving surgical resectability and thus potentially increasing the chances of cure.

---

**Citation:** Ermongkonchai T, Khor R, Muralidharan V, Tebbutt N, Lim K, Kutaiba N, Ng SP. Stereotactic radiotherapy and the potential role of magnetic resonance-guided adaptive techniques for pancreatic cancer. *World J Gastroenterol* 2022; 28(7): 745-754


---

**INTRODUCTION**

Pancreatic cancer is one of the leading causes of cancer deaths, with a 5-year overall survival (OS) rate of less than 10%[1]. Surgical resection is the only curative option, but is seldom feasible due to a lack of early detection markers, late presentation with locally advanced disease or the lesion being medically inoperable[2-6]. In the cohort of patients who received surgery in the PREOPANC-1 randomised trial, a subgroup analysis in patients with borderline resectable disease demonstrated a survival advantage in those receiving preoperative chemoradiotherapy compared to those receiving immediate surgery[7]. However, the data for definitive radiotherapy (RT) in unresectable pancreatic cancers is conflicting. Traditionally, locally advanced pancreatic cancers (LAPC) unsuitable for curative surgery are treated with chemotherapy regimens or conventionally fractionated radiotherapy (CFRT), or both[8]. However, the role of RT is controversial as radiation-induced toxicities remain a concern. Conventional radiotherapy is often associated with significant grade ≥ 3 toxicities while achieving a median OS of only 5 to 15 mo[2]. The LAP-07 trial demonstrated that the survival outcomes of those who received conventionally fractionated chemoradiotherapy is not superior to chemotherapy alone. However, despite its known caveats, the trial indicated that there is a benefit from RT in multimodal regimens in achieving improved local control (LC), which approached 70% at 12 mo[9].

Stereotactic body radiotherapy (SBRT) is an emerging RT technique due to its ability to deliver highly ablative radiation doses in several fractions[10]. A study by Park et al[4] found that the use of a five-fraction SBRT regimen achieved improved quality-of-life scores and tolerable acute toxicities, with comparable late grade ≥ 3 toxicities to intensity-modulated radiotherapy (IMRT) (15.9% SBRT vs 13.7% IMRT)[4]. But while SBRT strives for more accuracy and precision, there are some obstacles that prevent further dose escalation without compromising safety. First is the susceptibility of the pancreas to intra-fractional movement during respiratory cycles and digestion. Secondly, the adjacent surrounding organs-at-risk (OAR) which comprises of the stomach, duodenum and small intestine are highly radiosensitive, therefore care needs to be taken to limit doses to these structures to avoid significant treatment-related toxicity. And finally, the current imaging modalities and fiducial markers provide poor visualisation of targets during treatment planning[11].
The recent development of magnetic resonance-guided RT (MRgRT) provides potential to circumvent these challenges, as magnetic-resonance imaging (MRI) offers excellent soft-tissue contrast that can guide dosimetric adjustments to the target volume and limit OAR exposure. This review will evaluate the role of SBRT in the treatment of LAPC, its shortcomings, and present the potential use of MR-guided adaptive techniques to mitigate those caveats.

MATERIALS AND METHODS

Searches were conducted in the online databases PubMed and Ovid (Medline) from August to September 2020, using Medical Subject Headings (MeSH) terms/keywords of pancreatic cancer, stereotactic, radiotherapy and magnetic-resonance. Records were included if it studied the treatment outcomes of SBRT and/or MRgRT in unresectable pancreatic cancers. The excluded literature were review articles or studies done on metastatic disease. Studies that involved resectable tumours or used chemoradiotherapy as adjuvant treatment post-surgery were also omitted. Only results in the English language were included. Additional literature was also sought from references of included studies. A final shortlist of studies was selected based on relevance. A study was considered as relevant if it investigated the effect of SBRT and/or MRgRT on any survival metric in patients with inoperable LAPC.

RESULTS

Figure 1 illustrates the search and screening processes done to assess the eligibility of studies. A total of 1630 records were found from the databases using the search strategy, with an additional 10 retrieved from references of included studies. There was a total of 411 duplicates, and after removal of these we resulted with 1229 records. Screening was conducted by the primary author. The first screening phase was done by screening the titles and abstracts of the 1229 records, which resulted in 93 potential studies. The second screening phase assessed full texts, and 46 further studies were excluded for reasons such as use of novel therapies, investigating metrics not relevant to survival outcomes in pancreatic cancer, or using in-vivo animal models. This resulted in 47 eligible texts and out of those, 36 were used to synthesise the discussion. The final 36 texts chosen represented the latest seminal work pertaining to SBRT and MRgRT in treatment of pancreatic cancer.

DISCUSSION

SBRT in patients with LAPC

For patients with unresectable LAPC, chemotherapy has been the mainstay of treatment. Early radiation techniques such as CFRT and IMRT have called into question the value of irradiation in LAPC management due to their considerable toxicity profiles[4,9], with minimal to no impact on survival outcomes[9]. However, SBRT is an advanced radiation technique which can be delivered on the same linear accelerator at most centres. It has gained attraction due to three main reasons: Firstly, it allows delivery of high biologically effective doses (BED) split into several fractions (typically 3-5). Secondly, the technique allows a sharp radiation dose falloff at the edge of target volumes, thereby reducing doses to OARs[12]. Thirdly, it offers an overall shorter treatment time, as SBRT is normally delivered in 1-3 wk, compared to CFRT which takes 5-6 wk[13,14]. Hence, SBRT ensures there is minimal interruption to chemotherapy, which is important given that the main pattern of failure in this disease is distant metastasis (DM)[3]. In addition to this, patients with limited prognoses will be able to complete RT courses in 3 wk instead of 6 wk (which may account for a quarter of their remaining lifespan). This greatly improves quality-of-life, as it requires less commuting and reduces associated costs on patients and families[10,13].

Table 1 summarises the studies of SBRT in unresectable pancreatic cancer. The majority of studies demonstrated an OS of 10-16 mo, freedom from local disease progression (FFLP) rates of approximately 80% and progression-free survival (PFS) of 8-10 mo with SBRT[2-4,13,15-17]. A systematic review by Petrelli et al[18] assessed prospective trials and retrospective studies of SBRT use in LAPC, with the pooled results showing a median OS of 17 mo[18]. Other studies compared SBRT’s efficacy compared to other RT techniques. A retrospective review by Zhong et al[13] showed that patients who received SBRT had improved median OS times and 2-year OS rates relative to CFRT[13]. Similar results were found by Dohopolski et al[3] who also demonstrated a higher median OS for the SBRT group (12.6 mo) compared to its counterpart (11.2 mo)[3]. Other studies also showed that patients who had SBRT achieved at least similar outcomes as those who had IMRT[4,19]. Park et al[4] demonstrated no significant difference in median OS between those who had SBRT vs IMRT[4]. However, Shaib et al[19] found that SBRT achieves at least a month longer median OS (8.6 mo vs 6.7 mo; P < 0.001) and more than double compared to supportive care alone (8.6 mo vs 3.4 mo; P < 0.001)[19]. However, large prospective trials
Table 1: Studies of stereotactic body radiotherapy in locally advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Participants</th>
<th>Dosimetry</th>
<th>Outcome</th>
<th>Toxicity</th>
<th>Resectability post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman et al [15], 2015, Phase 2 Trial</td>
<td>49 LAPC</td>
<td>33 Gy/5 fractions</td>
<td>(1) Median OS 13.9 mo; (2) 59% 1-yr OS; and (3) 18% 2-yr OS</td>
<td>(1) 1 patient acute grade 4 duodenal ulcer; (2) 10% acute grade ≥ 3; (3) 11% late grade ≥ 2; and (4) 6% serious late GI toxicity</td>
<td>10% resectable after treatment</td>
</tr>
<tr>
<td>Comito et al [2], 2017, Phase 2 trial</td>
<td>43 LAPC</td>
<td>45 Gy/6 fractions</td>
<td>Median OS 13 mo</td>
<td>(1) 49% acute grade 1 or 2; (2) 0 acute grade ≥ 3; (3) 2 patients late GI gastritis; and (4) 0 late grade ≥ 3</td>
<td>7% resectable after treatment</td>
</tr>
<tr>
<td>Dehopolksi et al [3], 2017, Retrospective</td>
<td>696 LAPC</td>
<td>24-40 Gy/3-5 fractions</td>
<td>Median OS 12.6 mo (compared to 11.2 mo for CFRT)</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Park et al [4], 2017, Retrospective</td>
<td>44 unresectable</td>
<td>30-33 Gy/5 fractions</td>
<td>(1) 56% 1-yr OS; (2) 26% 2-yr OS; and (3) Median OS 15.7 mo (no significant difference from IMRT)</td>
<td>(1) 7% acute grade ≥ 2 GI toxicity (24% for IMRT); (2) 5% grade ≥ 3 haematological toxicity (26% for IMRT); and (3) 9% late GI bleed</td>
<td>7% resectable after treatment (no significant difference from IMRT)</td>
</tr>
<tr>
<td>Yecheieli et al [10], 2017, Retrospective</td>
<td>18 unresectable</td>
<td>30-36 Gy/3-5 fractions</td>
<td>(1) Median recurrence-free survival 6.8 mo; and (2) Median OS 6.4 mo</td>
<td>(1) 50% no toxicity; (2) 15% grade ≥ 3; and (3) 10% GI bleed</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Zhong et al [13], 2017, Retrospective</td>
<td>631 LAPC</td>
<td>Median 40 Gy/5 fractions</td>
<td>(1) 22% 2-yr OS (17% for CFRT); and (2) Median OS 13.9 mo (11.6 mo for CFRT)</td>
<td>0 grade ≥ 3</td>
<td>11% resectable after treatment (9% for CFRT)</td>
</tr>
<tr>
<td>Mazzola et al [14], 2018, Retrospective</td>
<td>33 LAPC</td>
<td>36-45 Gy/6 fractions</td>
<td>(1) 81% 1-yr LC; and (2) 75% 1-yr OS</td>
<td>(1) 15% acute grade 1; (2) 9% acute grade ≥ 3; and (4) No late toxicity</td>
<td>18% resectable after treatment</td>
</tr>
<tr>
<td>Jung et al [16], 2019, Retrospective</td>
<td>95 LAPC</td>
<td>24-36 Gy/4-5 fractions</td>
<td>(1) Median OS 16.7 mo; and (2) 67% 1-yr OS</td>
<td>(1) 3% acute grade 3 GI; and (2) 3% late grade 3</td>
<td>7% resectable after treatment</td>
</tr>
<tr>
<td>Shaib et al [19], 2020, Retrospective</td>
<td>6950 LAPC (64 received SBRT)</td>
<td>Median 30 Gy</td>
<td>(1) Median OS 8.6 mo (6.7 mo for IMRT, 3.4 mo for no RT); (2) 32% 1-yr OS (22% for IMRT, 15% for no RT); and (3) 9% 2-yr OS (7% for IMRT, 5% for no RT)</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Toesca et al [17], 2018, Retrospective</td>
<td>149 unresectable</td>
<td>20-45 Gy/3-6 fractions (high-dose group ≥ 40 Gy, standard-dose group &lt; 40 Gy)</td>
<td>(1) Median OS 16 mo both groups; (2) Median OS 23 mo for high-dose group (14 mo for standard-dose group); and (3) 82% 1-yr OS for high-dose group (57% for standard-dose group)</td>
<td>(1) 10% grade ≥ 2 for high-dose group; (2) 15% for low-dose group; and (2) 6% grade ≥ 3 for high-dose group (7% for low-dose group)</td>
<td>5% resectable after treatment</td>
</tr>
</tbody>
</table>

