ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2020 January 27; 12(1): 1-33

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 12 Number 1 January 27, 2020

ORIGINAL ARTICLE

Basic Study

Retrospective Cohort Study

Retrospective Study

CASE REPORT

World Journal of Gastrointestinal Surgery

Monthly Volume 12 Number 1 January 27, 2020

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Jesus Prieto, MD, PhD, Professor, Department of Medicine, Hepatology Unit, University of Navarra and Clinica Universitaria de Navarra, Pamplona 31080, Spain

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
January 27, 2020

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

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2020 January 27; 12(1): 1-8

DOI: 10.4240/wjgs.v12.i1.1

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Basic Study

Pathological abnormalities in splenic vasculature in non-cirrhotic portal hypertension: Its relevance in the management of portal hypertension

Shahana Gupta, Biju Pottakkat, Surendra Kumar Verma, Raja Kalayarasan, Sandip Chandrasekar A, Ajith Ananthakrishna Pillai

ORCID number: Shahana Gupta 0000-0003-2876-1701; Biju Pottakkat 0000-0002-8474-0270; Surendra Kumar Verma 0000-0002-2884-5561; Raja Kalayarasan 0000-0003-4056-8672; Sandip Chandrasekar A 0000-0001-6097-8754; Ajith Ananthakrishna Pillai 0000-0002-6860-5765.

Author contributions: All authors have made substantial contributions to conception and design of study, acquisition, analysis and interpretation of data; They have contributed equally to drafting of the manuscript and made critical revisions related to important intellectual content of the manuscript; All authors have approved the final version of the manuscript.

Institutional review board statement: The study has been approved by Post graduate Research Committee (PGRMC) and Institute Ethics Committee (IEC) of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondycherry, India, an Institute of National Importance under Government Of India.

Conflict-of-interest statement:

Shahana Gupta, Biju Pottakkat, Raja Kalayarasan, Sandip Chandrasekar A, Department of Surgical Gastroenterology, JIPMER, Pondicherry 605006, India

Surendra Kumar Verma, Department of Pathology, JIPMER, Pondicherry 605006, India

Ajith Ananthakrishna Pillai, Department of Cardiology, JIPMER, Pondicherry 605006, India

Corresponding author: Biju Pottakkat, MD, Professor, Additional Professor and Head, Department of Surgical Gastroenterology, JIPMER, Super-speciality Block 4th Floor, Pondicherry 605006, India. bijupottakkat@gmail.com

Abstract

BACKGROUND

Portal hypertension (PH) is associated with changes in vascular structure and function of the portosplenomesenteric system (PSMS). This is referred to as portal hypertensive vasculopathy. Pathological abnormalities of PSMS has been described in the literature for cirrhotic patients. Raised portal pressure and hyperdynamic circulation are thought to be the underlying cause of this vasculopathy. In view of this, it is expected that pathological changes in splenic and portal vein similar to those reported in cirrhotic patients with PH may also be present in patients with non-cirrhotic PH (NCPH).

AIM

To investigate pathological abnormalities of splenic vein in patients with NCPH, and suggest its possible implications in the management of PH.

METHODS

A prospective observational study was performed on 116 patients with NCPH [Extrahepatic portal vein obstruction (EHPVO): 53 and non-cirrhotic portal fibrosis (NCPF): 63] who underwent proximal splenorenal shunt (PSRS), interposition shunt or splenectomy with devascularization in JIPMER, Pondicherry, India, a tertiary level referral center, between 2011-2016. All patients were evaluated by Doppler study of PSMS, computed tomography porto-venogram and upper gastrointestinal endoscopy. An acoustic resonance forced impulse (ARFI) scan and abdomen ultrasound were done for all cases to exclude

None of the authors have any conflict of interest to declare.

Specialty type: Gastroenterology and hepatology

Received: August 5, 2019
Peer-review started: August 5, 2019
First decision: August 31, 2019
Revised: September 25, 2019
Accepted: November 7, 2019
Article in press: November 7, 2019
Published online: January 27, 2020

P-Reviewer: Caronna R, Dragoteanu MN, Isik A
S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Ma YJ

cirrhosis. Intraoperative and histopathological assessment of the harvested splenic vein was performed in all. The study group was divided into delayed and early presentation based on the median duration of symptoms (*i.e.* 108 mo).

RESULTS

The study group comprising of 116 patients [77 (66%) females and 39 (34%) males] with NCPH had a median age of 22 years. Median duration of symptoms was 108 mo. The most common presentation in both EHPVO and NCPF patients was upper gastrointestinal bleeding (hematemesis and melena). The ARFI scan revealed a median score of 1.2 (1.0-1.8) m/s for EHPVO and 1.5 (0.9-2.8) m/s for NCPF. PSRS was performed in 84 patients (two of whom underwent interposition PSRS using a 10 mm Dacron graft); splenoadrenal shunt in 9; interposition mesocaval shunt in 5; interposition 1st jejunal to caval shunt in 1 patient and devascularization with splenectomy in 17 patients. Median pre-splenectomy portal pressure was 25 (range: 15-51) mm Hg. In 77% cases, the splenic vein was abnormal upon intraoperative assessment. Under macroscopic examination, wall thickening was observed in 108 (93%), venous thrombosis in 32 (28%) and vein wall calcification in 27 (23%) cases. Upon examination under a surgical magnification loupe, 21 (18%) patients had intimal defects in the splenic vein. Histopathological examination of veins was abnormal in all cases. Medial hypertrophy was noted in nearly all patients (107/116), while intimal fibrosis was seen in 30%. Ninety one percent of patients with intimal fibrosis also had venous thrombosis. Vein wall calcification was found in 22%, all of whom had intimal fibrosis and venous thrombosis. The proportion of patients with pathological abnormalities in the splenic vein were significantly greater in the delayed presentation group as compared to the early presentation group.

CONCLUSION

Pathological changes in the splenic vein similar to those in cirrhotic patients with PH are noted in NCPH. We recommend that PH in NCPH be treated as systemic and pulmonary hypertension equivalent in the gastrointestinal tract, and that early aggressive therapy be initiated to reduce portal pressure and hemodynamic stress to avoid potential lethal effects.

Key Words: Portal hypertensive vasculopathy; Non-cirrhotic portal hypertension; Splenic vasculature; Hyperdynamic circulation; Shunt surgery

Core tip: Portal hypertensive vasculopathy is well-investigated in cirrhotics. Raised portal pressure and hyperdynamic circulation are thought to be the underlying cause. Pathological changes in the splenic vein are similar in cirrhotic and non-cirrhotic portal hypertension (NCPH). They are not primarily due to venous degenerative changes, and are similar to those observed in the pulmonary vasculature in pulmonary hypertension. Portal hypertension in NCPH should be viewed as a systemic and pulmonary hypertension equivalent in the gastrointestinal tract. We show that these pathological venous changes in NCPH are observed in a greater proportion of patients in the delayed presentation group ($P < 0.003$). Interventions to reduce portal pressure should therefore be initiated at diagnosis of NCPH. Damage to the vasculature starts early and can be prevented from progressing to venous thrombosis and its sequelae if early surgical intervention is initiated to reduce portal pressure.