LAPC: Locally advanced pancreatic cancer; OS: Overall survival; GI: Gastrointestinal; CFRT: Conventionally fractionated radiotherapy; IMRT: Intensity modulated radiotherapy; LC: Local control; SBRT: Stereotactic body radiotherapy; RT: Radiotherapy.

are needed to definitively conclude SBRT’s efficacy compared to conventional techniques, but the evidence so far suggests that SBRT is associated with better survival outcomes.

Another advantage of SBRT is its favourable toxicity profiles. Studies in Table 1 report no more than 15% and 10% of patients receiving SBRT suffering from acute grade ≥ 3 toxicities and late side effects (such as duodenal bleeding and gastric ulcer perforation), respectively. Compared to IMRT, SBRT had significantly lower acute grade ≥ 2 gastrointestinal toxicity rates (7% vs 24%) [4]. Petrelli et al [18]’s systematic review found late grade 3 to 4 toxicity rates of up to 11% in their studies, with only 3 of their included studies reporting > 10% risk of severe gastrointestinal ulceration [18]. The patients of those studies all received higher doses per fraction due to previously failed RT [18], suggesting that a relationship exists between delivered doses and toxicity severity in SBRT treatment. The lower toxicity rates may be attributed to SBRT’s rapid dose fall-offs and the utilisation of motion mitigation methods. The pancreas is a retroperitoneal organ embedded around gastrointestinal structures, hence it undergoes significant motion during respiratory cycles and physiological processes such as digestion. The two commonly used motion mitigation methods during SBRT are respiratory gating and abdominal compression. Respiratory gating uses an external surrogate marker that represents the internal tumour position, where the radiation beam is only delivered when this marker correlates to a certain phase of the respiratory cycle. Abdominal compression requires applying pressure onto the abdomen to suppress diaphragmatic movements, but is less preferred due to patient discomfort and the occasional
displacement of OARs closer to the radiation volume[11]. A prospective study by Campbell et al[11] confirmed that both methods reduce motion and OAR exposure compared to no mitigation, however respiratory gating achieves greater motion reduction than abdominal compression by more than 20% [11]. Interestingly, while the studies only included unresectable patients, a small proportion were able to receive surgical resection after their SBRT course. As shown in Table 1, the rate of conversion to surgical resectability by SBRT was 5%-18%. In these studies, surgical resectability was decided upon multidisciplinary review including operating surgeons. This is important because if SBRT can induce local tumour regression and subsequently convert the tumour from unresectable to resectable, then it can possibly improve the chances of cure. The study by Mazzola et al[14] yielded the highest rates of resectability at 18%, all of which were participants that received higher doses of SBRT at 42-45 Gy in 6 fractions[14]. Meanwhile, Petrelli et al[18] found that higher total doses and number of fractions are significantly associated with 1-year locoregional control[18]. These results suggest that dose escalation may be the key determinant in achieving LC and thus conversion to surgical resectability. Currently, for five-fraction regimens, dose escalations of up to 60 Gy is feasible without compromising adequate target coverage and OAR constraints[20,21].

Alternative fractionation schemes
Recent evidence indicates that patients may benefit from alternative fractionation regimens, especially for those with gross tumour abutment into surrounding structures or invasion into peripancreatic nodes. The rationale is to prolong the treatment regime (≥ 10 fractions) such that higher overall BEDs can be delivered while still accounting for OAR toxicity. Reyngold et al[22] studied ablative schemes of 75 Gy in 25 fractions (BED = 97.5 Gy) and 67.5 Gy in 15 fractions (BED = 97.88 Gy) for patients with significant tumour abutment to the stomach/intestines, demonstrating a median OS of 18.2 mo and a 2-year OS of 38%[22]. This is an improvement from standard 1-5 fraction regimens, as the reported 2-year OS from those studies ranged from 9%-26%[4,13,15,19].

Caveats of current SBRT
Despite the advances of SBRT, its overall management of LAPC is limited by its imaging modalities. SBRT utilises computed tomography (CT)-based techniques such as 4-Dimensional CT (4DCT) and Cone Beam CT to assess tumour movement and carry-out the motion mitigation techniques[23]. This is a limitation because CT has poor soft-tissue contrast and is unable to accurately determine the appropriate therapy volumes. Furthermore, CT often involves larger planning target volumes (PTV) or use of an internal target volume (ITV) to account for tumour motion, thus putting the surrounding OARs at increased toxicity risk and ultimately preventing any possibility of dose escalation[24]. Furthermore, 4DCT only provides the average of motion amplitude over several respiratory cycles. Since the fourth dimension represents “phase” of respiration rather than being real-time, tumour motion might even be underestimated[25]. This explains why despite SBRT’s evidence in reducing acute toxicity, there are still significant concerns with late toxicity as previous published studies report rates of up to 47% of late grade ≥ 2 toxicity[2]. Therefore, SBRT is constrained by dose-limitations placed on the
surrounding OARs. Another concern is its steep dose gradient and the marginal misses that may result [26]. This is made more challenging given that conventional CT tends to underestimate the true pathologic size of the pancreatic tumour [27]. To optimise SBRT’s therapy volumes and dose distribution, a better imaging modality needs to be incorporated.

**Emerging role of MRgRT**

MRgRT has been proposed as the solution to the inconsistencies of onboard imaging with RT. MRI provides superior soft-tissue visualisation compared to CT and thus allows better delineation of the target tumour from surrounding OARs. Its real-time feedback also tracks inter-fractional and intra-fractional organ changes [8, 28, 29]. Another benefit of MRI is its exploration of multiple breathing cycles over different days to quantify daily changes [25]. Therefore, MRgRT can be used to guide treatment plan adaptations, such that therapy volumes account for intra-treatment tissue changes [30]. This led to the advent of Stereotactic MR-guided Adaptive Radiotherapy (SMART), which is the application of the principles of MRgRT combined with SBRT. A non-randomised trial by Heerkens *et al.* [25] assessing the feasibility of MRgRT with SBRT showed that it is safe with dosimetric plans of at least 24 Gy, with no cases of acute or late grade ≥ 3 toxicity. They were also able to deliver higher doses under free-breathing conditions while ensuring adequate target coverage and OAR sparing [25]. SMART has become a promising technique in LAPC by possibly enabling SBRT dose escalation without exposing OARs to higher toxicity risk [8, 25].

Table 2 summarises recent studies of MRgRT use in LAPC. Rudra *et al.* [31] investigated the use of MRgRT with standard-dose and high-dose SBRT plans, and were able to demonstrate that dose escalation is possible. Patients in the high-dose group (receiving 40-52 Gy) achieved significantly higher survival rates compared to those in the standard-dose group (receiving 30-35 Gy), despite the former cohort having worse prognostic factors such as older age and higher Carbohydrate Antigen 19-9 biomarker levels [31]. There was no incidence of severe toxicity amongst the higher dose group, with all cases of grade ≥ 3 gastrointestinal toxicities reported from the standard-dose cohort [31]. A study by Luterstein *et al.* [8] on a patient case yielded similar results. The patient with clinical stage III (T4N1M0) LAPC was given a high BED of 72 Gy via SMART after chemotherapy and achieved LC at 16 mo post-radiation (21 mo since diagnosis) with no significant side effects or toxicities [8]. Furthermore, a multi-institutional study at the American Society for Radiation Oncology suggested that adaptive plans that allow safe delivery of BED > 70 Gy can achieve higher OS rates than BED < 70 Gy without impacting surrounding OARs [8]. These results indicate that MRgRT’s precision can potentially address prior issues with RT. And since previous studies recommend that five-fraction regimens should use a dose prescription of 40 Gy to cover the gross tumour [32], the advances of MRgRT provides potential to maximise this limit in the future without compromising safety.