Citation: Gupta S, Pottakkat B, Verma SK, Kalayarasan R, Chandrasekar A S, Pillai AA. Pathological abnormalities in splenic vasculature in non-cirrhotic portal hypertension: Its relevance in the management of portal hypertension. *World J Gastrointest Surg* 2020; 12(1): 1-8
URL: https://www.wjgnet.com/1948-9366/full/v12/i1/1.htm
DOI: https://dx.doi.org/10.4240/wjgs.v12.i1.1

INTRODUCTION

Portal hypertension (PH) is associated with changes in vascular structure and function of the portosplenomesenteric system (PSMS). This is referred to as portal hypertensive vasculopathy (PHV)[1]. Pathological abnormalities of PSMS have been described in the literature for cirrhotic patients[2,3]. Raised portal pressure and hyperdynamic circulation (HC) are thought to be the underlying cause of this vasculopathy[3]. In view of this, it is expected that pathological changes in splenic and portal vein similar to those reported in cirrhotic patients with PH may also be present in patients with non-cirrhotic PH (NCPH). To the best of our knowledge, studies on spleno-portomesenteric vasculopathy in patients with NCPH have not appeared in the literature. In this paper, we report on the pathological abnormalities in the splenic vein of patients with NCPH.

MATERIALS AND METHODS

Ethic statements

A prospective observational study was carried out on 116 consecutive patients with NCPH [extrahepatic portal vein obstruction (EHPVO): 53 and non-cirrhotic portal fibrosis (NCPF): 63] who underwent proximal splenorenal shunts, interposition shunts or splenectomy with devascularization in our Institute between February 2011–December 2016 after obtaining approval from the Institute Ethics Committee.

Imaging examinations

All patients were initially evaluated by Doppler study of PSMS, computed tomography porto-venogram and upper gastrointestinal endoscopy. Acoustic resonance forced impulse (ARFI) scans and abdomen ultrasounds were performed for all cases to exclude cirrhosis. Intra-operatively, portal pressure was assessed by measuring pressure in the omental vein using a 22G venous cannula and a transducer. Macroscopic appearance of the splenic vein wall, *e.g.*, presence of calcification, thrombosis, thickening (global or focal) were assessed. Examination under a surgical magnification loupe was performed to look for focal aneurysmal dilatations and intimal defects. A frozen section analysis of the vein wall was performed in all cases. Specimen of the splenic vein and artery were obtained after retrieving the spleen, and a segment of each was sent for histopathological examination.

Histopathological examination

All vessel wall specimens were processed and stained with Hematoxylin-Eosin (HE) and examined under a light microscope. Frozen specimen sections were stained with rapid HE stain after appropriate processing. Characteristics of the splenic venous wall *e.g.*, presence of medial hypertrophy, wall thickening, intimal fibrosis, adventitial attenuation along with evidence of thrombus formation in the splenic vein and vein wall calcification, were assessed using both histopathology and frozen section analyses. The study group was divided into delayed and early presentation based on the median duration of symptoms (*i.e.* 108 mo).

The splenic arterial wall was also assessed for medial hypertrophy and intimal thickening. Intra-operatively, trucut and wedge liver biopsies were taken in all cases to exclude cirrhosis. Specimens of the splenic vein and artery in cases with immune thrombocytopenic purpura (ITP, n = 22) and hemolytic anemia (n = 10) who underwent splenectomy were sent for histopathological examination for comparison as assumed normal controls.

Statistical analysis

Nonparametric variables were expressed as medians (range). Frequency of occurrence were expressed as proportions. Statistical analysis was performed using the statistical program GraphPad INSTAT version 3 (GraphPad Software, Inc., La Jolla, CA, United States). Proportions were compared using Fischer's exact tests.

RESULTS

In the study group comprised of 116 patients (77, 66% females and 39, 34% males) with NCPH, the median age was 22 (range: 12-55) years. They presented with symptoms for

a median duration of 108 (1-240) mo. Sixty-seven patients had the disease for more than 108 mo. While both EHPVO and NCPF are more common in females (65% and 85%, respectively); EHPVO was seen more frequently (60%) in the younger age group (< 25 years), while NCPF was more common (54%) in older (> 40 years) patients. Cirrhosis was excluded in the study group by ARFI scan, which revealed a median score of 1.2 (range: 1.0-1.8) m/s for EHPVO and 1.5(range: 0.9-2.8) m/s for NCPF. The distribution of shunt surgeries performed are given in Table 1. Median pre-splenectomy portal pressure was 25 (range: 15-51) mm Hg.

Intra-operatively, upon macroscopic examination, wall thickening was observed in 108 (93%), venous thrombosis in 32 (28%) and vein wall calcification in 27 (23%) cases. Upon examination under surgical magnification loupe, 21 (18%) patients had intimal defects in the splenic vein. In 89/116 (77%) cases, the splenic vein was found to be abnormal under intraoperative assessment (based on the presence of one or more of the following features: wall thickening, wall calcification, presence of thrombus, and intimal defects). On histopathological examination of veins, however, splenic veins in all patients were found to be abnormal (based on the presence of one or more of the pathological characteristics mentioned above). The study group was divided into delayed and early presentation based on the median duration of symptoms (*i.e.* 108 mo) (Table 2). The proportion of patients with pathological abnormalities in the splenic vein were significantly more in the delayed presentation group compared to the early presentation group (Table 2). While the incidence of thrombosis at the anastomotic end was more in the delayed presentation group, the difference was not statistically significant. All patients in the delayed presentation group had Grade III/IV esophageal varices in endoscopy. Of these 67 patients, 47 (70%) had NCPF.

Pathological examination of the splenic vein of patients without any PH who underwent splenectomy (open and laparoscopic) was also performed for comparison as assumed normal controls. This group included 22 patients (median age 20 years; 95% females) with ITP and ten patients (median age 26 years; 90% females) with hemolytic anemia and splenomegaly. The splenic veins of patients with ITP was found to be normal, whereas medial hypertrophy and intimal fibrosis was seen in patients with splenomegaly and hemolytic anemia.

Figure 1 shows typical histopathological appearances of all the characteristics of abnormal veins. Frozen section analysis of the splenic venous wall corroborated with histopathological assessment in all but two cases, *i.e.* 98%. A splenic venous aneurysm was found in one case, while a splenic artery aneurysm was found in 11 patients. Histopathological examination of the splenic artery was performed in all cases. Eighty nine percent (103/116) of patients had medial hypertrophy, of whom 6% (8) had intimal thickening. Liver biopsies taken intraoperatively showed normal liver histology in all cases with EHPVO, 30/63 (48%) cases with NCPF, and both mild periportal inflammatory changes and periportal fibrosis in the rest of the NCPF cases.

DISCUSSION

Damage to the intima of visceral veins and contractile structures in the visceral arterial wall, termed as PHV, has been observed in patients with cirrhosis and PH[1-3]. In several studies, different mechanisms of pathogenesis of PHV have been proposed. PHV is most likely primarily related to hemodynamic changes in the portal system, particularly to high pressure perfusion of veins in cirrhotics. Other proposed contributing factors may include immune response, gene modulation, vasoactive substances, and intrahepatic blood flow resistance[3,4].

Increased pressure in the portal system compresses feeding vessels, called vasa vasorum, and reduces partial pressure of oxygen in them. This results in ischemic damage and consequent nutritional depletion of vascular intima. Increased pressure with stiffening of walls (and medial layer hypertrophy) leads to displacement of vessel wall architecture and consequent shear strain on the adventitial layer, which further lodges the vasa vasorum. Injury to the vasa vasorum leads to ischemia of the vein wall with degeneration of internal elastic lamina and media. Ischemia leads to the release of growth factors and seepage of extracellular matrix into media with a resultant change in the medial smooth muscle phenotype and hypertrophy. In the venous system, intimal changes are associated with luminal thrombosis due to activation of platelets and fibrin.