With the implementation of MRgRT in its early stages, some caveats have emerged such as workflow disruptions. Utilising MRI to guide therapy also poses new challenges unique to the MRI magnet, including but not limited to patient selection and MRI safety. This needs particular consideration as the MRI magnet is now being used outside of a radiology department where MRI safety protocols are firmly embedded into work practices. As with any novel modality or technological advancement, there will be a learning curve and an initial period to bolster awareness of safety requirements.

Concomitantly, adaptive techniques also require increased time investment as plans need to be re-optimised between fractions. Hence, MRgRT is costly and resource-intensive because it involves multidisciplinary teams to re-contour images, review and re-approve the adapted plans daily [28, 30]. There is now an emerging interest to use artificial intelligence tools such as auto-contouring methods and radiomics to increase the workflow efficiency of treatment planning.

**Strengths and limitations of the review**

Our review methodology covers a wide range of literature, but it comes with limitations. The review mostly sought evidence from large retrospective studies without individual data for each patient. Hence, it was difficult to identify confounding factors that may exist due to the variability of patient characteristics. The review also excluded studies on patients with DM as it aimed to investigate SBRT’s effect locally. This may artificially elevate survival rates as those without DM will naturally have better outcomes.

The included evidence came with strengths and limitations. Firstly, SBRT has mature follow up data from several large retrospective analyses, with evidence dating back over a decade. This provided ample evidence to suggest that SBRT is a safe and beneficial technique for multimodal management of LAPC. However, the heterogeneity in study designs contributes to a large variability in the data. Since LAPC management differs on a case-by-case basis according to tumour staging and the physician’s clinical judgement, many of these studies include patient cohorts that received different chemotherapy regimens from each other. As a result, it is unsure how much survival benefit can be attributed to SBRT. It is also noteworthy that many of these studies could involve selection bias, since the most unwell patients often received no treatment and went into palliative care. This led to “healthier” subjects chosen for SBRT and thus better OS rates. Many of the included studies are retrospective analyses of database records, presenting another source of selection bias. Meanwhile, there is limited research on MRgRT so far, thus definitive conclusions about this technique cannot be made. There is a need for large
## Table 2 Studies of magnetic resonance-guided radiotherapy in locally advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Participants</th>
<th>Dosimetry</th>
<th>Outcome</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heerkens et al[25], 2018, Trial</td>
<td>20 (18 LAPC, 2 unresectable)</td>
<td>24 Gy/3 fractions</td>
<td>(1) Median OS 8.5 mo; (2) 69% improved QOL compared to baseline at 1 mo; and (3) 33% improved QOL compared to baseline at 12 mo</td>
<td>No grade ≥ 3 acute or late toxicity</td>
</tr>
<tr>
<td>Luterstein et al[8], 2018, Case Report</td>
<td>1 LAPC</td>
<td>40 Gy/5 fractions</td>
<td>LC at 16 mo</td>
<td>None</td>
</tr>
<tr>
<td>Rudra et al[31], 2019, Retrospective</td>
<td>44 unresectable (22 received SBRT)</td>
<td>30-35 Gy/5 fractions (standard-dose group, n = 6); 40-52 Gy/5 fractions (high-dose group, n = 16)</td>
<td>(1) 49% 2-yr OS (high-dose group); (2) 30% 2-yr OS (standard-dose group); (3) 77% 2-yr FFDF (high-dose group); and (4) 57% 2-yr FFDF (standard-dose group)</td>
<td>Acute: (1) 7% grade ≥ 3 GI (all in standard-dose group); and (2) 2% grade 4</td>
</tr>
</tbody>
</table>

LAPC: Locally advanced pancreatic Cancer; OS: Overall survival; QOL: Quality of life; LC: Local control; SBRT: Stereotactic body radiotherapy; FFDF: Freedom from distant failure; GI: Gastrointestinal.

Prospective trials on SBRT and MRgRT, with comparisons to other treatment modalities to validate the results of previous retrospective studies. However, given LAPC’s generally poor outcomes, long-term prospective studies will be challenging.

## CONCLUSION

SBRT is an advanced radiation technique that allows delivery of ablative doses in several fractions. It is highly precise, time-efficient and can limit OAR exposure when combined with motion mitigation techniques. SBRT is associated with improved treatment outcomes and safer toxicity profiles compared to other conventional RT techniques. And by implementing MR-guided imaging techniques with SBRT, the excellent soft-tissue contrast of MRI enables the physician to make daily plan adaptations such that target volumes are optimised according to intra- and inter-fractional tissue changes. This enables the possibility of dose escalation, which may be the key in achieving long-term LC and converting unresectable LAPC into operable cases. The current evidence on MR-guided SBRT is still limited, but early protocols have suggested its promise. Further research should focus on validating the feasibility, safety and efficacy of MRgRT with comparison to other treatment modalities.

## ARTICLE HIGHLIGHTS

### Research background

Pancreatic cancer is associated with significant mortality, and unresectable tumours are commonly treated with chemoradiotherapy regimens. Conventional radiotherapy (RT) techniques have minimal impact on survival and often cause considerable toxicities. Stereotactic body radiotherapy (SBRT) is an advanced radiotherapy technique that delivers highly ablative doses in several fractions, with a steep dose fall-off outside target volumes.

### Research motivation

Previous studies have supported the benefit of radiotherapy in multi-modal management of unresectable pancreatic cancers. However, there is no consensus of which RT technique yields the best survival outcomes. There is also a need for research to explore onboard imaging such as magnetic resonance-guided radiotherapy (MRgRT), which will enable treatment plans to be optimised according to intra-treatment tissue changes.

### Research objectives

We aim to collate the latest data on SBRT and evaluate its survival outcomes and toxicity profiles, with comparison to conventional RT techniques. Our review will also cover the safety and efficacy of MRgRT.

### Research methods

Searches were conducted on PubMed and Ovid (Medline), resulting in 1229 records. After multiple rounds of screening, 36 texts were chosen to synthesise the discussion. Records were included if they studied SBRT or MRgRT in unresectable cancers, and excluded if they involved metastatic disease, resectable tumours or used chemoradiotherapy as adjuvant to surgery.
**Research results**

SBRT is associated with improved survival outcomes and toxicity profiles compared to conventional RT techniques. A small proportion of unresectable patients were able to undergo surgical resection after their SBRT course. Conversion to resectability was associated with higher doses. However, dose escalation in SBRT is limited by the onboard computed tomography (CT) imaging due to its poor soft-tissue contrast. MRgRT may address these issues as magnetic resonance imaging (MRI) provides excellent tissue visualisation and is appropriate for real-time scanning. Early data indicates MRgRT as a safe and efficacious technique.

**Research conclusions**

SBRT may lead to improved survival outcomes and safer toxicity profiles compared to conventional RT, but is ultimately limited by onboard CT imaging. The addition of MRI-guided techniques allows the potential for dose escalation, which may be the key to achieving surgical resectability and possibly increasing the chances of cure.

**Research perspectives**

There is a need for large prospective trials to definitively conclude if SBRT is superior to other RT techniques. Large studies are also required to validate the safety, feasibility and efficacy of MRgRT with comparison to other RT techniques.

**FOOTNOTES**

**Author contributions:** Ermongkonchai T performed the literature search and wrote the manuscript; Khor R, Muralidharan V, Tebbutt N, Lim K, Kutaiba N and Ng SP performed editing and contributed to the quality of the manuscript.

**Conflict-of-interest statement:** No conflict-of-interest to be declared by authors of this article.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: [https://creativecommons.org/Licenses/by-nc/4.0/](https://creativecommons.org/Licenses/by-nc/4.0/)

**Country/Territory of origin:** Australia

**ORCID number:** Tai Ermongkonchai 0000-0002-2210-5773; Richard Khor 0000-0002-7057-2747; Vijayaragavan Muralidharan 0000-0001-8247-8937; Niall Tebbutt 0000-0003-2613-5168; Kelvin Lim 0000-0002-5216-8994; Numan Kutaiba 0000-0003-4627-9847; Sweet Ping Ng 0000-0003-1721-0680.

**S-Editor:** Fan JR

**L-Editor:** A

**P-Editor:** Fan JR

**REFERENCES**


5. Qing SW, Ju XP, Cao YS, Zhang HJ. Dose escalation of Stereotactic Body Radiotherapy (SBRT) for locally advanced


Crohn’s disease-related ‘gastrocnemius myalgia syndrome’ successfully treated with infliximab: A case report

Julien Catherine, Hazim Kadhim, Frédéric Lambot, Claire Liefferinckx, Virginie Meurant, Lukas Otero Sanchez

BACKGROUND
Extra-intestinal manifestations in inflammatory bowel diseases (IBD) are frequent and involve virtually all organs. Conversely, the clinical characteristics and course of inflammatory myopathies in IBD remain poorly described and mostly related to orbital myositis. Moreover, alternative therapeutic strategies in non-responder patients to corticosteroid therapy must still be clarified.

CASE SUMMARY
A 33-year-old woman with a history of unclassified colitis presented with acute bilateral calf pain. On admission, her clinical and biological examinations were non-specific. However, magnetic resonance imaging showed bilateral inflammatory changes in gastrocnemius muscles suggestive of myositis. Muscle biopsy confirmed the diagnosis of myositis and demonstrated an inflammatory infiltrate...
mainly located in the perimysial compartment including lympho-plasmocytic cells with the formation of several granulomatous structures while the endomysium was relatively spared. The combined clinical, biological and histomyopathological findings were concordant with the diagnosis of ‘gastrocnemius myalgia syndrome’ (GMS), a rare disorder associated with Crohn’s disease (CD). Ileocolonoscopy confirmed CD diagnosis and systemic corticosteroids (CS) therapy was started, resulting in a rapid clinical improvement. During CS tapering, however, she experienced a relapse of GMS together with a severe active ileocolitis. Infliximab was started and allowed a sustained remission of both conditions at the latest follow-up (20 mo).

CONCLUSION
The GMS represent a rare CD-associated inflammatory myopathy for which anti-tumour necrosis factor-α therapy might be considered as an effective therapeutic option.

Key Words: Crohn’s disease; Extra-intestinal manifestation; Gastrocnemius myalgia syndrome; Granulomatous myositis; Anti-tumour necrosis factor-α therapy; Case report

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Inflammatory myopathies are scarce in the setting of inflammatory bowel diseases (IBD) and could be wrongly attributed to IBD-related osteoarticular manifestations or to medications’ side effects. This case describes a very atypical presentation of myositis restricted to the legs called the ‘gastrocnemius myalgia syndrome’, an entity only described during Crohn’s disease. Its restricted location to the legs as well as normal creatine kinase levels in serum reflecting a predominant interstitial immune reaction are key characteristics in reported cases. Although corticosteroids are often used as first-line therapy, cortico-dependence is not rare and anti-tumour necrosis factor-α agents might represent an effective therapeutic option.

INTRODUCTION
The multi-system nature of inflammatory bowel diseases (IBD) is widely known. The extraintestinal manifestations (EIMs) of IBD are diverse and deferred from IBD diagnosis in a quarter of the cases. It has been estimated that 6% to 47% of patients with IBD experience at least one EIM[1]. The most frequently reported EIMs include peripheral and/or axial arthropathy, cutaneous lesions, ophthalmological immune-inflammatory manifestations and hepatobiliary affections[2]. However, EIMs can involve almost any organ or tissue, and some rare manifestations, such as specific muscular involvement can also occur and might even herald an hidden IBD[3].

The occurrence of muscular involvement in IBD is scarce, and mostly related to orbital myositis, a subtype of orbital pseudotumor principally reported during Crohn’s disease (CD)[4,5]. Myositis affecting the limbs is a much rarer entity, and is mostly localized in the lower extremities, involving the gastrocnemius muscles, a clinical entity designated as “gastrocnemius myalgia syndrome” (GMS)[3]. To date, very little is known about the full spectrum of myositis occurring during the course of IBD.

We hereby report the first CD-associated GMS in a Belgian patient that turned out to be “granulomatous myositis”, an exceptionally rare subtype. In addition, we performed a literature review by searching EMBASE, MEDLINE, Scopus, and the Cochrane Library databases for studies published between January 1, 1970, and July 7, 2021, using the following keywords or MeSH terms: ‘Inflammatory Bowel Diseases’, ‘Crohn’s Disease’, ‘Ulcerative colitis’, ‘Myositis’, ‘Gastrocnemius myalgia syndrome’ and ‘Granulomatous Myositis’. Finally, we discuss the role of anti-tumour necrosis factor (TNF)-α therapy in this specific context.
CASE PRESENTATION

Chief complaints
A 33-year-old woman presented at the emergency department with a 5-d history of isolated tenderness in both calves leading to walking difficulties.

History of present illness
She denied any traumatism but reported a colitis relapse 30 d before her admission which resolved with a short-course of modified-release beclomethasone therapy.

History of past illness
The patient had a history of allergic asthma, *Heliobacter pylori* gastritis and unclassified colitis. Previous investigations performed during colitis flares did not discriminate a specific IBD pattern concluding in an unclassified colitis. The patient was not taking any chronic medication. Her familial history was not contributive.

Physical examination
Clinical findings on admission included bilateral swelling of both calves which were warm and painful to palpation. Motricity and sensitive perception were preserved. Examination of other muscles, joints and the spine was unremarkable and her abdomen was soft and non-tender.

Laboratory examinations
Initial laboratory investigations showed a C-reactive protein level at 106.6 mg/L (normal range, 0.4-12 mg/L) with mild neutrophilic leukocytosis (8770/mm$^3$, normal range 1900-8000/mm$^3$). Creatinine kinase (CK), aspartate aminotransferase, lactate dehydrogenase and D-dimer serum levels were within reference values. Hemocultures were negative as well as antinuclear, antineutrophil cytoplasmic and anti-*saccharomyces cerevisiae* antibodies.

Imaging examinations
Ultrasonography of lower limbs revealed a bilateral 5-millimeter-thick edema surrounding gastrocnemius muscles in the absence of vascular abnormality while a magnetic resonance imaging showed marked inflammation of muscles and their fascia in both legs, suggested by a high signal on T2-weighted images and a strong gadolinium enhancement on fat-suppressed T1-weighted images (Figure 1).

Muscular biopsy
A muscular biopsy of the right gastrocnemius revealed a remarkable inflammatory reaction that particularly involved the perimysial compartment. The infiltrate mainly comprised dense lymphoplasmocytic cells with the formation of several granulomatous structures wherein several histiocytes, sometimes multinucleated, were observed (Figure 2A, C and D). Endomysial inflammatory infiltrate was however less remarkable and rather discrete and focal. There was besides a very mild and discrete perivascular affinity for the inflammatory infiltrate but there was no frank/convincing vasculitis in the examined sections (Figure 2B). A few muscle fibers showed suspected myofibrillar disintegration. Immunohistochemical analyses showed an outstanding cohort of CD3 positive cells (with a slight predominance of CD8$^+$ over CD4$^+$ cells) (Figure 2C and D). Electron microscopy was generally unremarkable and showed rare lipofuscin deposits. Moreover, rare mastocytes were observed.

FINAL DIAGNOSIS
This histomyopathological affection in this clinical context was concordant with the GMS, a rare disorder classically associated with CD. Moreover, a new ileocolonoscopy was performed during the hospital stay and revealed endoscopic pattern in favor of CD diagnosis, despite the absence of intestinal granuloma on histopathologic examination.

TREATMENT
Considering these results, the patient was started on a prednisone equivalent dose of 1 mg/kg, resulting in a rapid clinical and biochemical remission.
OUTCOME AND FOLLOW-UP

Two months later, the patient experienced intestinal symptoms associated with a recurrence of pain in both legs during corticosteroids (CS) tapering. The ileocolonoscopy performed at that time showed a very severe ileocolitis [CD Endoscopic Index of Severity (CDEIS) scored at 31] with no histopathologic evidence of granuloma for which intravenous methylprednisolone (1 mg/kg for 5 d) and infliximab (5 mg/kg at week 0, 1 and 4) therapies were started to target both muscular and intestinal disease leading to clinical remission of both ileocolitis- and myositis-related symptoms. Oral corticotherapy was then prescribed and slowly tapered while infliximab was continued (5 mg/kg, every 8 wk). Twenty months later, both ileocolitis and myositis were quiescent.

DISCUSSION

Inflammatory myopathies (IM) occurring in the setting of IBD are considered as rare EIMs and have been roughly described in the literature to date[6]. We report the first CD-associated GMS in a Belgian patient that besides turned out to be “granulomatous”. This represents a very exceptional subtype as there has been only two such reported cases. To the best of our knowledge, only 15 cases of GMS are described in the international literature and always occurred in patients with CD (Table 1). Apart from GMS, orbital myositis, which is currently considered as a subtype of idiopathic orbital inflammation, has also been reported in patients with IBD, mainly CD[5]. Few cases of dermatomyositis (DM) and polymyositis have also been described during the course of IBDs and a recent study showed that DM was more frequent in ulcerative colitis patients than CD patients and control subjects[7]. Nevertheless, the true incidence of IM occurring in this context is probably underestimated as myalgia can be confused with joint manifestations or with non-inflammatory muscle disorders (e.g., secondary to hypokalemia or medications) and by the fact that clinicians may rule out myositis’ diagnosis in the absence of CK elevation in serum.