Proliferative intima, thrombus adherent to the venous wall, smooth muscle hypertrophy, and increased extracellular matrix was found in both the splenic and gastric coronary veins of cirrhotic patients[3]. In cirrhotic patients, vessels are reported

Table 1 Surgical procedures performed

	Surgical procedure	*n* (%)
1	Proximal splenorenal shunt (including two interposition proximal splenorenal shunts using 10 mm Dacron graft)	84 (72.4)
2	Splenoadrenal shunt	9 (7.7)
3	Interposition mesocaval shunt	5 (4.3)
4	Interposition first jejunal to caval shunt	1 (0.9)
5	Devascularization and splenectomy	17 (14.6)
	Total	116 (100)

Table 2 Histopathological characteristics of splenic vein wall in patients with non-cirrhotic portal hypertension

Pathological abnormalities	Delayed presentation group, *n* = 67	Early presentation group, *n* = 49	*P* value
Medial hypertrophy, *n* (%)	67 (100)	40 (81.6)	0.003
Wall thickening, *n* (%)	67 (100)	40 (81.6)	0.003
Intimal fibrosis, *n* (%)	32 (47.8)	3 (6.1)	< 0.001
Adventitial attenuation, *n* (%)	30 (44.8)	5 (10.2)	< 0.001
Thrombosis, *n* (%)	32 (47.8)	0 (0)	< 0.001
Vein wall calcification, *n* (%)	26 (38.8)	0 (0)	< 0.001
Thrombosis at anastomotic end, *n* (%)	13 (19.4)	3 (6.1)	0.0556