The first case of myositis affecting gastrocnemius muscles in CD was reported in 1979 by Ménard et al [8] who described a 44-year-old man with granulomatous myositis localized to the calf occurring two months before CD diagnosis[8]. Since then, several cases have been reported, sharing the classically following features: (1) Calf-limited myalgia revealing localized myositis; (2) Normal serum CK levels; and (3) A high early-response rate to CS therapy[9]. In 2003, this entity was denominated as “GMS” by Christopoulos et al[3], a term adopted in the literature ever since[10]. Most patients developed GMS months or years after the onset of CD but myositis could precede gastrointestinal manifestations by up to 10 years[11]. When CD had been diagnosed before GMS, the intestinal disease was active in most cases at myositis’ diagnosis (Table 1). Other EIMs were associated with GMS in 50% of patients which is in accordance with previous observations that patients who presented an EIM are at higher risk to develop another one[1].
Table 1 Case descriptions of gastrocnemius myalgia syndrome reported in Crohn's disease

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age (yr)/sex at GMS onset</th>
<th>Initial presentation, time-to-onset</th>
<th>Active CD at time of GMS dx</th>
<th>CK serum level</th>
<th>Biopsy</th>
<th>Treatment</th>
<th>Corticosteroids-dependence (d) or resistance (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minard et al[8], 1976</td>
<td>44/M</td>
<td>Muscular, 2 mo</td>
<td>No</td>
<td>N</td>
<td>Granulomatous myositis</td>
<td>PDS (80 mg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Gilliam et al[13], 1981</td>
<td>19/M</td>
<td>Digestive, 6 mo</td>
<td>Yes</td>
<td>N</td>
<td>Necrotizing vasculitis</td>
<td>PDS (60 mg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Hall et al[10], 1985</td>
<td>32/F</td>
<td>Muscular, 120 mo</td>
<td>Yes</td>
<td>N</td>
<td>Non-granulomatous myositis</td>
<td>5-ASA, PDS (25 mg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Drabble and Gani [14], 1992</td>
<td>50/M</td>
<td>Digestive, 168 mo</td>
<td>Yes</td>
<td>N</td>
<td>Not performed</td>
<td>Hydrocortisone (400 mg/d), PDS</td>
<td>No</td>
</tr>
<tr>
<td>Dindier et al[11], 1997, Case 1</td>
<td>26/F</td>
<td>Muscular, 48 mo</td>
<td>Yes</td>
<td>N</td>
<td>Necrotizing vasculitis</td>
<td>PDS (60 mg/d), CYC, 5-ASA</td>
<td>Yes (r)</td>
</tr>
<tr>
<td>Dindier et al[11], 1997, Case 2</td>
<td>21/F</td>
<td>Simultaneous</td>
<td>Yes</td>
<td>N</td>
<td>Vasculitis</td>
<td>PDS (1 mg/kg/d), AZA</td>
<td>Yes (d)</td>
</tr>
<tr>
<td>Christopoulos et al[3], 2003</td>
<td>19/F</td>
<td>Simultaneous</td>
<td>Yes</td>
<td>N</td>
<td>Granulomatous myositis</td>
<td>PDS (0.5 mg/kg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Ulrich et al[15], 2009</td>
<td>25/F</td>
<td>Digestive, 84 mo</td>
<td>Yes</td>
<td>N</td>
<td>Vasculitis</td>
<td>PDS (50 mg/d), AZA, IFX</td>
<td>Yes (d)</td>
</tr>
<tr>
<td>Co et al[16], 2010</td>
<td>15/F</td>
<td>Digestive, 8 mo</td>
<td>Yes</td>
<td>N</td>
<td>Not performed</td>
<td>IFX</td>
<td>/</td>
</tr>
<tr>
<td>Mogul et al[17], 2010</td>
<td>15/M</td>
<td>Digestive, 60 mo</td>
<td>No</td>
<td>N</td>
<td>Non-granulomatous myositis</td>
<td>PDS (40 mg/d), MTX</td>
<td>No</td>
</tr>
<tr>
<td>Piette et al[18], 2010</td>
<td>45/M</td>
<td>Simultaneous</td>
<td>Yes</td>
<td>(5-13 × N)</td>
<td>Vasculitis</td>
<td>PDS (1 mg/kg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Goldshmid et al [19], 2011</td>
<td>24/F</td>
<td>Simultaneous</td>
<td>Yes</td>
<td>(330 U/L)</td>
<td>Not performed</td>
<td>MPDS (100 mg/d), IFX, AZA</td>
<td>Yes (d)</td>
</tr>
<tr>
<td>Vadala di Prampero et al [20], 2016</td>
<td>26/M</td>
<td>Digestive, 72 mo</td>
<td>Yes</td>
<td>N</td>
<td>Non-granulomatous myositis</td>
<td>PDS (60 mg/d), AZA, IFX (chronic), Adalimumab</td>
<td>Yes (d)</td>
</tr>
<tr>
<td>Safdar[12], 2017</td>
<td>33/F</td>
<td>Digestive, 120 mo</td>
<td>Yes</td>
<td>N</td>
<td>Not performed</td>
<td>PDS, IFX</td>
<td>Yes (r)</td>
</tr>
<tr>
<td>Osada et al[9], 2018</td>
<td>38/M</td>
<td>Digestive, 3 mo</td>
<td>Yes</td>
<td>N</td>
<td>Non-granulomatous myositis</td>
<td>PDS, AZA, 5-ASA</td>
<td>Yes (d)</td>
</tr>
<tr>
<td>Current case</td>
<td>33/F</td>
<td>Simultaneous</td>
<td>Yes</td>
<td>N</td>
<td>Granulomatous myositis</td>
<td>MDPS (0.8/kg/d), IFX</td>
<td>Yes (d)</td>
</tr>
</tbody>
</table>

1These treatment modalities are those that induced a persistent remission of myositis-related symptoms.
GMS: Gastrocnemius myalgia syndrome; CD: Crohn’s disease; MDPS: Mitochondrial-derived peptides; IFX: Infliximab; ASA: Aminosalicylate; AZA: Azathioprine; PDS: Peroxydisulfate.

While clinical and biological features in patients with GMS are generally characteristics, histomorphological findings are rather heterogeneous. In fact, our case is only the third in which granulomatous lesions were observed while all remaining reported cases were characterized by non-granulomatous inflammation (4 cases) or localized vasculitis (5 cases) (Table 1). However, whatever the histopathologic image observed, the inflammatory infiltrate was more often localized in the perimysium and more discrete in the endomysium, probably explaining why most patients with GMS have normal CK values. GMS could therefore represent a form of localized “perimyositis” with no or limited myofiber injury. This observation also suggests that the immune response is directed against connective tissue components or vessels rather than against the myofibers themselves.

Finally, while GMS was initially controlled in this case by oral CS therapy, it ultimately relapsed during tapering. In this context, the presence of a concomitant severe active ileocolitis prompted us to start an anti-TNF-α agent. While CS were the first-line treatment prescribed in almost all cases of GMS, their efficacy, however, was not enduring as 6/16 patients (including ours) relapsed during dose de-escalation (Table 1). Moreover, two other patients were initially refractory to CS[12,13]. Various drugs were used in these corticosteroid-dependent or refractory cases. Anti-TNF-α agents were constantly associated with GMS remission in the six cases where they were introduced, suggesting that the
Figure 2 Biopsy specimen from the right gastrocnemius muscle showing the intense immune-inflammatory reaction. A: This hematoxylin and eosin-stained section shows the granulomatous nature (arrowhead) of this Crohn’s disease-associated skeletal myositis, predominating in the perimysial compartment. B: Discrete and focal immune infiltrates are found in the endomysium and around vascular structures (arrows); C and D: Immunohistochemical staining characterize immune cell-types involved therein: Co-staining for CD3 (brown staining) and CD20 lymphocytes (red staining) shown in C reveals predominance of CD3+ lymphocytes over CD20+ cells. CD4 and CD8 T cells subtyping shown in D (brown and red staining respectively) further reveals a slight predominance of CD8+ over CD4+ cells.

muscular and intestinal affections in this context could share a common pathophysiological mechanism. Importantly, our case represents the first GMS with granulomatous inflammation treated with an anti-TNF-α agent. Further case descriptions and/or case series will be required to ascertain the role of such therapy in this specific context.

CONCLUSION

In conclusion, we report a rare extra-intestinal manifestation of CD, namely a GMS, characterized by a very rarely reported granulomatous perimyositis. The rapid relapse of GMS during CS tapering and the emergence of a severe active ileocolitis prompted the introduction of an anti-TNF-α agent that resulted in persistent clinical remission of both disorders. This might further suggest the effectiveness of such agents in CS-dependent or refractory cases. Finally, physicians should remain aware of the eventual emergence of a such complicating myositis when musculo-skeletal symptoms arise in IBD patients even in the absence of CK elevation.

ACKNOWLEDGEMENTS

We thank Anaïs Boisson (Laboratory of Molecular Immunology, Jules Bordet Institute, Brussels, 1000, Belgium) who performed immunohistochemistry stainings.

FOOTNOTES

Author contributions: Lambot F, Catherine J and Otero Sanchez L managed the patient; Kadhim H did myopathology
diagnosis and analyses; Catherine J, Otero Sanchez L and Meurant V designed the study and collected data; Catherine J and Otero Sanchez L drafted and wrote the manuscript; Liefferinckx C, Lambot F and Kadhim H provided their expertise throughout the course of the work by revising and editing the manuscript; all authors approved the final version of the manuscript to be published.

Supported by National Fund for Scientific Research (F.R.S-FNRS) as research fellows to Catherine J and Otero Sanchez L; Fonds Erasme to Otero Sanchez L; and F.R.S-FNRS as postdoctoral fellow to Liefferinckx C.

Informed consent statement: The study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by the institutional review board of CHU Tivoli (approval number #1396). Patient’s informed consent was obtained by Meurant V.

Conflict-of-interest statement: Liefferinckx C received consultancy fees from Takeda and Galapagos; speaker fees from Sandoz, Janssen and AbbVie.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Belgium

ORCID number: Julien Catherine 0000-0001-8825-8126; Hazim Kadhim 0000-0003-4943-9172; Frédéric Lambot 0000-0003-3585-3444; Claire Liefferinckx 0000-0002-2046-4051; Virginie Meurant 0000-0002-7626-8545; Lukas Otero Sanchez 0000-0002-8013-1371,

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

Catherine J et al. CD-associated GMS treated with infliximab


Gallbladder biliary lithotripsy: A new rationale applied to old treatment

Lorenzo Dioscoridi, Massimiliano Mutignani

Abstract

Pure endoscopic treatment of combined cholelithiasis and choledocholithiasis is possible due to the chance to use together both endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) approaches. This endotherapy permits to treat biliary stones in the main bile duct by standard ERCP and gallbladder stones by EUS-guided cholecystoduodenostomy eventually associated to intracorporeal lithotripsy to achieve optimal results.

Key Words: Endoscopic ultrasound-guided gallbladder drainage; Biliary lithotripsy; Gallstone lithotripsy; Gallbladder biliary lithotripsy; New rationale

Core Tip: Combining endoscopic approaches of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) let to treat simultaneously biliary stones both in the gallbladder and in the main bile ducts. ERCP standard approach can be associated to EUS-guided gallbladder drainage to avoid recurrences in patients unfit for surgery. To optimize this treatment, gallbladder stones can be fragmented by intracorporeal lithotripsy so their fragments can easily pass through the stent in place for cholecystoduodenostomy. This miniminvasive approach seems promising on the base of available literature.

Citation: Dioscoridi L, Mutignani M. Gallbladder biliary lithotripsy: A new rationale applied to old treatment. World J Gastroenterol 2022; 28(7): 763-765

URL: https://www.wjgnet.com/1007-9327/full/v28/i7/763.htm
TO THE EDITOR

We read with interest the paper by Cianci and Restini[1]. The authors interestingly discussed on indications, advantages and disadvantages of laparo-endoscopic rendez-vous, pure laparoscopic common bile duct exploration and sequential laparoscopic-endoscopic retrograde cholangiopancreatography (ERCP) approach in combined cholethiasis and choledocholithiasis. We would like to focus on a totally endoscopic approach to this pathology.

We totally agree with Cianci and Restini[1] that ERCP cannot be considered definitive in the treatment of cholecysto-choledocholithiasis, even if associated with lithotripsy, since the genesis of the stones is secondary to the lithogenic bile in the gallbladder. Thus, can we act endoscopically also on gallbladder stones?

Recently, EUS-guided cholecystoduodenostomy was found comparable to laparoscopic cholecystectomy in terms of clinical outcomes[2]. Recurrent biliary events after EUS-guided gallbladder drainage can be even lowered by associated lithotripsy.

Historically, many studies demonstrated the ineffectiveness of the gallstone lithotripsy alone with high recurrence rate associated to high rate of adverse events, especially in case of multiple and large stones[3,4]. In the recent years, the role of this treatment was re-established because of the new endoscopic approaches described for acute cholecystitis; particularly, the increasing role of EUS-guided cholecysto-duodenostomy[5,6] has two main interesting implications in this perspective.

Firstly, EUS-guided gallbladder drainage can be considered as definitive therapy especially in elderly patients unfit for surgery, differently from percutaneous cholecystostomy[4]. After endoscopic stable gallbladder drainage in the duodenum, the gallbladder loses its property to concentrate the bile and, so on, to form new gallstones.

In this setting, the opportunity to destroy the gallstones is interesting, on one hand, to avoid eventually obstruction of the biliary edge of the stent (and subsequent relapses of symptoms) or, on the other hand, further migration of biliary gallstones into the infundibulum or into the biliary tree (and subsequent obstruction of the main bile duct), especially in case of hard and large stones.

Intracholecystic lithotripsy can be theoretically performed as biliary standard lithotripsy because effectiveness and adverse events should not be different, as described in few first experiences[6-8]. On the other side, standard endoscopic treatment for lithiasis of the common bile duct can be provided in the same combined session.

The main limitations of EUS-guided gallbladder drainage are still the need of a sufficient loosening of the gallbladder (evaluated at the preliminary EUS) to guarantee a safe puncture and the absence of extraluminal pericholecystic fluid collection.

Moreover, intracorporeal lithotripsy in the setting acute cholecystitis can be associated with higher risk of perforation because of the acute inflammation of the gallbladder walls[7-9]. We encourage further studies on this focus to verify these first results and to improve the outcomes and indications of endoscopic treatments in this field, especially for patients unfit for surgery.

FOOTNOTES

Author contributions: Dioscoridi L and Mutignani M designed research; Dioscoridi L wrote the letter; Mutignani M revised the letter.

Conflict-of-interest statement: None of the authors declare any conflict of interests related to the present paper.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Italy

ORCID number: Lorenzo Dioscoridi 0000-0003-4975-018X; Massimiliano Mutignani 0000-0002-1272-4888.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR
REFERENCES


LETTER TO THE EDITOR

Gastrointestinal microbiome and *Helicobacter pylori*: Eradicate, leave it as it is, or take a personalized benefit–risk approach?

Stanislav Sitkin, Leonid Lazebnik, Elena Avalueva, Svetlana Kononova, Timur Vakhitov

**Abstract**

*Helicobacter pylori* (*H. pylori*) is generally regarded as a human pathogen and a class 1 carcinogen, etiologically related to gastric and duodenal ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. However, *H. pylori* can also be regarded as a commensal symbiont. Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization in infancy is facilitated by T helper type 2 immunity and leads to the development of immune tolerance. Fucosylated gastric mucin glycans, which are an important part of the innate and adaptive immune system, mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization. *H. pylori* may have beneficial effects on the host by regulating gastrointestinal (GI) microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. The potential protective role against inflammatory bowel disease may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria may suggest it regulates the GI microbiota. Eradication of *H. pylori* can cause various adverse effects and alter the GI microbiota, leading to short-term or long-term dysbiosis.
Overall, studies have shown that gastric Actinobacteria decrease after *H. pylori* eradication, Proteobacteria increase during short-term follow-up and then return to baseline levels, and Enterobacteriaceae and *Enterococcus* increase in the short-term and interim follow-up. Various gastric mucosal bacteria (*Actinomyces, Granulicatella, Parvimonas, Peptostreptococcus, Prevotella, Rothia, Streptococcus, Rhodococcus, and Lactobacillus*) may contribute to precancerous gastric lesions and cancer itself after *H. pylori* eradication. *H. pylori* eradication can also lead to dysbiosis of the gut microbiota, with increased Proteobacteria and decreased Bacteroidetes and Actinobacteria. The increase in gut Proteobacteria may contribute to adverse effects during and after eradication. The decrease in Actinobacteria, which are pivotal in the maintenance of gut homeostasis, can persist for > 6 mo after *H. pylori* eradication. Furthermore, *H. pylori* eradication can alter the metabolism of gastric and intestinal bacteria. Given the available data, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the decision to eradicate *H. pylori* should be based on an assessment of the benefit-risk ratio for the individual patient. Thus, the current guidelines based on the unconditional “test-and-treat” strategy should be revised. The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication can cause antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea and colitis and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca*. Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or dysbiosis of the GI microbiota, supplementation of probiotics, prebiotics, and microbial metabolites (*e.g.*, butyrate + inulin) should be considered to decrease the negative effects of eradication.

**Key Words:** *Helicobacter pylori*; Eradication; Gastrointestinal microbiota; Dysbiosis; Fucosylated glycan; Inflammatory bowel disease

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** *Helicobacter pylori* (*H. pylori*) is generally regarded as a human pathogen, but it can act as a commensal symbiont. *H. pylori* colonization may have beneficial effects on the host by regulating gastrointestinal microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. *H. pylori* eradication can cause various adverse effects and alter the gastrointestinal microbiota, leading to dysbiosis. Therefore, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the therapeutic decision should be based on a personalized assessment of the benefit vs risk.

**Citation:** Sitkin S, Lazebnik L, Avalueva E, Kononova S, Vakhitov T. Gastrointestinal microbiome and *Helicobacter pylori*: Eradicate, leave it as it is, or take a personalized benefit–risk approach? *World J Gastroenterol* 2022; 28(7): 766-774

**URL:** https://www.wjgnet.com/1007-9327/full/v28/i7/766.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v28.i7.766

**TO THE EDITOR**

We read with great interest the article by Niu et al.[1], which showed that the effectiveness of quadruple *Helicobacter pylori* (*H. pylori*) eradication therapy containing bismuth depended on the gastric microbiota, and a high rate of *H. pylori* eradication was associated with the presence of *Rhodococcus, Lactobacillus*, and *Sphingomonas*, which were significantly enriched in the gastric mucosa in the successful eradication group[1]. The role of lactobacilli, mainly beneficial bacteria, in *H. pylori* infection, including eradication, has been well studied[2]. However, the authors showed for the first time the importance of *Rhodococcus* and *Sphingomonas*, which are more likely to be opportunistic or pathobiont species with unclear functions in the human gastrointestinal (GI) tract[3,4], in successful eradication of *H. pylori*[1]. It is noteworthy that in gastric cancer (GC), when the abundance of *H. pylori* decreased, several taxa (including *Rhodococcus* and *Lactobacillus*, discussed by Niu et al[1]) in the gastric mucosa significantly increased, which may indicate their potential involvement in GC after *H. pylori* infection[5]. In addition, *H. pylori* was negatively correlated with some opportunistic bacteria/pathobionts such as *Haemophilus, Streptococcus, Neisseria*, and *Fusobacterium* in the success group[1]. The results obtained by Niu et al[1] may suggest that *H. pylori* competes not so much with beneficial bacteria as with pathobionts, and eradication may ultimately worsen the gastric microbiota.
Indeed, not only does the composition of the gastric microbiota affect H. pylori eradication, but eradication significantly affects the microbiota of both the stomach and intestine, which can lead to marked and long-term dysbiotic changes. Dysbiosis of the microbiota after H. pylori eradication can be caused by many factors: by the action of antibiotics and proton pump inhibitors; by the loss of H. pylori leading to changes in the immune response of the GI mucosa; and by changes in the microenvironment of the GI tract, including those in microbial metabolic pathways and changes in gastric acidity associated with both pharmacotherapy and loss of H. pylori[6,7]. Features of the dysbiotic changes, their duration, and the rate of restoration of the disturbed microbiota vary greatly in different studies.

**Diverse effects of H. pylori eradication on gastric and intestinal microbiota**

Recent studies have demonstrated not only short-term but also long-term (≥ 6 mo) changes in the gastric microbiota after H. pylori eradication. In about half of cases (52.3%), eradication led to the predominance of proinflammatory *Acinetobacter* in gastric corpus mucosa with a decrease in microbial diversity in patients with endoscopic follow-up for > 1 year[8]. An earlier study showed that *Acinetobacter* was enriched in patients with persistent gastric inflammation 1 year after H. pylori eradication[9]. Moreover, some bacteria in the gastric mucosa (*Actinomyces, Granulicatella, Parvimonas, Peptostreptococcus, Prevotella, Rothia, and Streptococcus*), which are predominantly of oral origin, were associated with precancerous gastric lesions (atrophy and/or intestinal metaplasia) 1 year after H. pylori eradication[9]. *Actinomyces*, whose abundance can increase in the absence of H. pylori, might significantly increase the risk of GC[10]. Thus, some studies demonstrated a contribution of various gastric bacteria to precancerous gastric lesions after H. pylori eradication[9]. In general, *Actinobacteria* decreased after H. pylori eradication, *Proteobacteria* increased during short-term follow-up and then returned to baseline levels, and *Enterobacteriaceae* and *Enterococcus* increased in the short-term and interim follow-up[11]. Alternatively, it has been shown that in regions with high GC risk, H. pylori is one of the main factors in gastric dysbiosis and successful eradication can lead to the restoration of gastric microbiota[12].

*H. pylori* eradication also affects the gut microbiota. Bismuth quadruple therapy leads to short-term dysbiosis of the gut microbiota with an increased abundance of *Proteobacteria* and decreased abundances of *Bacteroidetes* and *Actinobacteria*. The increase in gut *Proteobacteria* may contribute to adverse effects during eradication therapy[13]. In another study, *H. pylori* eradication was associated with significant alterations in the gut microbiota that did not completely recover 6 wk after treatment[7]. In general, there was a decrease in *Actinobacteria*, which are pivotal in the maintenance of gut homeostasis, compared with baseline throughout the follow-up (> 6 mo) after eradication[11]. Furthermore, eradication therapy alters microbial functional pathways and the metabolism of gastric and gut bacteria[3,14].

Conversely, other studies showed that successful *H. pylori* eradication exerts beneficial effects on gut microbiota, including increased probiotic *Bifidobacterium* and downregulation of drug-resistance mechanisms[12]. Liou et al[15] generally confirmed the long-term safety of *H. pylori* eradication therapy but reported incomplete restoration of microbial diversity after 1 year and clinically irrelevant but significant increases in body mass index (BMI) and body weight at that time.

Interestingly, an increase in body weight/body mass index after *H. pylori* eradication had been identified earlier[16]. Suggested mechanisms of this effect range from an improvement in the symptoms of postprandial dyspepsia[16] to changes in the regulation of leptin and ghrelin[17] mediated by antibiotic-associated changes in the microbiota (especially by the imbalance between bacterial producers of lactate and acetate)[18]. In general, however, the data in various studies are contradictory and indicate weight gain, weight loss, or the absence of an effect of *H. pylori* eradication on body weight; this may be due to differences in the characteristics of the studied populations, such as age, nosology, and composition of the GI microbiota[19]. Further in-depth study of the microbiome-mediated effects of *H. pylori* and eradication therapy on human host metabolism, including nutrient uptake, energy homeostasis, bodyweight, hormone secretion, lipid profile, and glucose homeostasis/glycemic control, will provide clinically important findings for the management of *H. pylori* infection.

**H. pylori status and the human gut microbiome**

The presence or absence of gastric *H. pylori* can significantly affect the gut microbiota. For example, *Nitrospirae* were found exclusively in *H. pylori*-negative patients. The role of this phylum, containing nitrite-oxidizing bacteria, in the human microbiome is unclear. In a study by Wang et al[20], *Nitrospirae* were found in the gastric mucosa in all patients with GC but not in patients with chronic gastritis. The authors suggested that these bacteria may be involved in carcinogenesis through enhanced production of N-nitroso compounds. A recent study demonstrated a possible pathogenetic link between enriched colonic *Nitrospirae* and drug-resistant epilepsy, implying that *Nitrospirae* can increase nitrite toxicity and cause blood-brain barrier dysfunction[21].

Proinflammatory *Bacteroides ovatus* and *Fusobacterium varium*, associated with ulcerative colitis and adenomatous polyps[22,23] as well as trimethylamine-producing *Clostridium* sp. AT5[24] were enriched in *H. pylori*-negative samples, while *Bacteroides plebeius*, characteristic of the healthy groups (vs patients with adenomatous polyps)[23] and butyrate-producing *Eubacterium ramulus* were enriched in *H. pylori*-positive samples[7].
Conversely, *Butyricimonas* spp., including *Butyricimonas virosa*, associated with bacteremia in patients with GI cancer (colon and duodenal adenocarcinomas) and diverticulitis[25] as well as *Bacteroides coprophilus*, specifically enriched in ankylosing spondylitis[26], were enriched in *H. pylori*-positive individuals[7]. Prolinflammatory *Prevotella copri*, associated with rheumatoid arthritis and microscopic colitis as well as *Enterobacter cloacae* and *Klebsiella pneumoniae*, pathogens commonly associated with hospital infections, were also enriched in *H. pylori*-positive individuals[27]. Moreover, gut microbial vitamin B12 biosynthesis was significantly lower in *H. pylori*-positive individuals compared with *H. pylori*-negative individuals[27]. Dash et al[28] showed that the gut microbiota of *H. pylori*-infected individuals was characterized by a significantly increased abundance of *Succiniviibrio*, *Coriobacteriaceae*, *Enterococccae* and *Rikenellaceae* as well as *Candida glabrata* and other unclassified fungi. The authors suggested a possible role for these *H. pylori*-associated changes in the gut microbiota in intestinal barrier disruption and development of colorectal carcinoma[28].

**Potential protective and regulatory role of commensal *H. pylori***

Currently, *H. pylori* is generally regarded as a human pathogen and a class 1 carcinogen[29], responsible for 15% of the total cancer burden globally and up to 89% of all GC cases[30]. *H. pylori* is etiologically related to gastric and duodenal ulcers and mucosa-associated lymphoid tissue lymphoma. According to recent guidelines, it is almost always subject to unconditional eradication based on the “test-and-treat” strategy[31]. However, although *H. pylori* is present in > 50% of the world’s population, sequelae of infection occur in only 20% of infected individuals, and malignant complications, such as GC, occur in < 3% of infected people[7]. Therefore, there is also an alternative point of view that *H. pylori* is a commensal symbiont[32,33]. Back in 1998, Blaser[32] wrote that, “*H. pylori* can thus be regarded as indigenous or ‘normal’ flora, which most humans acquire within the first few years of childhood and then carry for life.”

Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization of newborns/infants is facilitated by T helper type 2 immunity and leads to the development of immune tolerance[34]. Most likely, the co-evolution of *H. pylori* and the human host over millennia has led to the fact that this bacterium is considered a commensal symbiont, not a pathogen, by the host’s immune system. This is indirectly confirmed by the fact that a1,2-fucosylated glycans of the GI epithelium, which are an important part of the innate and adaptive immune system (they create a symbiotic environment for the host and microbiota and protect against pathogens), mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization[35]. As a result, early colonization of *H. pylori* can have a positive effect on the host, for example on the regulation of the hormones leptin and ghrelin as well as on protection against some allergic (e.g., asthma) and autoimmune diseases and against inflammatory bowel disease (IBD)[36,34]. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria found in various studies[20,22-24] may suggest a regulatory function of *H. pylori* toward the GI microbiota. The available evidence for beneficial effects of *H. pylori* toward the GI microbiota, as well as potential protective effects against certain diseases, should not be ignored by the gastroenterological community.

Presence of *H. pylori* infection and reduced risk of IBD: Is there a causal relationship? The potential protective role of *H. pylori* in the development of IBD, shown in some studies[37], may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. An inverse association between *H. pylori* and potentially proinflammatory microbes (*Bacteroides ovatus*, *Fusobacterium varium*, *Rhodococcus*, *Sphingomonas*) supports a microbiome-modulating mechanism, while an immunomodulatory mechanism of protection against IBD may involve the activation of colonic mucus production by *H. pylori* via the NLRP3/caspase-1/interleukin-18 axis[38].

We suggest another possibility for the association between *H. pylori* infection and IBD, a non-causal relationship, which relates to the fucosylation status of host mucin glycans in the GIT. Individuals with a non-functional α(1,2)-fucosyltransferase 2 (FUT2) gene (they are termed non-secretors), who have loss-of-function mutations, cannot express α(1,2)-fucosylated glycans in the GI mucosa. Non-secretors (about 20% of the population) are more susceptible to infection by some pathogens (*Escherichia coli*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*) and have aberrant gut microbiota, with a reduction of beneficial *Bifidobacterium* spp. The FUT2 non-secretor phenotype increases susceptibility to Crohn’s disease, ulcerative colitis, primary sclerosing cholangitis, celiac disease, psoriasis, Behçet’s disease, type 1 diabetes, and so on but at the same time protects against *H. pylori*, which requires fucosylated glycans in the gastric mucosa for adhesion[35,39,40].

A recent study showed that patients with ulcerative colitis and Crohn’s disease had decreased FUT2 expression and α1,2-fucosylation in the colon[41]. In addition, *Fut2* deficiency in the intestinal epithelium exacerbated colitis in epithelium-specific *Fut2* knockout (*Fut2*−/−) mice, promoted the release of proinflammatory cytokines, and aggravated epithelial barrier damage[41]. The authors demonstrated for the first time that epithelium-specific *Fut2* deficiency increased susceptibility to IBD through modulation of the gut microbiome and microbiota-mediated lysophosphatidylcholine generation. Lysophosphatidylcholine may have deleterious effects on the colon by promoting the release of proinflammatory cytokines, damaging the tight junctions and epithelial barrier in the colon epithelium, and exacerbating colonic inflammation in *Fut2−/−* mice[41].
In turn, upregulation of FUT2-mediated fucosylation in the intestinal epithelium, for example by exogenous L-fucose, can protect the intestinal barrier, enhance tight junctions, and alleviate intestinal inflammation[42]. Similar to the colon, increased expression of the fucosyltransferase genes FUT2 and FUT1 in the gastric epithelium promotes H. pylori adhesion and ultimately infection[43]. Thus, we suggest that increased expression of FUT2 in the gastrointestinal mucosa can simultaneously mediate both H. pylori infection and protection against IBD via an H. pylori-independent mechanism. In this case, a causal relationship between the presence of H. pylori and a reduced risk of IBD is unlikely. However, it cannot be ruled out that H. pylori mediates the protective effect of fucosylation against IBD by modulation of the gut microbiota or through an immunomodulatory mechanism[38].

**Concluding remarks**

Given the available data, eradication cannot be an unconditional recommendation in every case of H. pylori infection, as in the vast majority of people H. pylori is most likely a commensal[32,33], possibly beneficial in mutualistic interaction with the host (for example protecting against some allergic and autoimmune diseases[36]). We join the opinion of Chen et al[7] that the decision to eradicate H. pylori should be based on an assessment of the benefit-risk ratio for the individual patient. We also support the position of Miller and Williams[44] that “universal eradication” of H. pylori may cause more harm than good for the infected persons. Thus, the current guidelines based on the unconditional “test-and-treat” strategy[31] should be revised, including to reduce the excessive number of indications for eradication and to avoid empirical eradication therapy without a previous diagnostic test for H. pylori infection.

It may be worth recommending unconditional eradication only in patients with concomitant mucosa-associated lymphoid tissue lymphoma[45] and/or in individuals at high risk of GC, for example in groups of high familial (hereditary) risk[46] or in high-risk areas/populations where eradication effectively reduces the risk of GC[47]. In the latter case, the advisability of such an approach is unquestionable, if it is evidence-based. For example, a recent systematic review and meta-analysis provided moderate-certainty evidence that searching for and eradicating H. pylori can reduce the subsequent incidence of GC and death from GC in healthy asymptomatic infected people; the risk of GC decreased by 46% after eradication therapy[48]. However, the authors concluded that as all but one of the eligible trials were conducted in East Asian populations (in China, Japan, or South Korea), and the only trial conducted in a non-Asian population (in Colombia) did not demonstrate any benefit of such an approach, the results of the systematic review cannot be extrapolated to populations outside East Asia[48].

A well-known paradox, the low incidence of GC in some regions of Africa, Asia (e.g., in India), and Latin America with a high prevalence of H. pylori infection, also requires in-depth study; this is called the African[49] or Asian/Indian enigma[50]. Although the existence of this phenomenon is sometimes disputed[51], studies have shown that H. pylori alone is most likely not enough for the development of GC, even with a high prevalence of highly pathogenic strains. Therefore, it is necessary to take into account not only the virulence factors of H. pylori and the oncogenic potential of specific strains of H. pylori but also the genetics and ethnicity of the human host population, their dietary habits (including antioxidant and sodium levels), smoking, alcohol consumption, socioeconomic status, and coinfection (parasitoses/helminthiases) modulating the potentially protective T helper type 2 immune response[49, 50].

An important factor influencing the serious consequences of H. pylori infection appears to be the co-evolution of H. pylori and the human host. A recent study demonstrated that the African human ancestry showed clear signs of co-evolution with H. pylori, while the European ancestry was maladapted. The Asian ancestry was intermediate but closer to the African ancestry[52]. This supports the hypothesis that H. pylori is a commensal symbiont rather than a human pathogen. Hopefully, a series of international prevalence surveys to investigate age-specific prevalence of H. pylori in areas of low and high GC risk, namely ENIGMA, recently launched under the auspices of the International Agency for Research on Cancer in Africa (Uganda), Asia (Iran), and Latin America (Chile, Costa Rica), will shed light on the regional characteristics of H. pylori infection and identify markers for GC risk stratification to offer reasonable preventive interventions for different populations[53].

In addition, H. pylori eradication is likely to be recommended in patients with cancer who are on therapy with immune checkpoint inhibitors or vaccine-based immunotherapy, for example in patients with non-small-cell lung cancer[54].

In patients with diseases negatively associated with H. pylori, such as IBD, microscopic colitis, celiac disease, asthma, multiple sclerosis, Barrett’s esophagus, esophageal adenocarcinoma, eosinophilic esophagitis, and so on, eradication should be carried out with caution, carefully weighing the risk-to-benefit in each case. Even though H. pylori eradication did not affect either the healing rate or the recurrence rate of pre-existing gastroesophageal reflux disease, the possibility of developing new erosive gastroesophageal reflux disease after eradication should always be kept in mind[55].

The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication (second-/third-line therapies) can cause antibiotic-associated diarrhea, including severe Clostridioides difficile-associated diarrhea and colitis[56] and antibiotic-associated hemorrhagic colitis due to Klebsiella oxytoca[57]. In this regard, we support the recent
conclusion of the American Gastroenterological Association experts that, “after multiple failed eradication attempts, the potential benefits of *H. pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated high-dose acid suppression and antibiotic exposure, particularly among individuals who are not at an identifiably higher risk of complications from persistent *H. pylori* infection (e.g., GC, peptic ulcer disease); in such scenarios, a shared decision-making approach should be seriously considered, especially in the elderly, those with frailty, and those with intolerance to antibiotics” (Best Practice Advice #9)[30].

Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or long-term dysbiotic changes in the GI microbiota, the supplementation of probiotics[58-61], prebiotics, and microbial metabolites (e.g., butyrate + inulin)[62] to reduce the negative effects of eradication should be considered[7]. In addition, alternative eradication regimens with limited or no antibiotic use, for example phage-based regimens[63], autoprobiotics[64], and natural agents and methods including traditional Chinese medicine[65], should be proposed, developed, and explored in future studies.

**ACKNOWLEDGEMENTS**

The authors are grateful to Dr. James Allen for editing a draft of this manuscript.

**FOOTNOTES**

**Author contributions:** Sitkin S contributed to the conception, review of literature, and drafting of the manuscript; All authors contributed to the writing and editing of the manuscript and approved the final version of the manuscript.

**Supported by** the Russian Science Foundation, No. 20-65-47026.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Country/Territory of origin:** Russia

**ORCID number:** Stanislav Sitkin 0000-0003-0331-0963; Leonid Lazebnik 0000-0001-8736-5851; Elena Avalueva 0000-0001-6011-0998; Svetlana Kononova 0000-0002-7373-7797; Timur Vakhitov 0000-0001-8221-6910.

**Corresponding Author’s Membership in Professional Societies:** European Crohn’s and Colitis Organisation (ECCO), Member ID: 37495.

S-Editor: Wang LL

L-Editor: Filipodia

P-Editor: Wang LL

**REFERENCES**


11. Hsu PL, Pan CY, Kao JY, Tsay FW, Peng NJ, Kao SS, Wu DC, Chen CL, Tsai HW, Chen HC, Wu MS; Taiwan Acid-Restricted Disease (TARD) Study Group. Helicobacter pylori eradication with bismuth quadruple therapy leads to dysbiosis of gut microbiota with an increased relative abundance of Proteobacteria and decreased relative abundances of Bacteroidetes and Actinobacteria. Helicobacter 2018; 23: e12498 [PMID: 29987654 DOI: 10.1111/hel.12498]


Patients with Gastroesophageal Reflux Disease: A Meta-Analysis of Randomized Controlled Studies.
Zhao Y

Efficacy of cancer immunotherapies.
Limagne E, Ghiringhelli F, Routy B, Verdeil G, Velin D.

Graham DY

Eradication therapy in an East Asian population: Meta-analysis.
Sugimoto M

Increase the Children Susceptibility for Type 1 Diabetes?
Giampaoli O

Protection against inflammatory bowel disease requires the NLRP3 inflammasome and IL-18.
Engler DB

Local gastric and systemic effects.
Bravo D


Helicobacter pylori and gastric diseases. BMJ 1998; 316: 1507-1510 [PMID: 9582144 DOI: 10.1136/bmj.316.7143.1507]