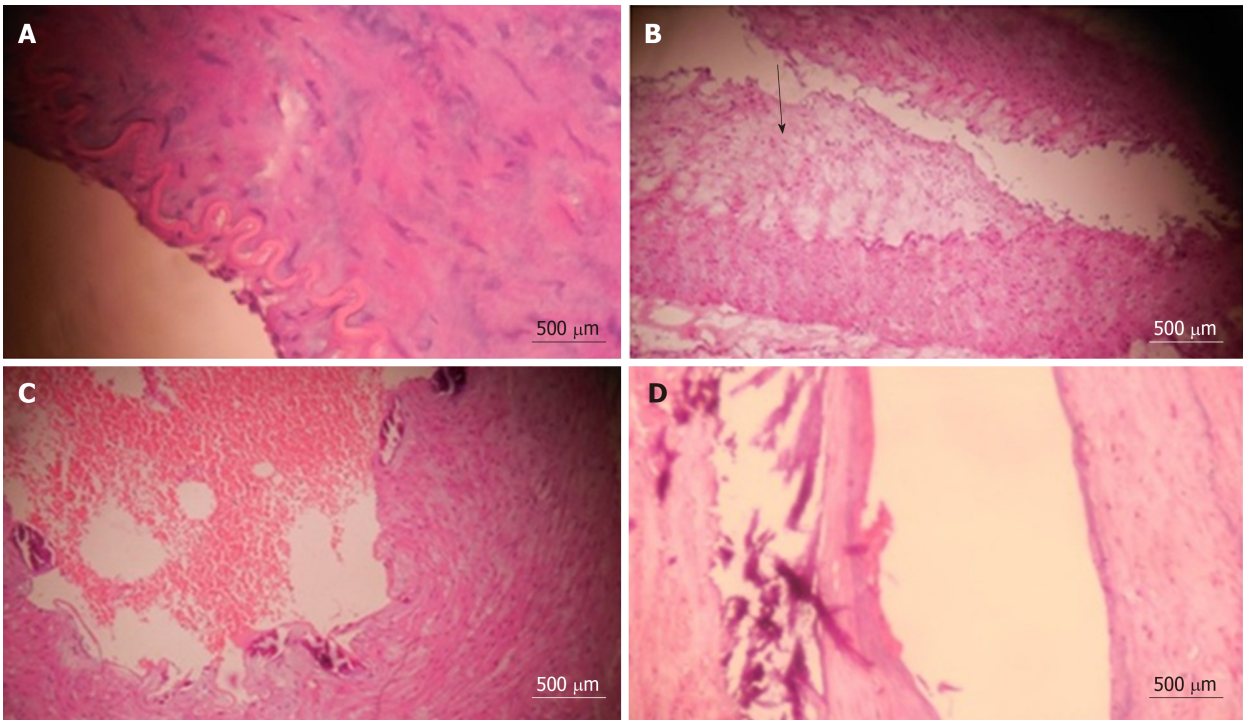

Figure 1 Typical histopathological appearances of all the characteristics of abnormal veins. A: Histopathology of splenic vein showing medial hypertrophy (Hematoxylin and eosin 40 ×, length of bar 500 μm); B: Histopathology of splenic vein showing intimal fibrosis (arrow) (Hematoxylin and eosin 40 ×, length of bar 500 μm); C: Histopathology of splenic vein showing splenic venous thrombosis (Hematoxylin and eosin 40 ×, length of bar 500 μm); D: Histopathology of splenic vein showing splenic venous wall calcification (Hematoxylin and eosin 40 ×, length of bar 500 μm).

to have a higher sensitivity to Angiotensin II, and this has been ascribed to injury of vascular endothelial cells and basement membrane by portal HC. Intimal damage probably influences contractile function of the vessels[5-7]. Smooth muscle cells of the vasculature are found to be predominantly of the synthetic type in them.

Examination of the splenic and portal veins in a series of patients with cirrhosis has led to a classification of the changes, which occur in successive stages[4]. The different stages give an indication of the extent or duration of the congestion. Thrombosis has been reported to be present in the group that showed the most significant changes in the vein walls. Intimal changes with small sub-endothelial muscle bundles arranged longitudinally were reported to succeed medial muscle hypertrophy in the portal vein. As a result of fibrous tissues replacing these muscles, intima appeared thickened and fibrotic. No evidence of any degenerative or atheromatous changes were reported. Since veins were found with medial muscular hypertrophy without intimal thickening but not the other way round, it appears reasonable to assume that the changes in the intima succeed those in the medial muscle. Changes in the splenic and portal vein were similar; the extent of change was of a lesser degree in the former. Extensive intimal thrombosis is reported to be a culmination of this chain of events[5]. Calcification in the wall of sclerotic veins has been reported to occur only in the late stages of evolution of these changes. Venous wall inflammation has been proposed to be one of the factors playing a vital role in the pathogenesis of phlebosclerosis and in the eventual development of wall calcification[5].

In our study of pathological features of splenic veins, we encounter features similar to those reported for cirrhotic patients. We have found the presence of medial hypertrophy and wall thickening in nearly all splenic veins (107/116; 92%). Intimal fibrosis was found in 35 (30%) patients, all of whom had medial hypertrophy. We noted that 32 of 35 (91%) patients with intimal fibrosis also had venous thrombosis. Vein wall calcification, which occurs in the late stage of PHV as noted above, was found in 26 (22%) patients, all of whom had intimal fibrosis and venous thrombosis.

Medial hypertrophy and intimal fibrosis was observed in patients without PH who underwent splenectomy for hemolytic anemia and had splenomegaly. This is probably a result of the presence of raised portal pressure and HC in this subgroup of patients. On the other hand, the splenic veins of all patients with ITP who had normal sized spleen and did not have any were found to be normal.

These changes in PSMS are similar to the ones observed in the pulmonary vasculature in cases of pulmonary artery hypertension[8]. Pulmonary arteriolar remodelling occurs in pulmonary hypertension (defined as mean pulmonary arterial pressure ≥ 25 mmHg). Histopathological changes including medial hypertrophy, intimal and adventitial fibrosis, thickening of the alveolar-capillary membrane, and luminal occlusion in small pulmonary arterioles have been reported. The mechanisms underlying the thickening of the pulmonary vascular medial layer have been linked mostly to cell proliferation and, more recently, to inhibition of cell apoptosis[9-11]. Raised mean pulmonary arterial pressure (≥ 25 mmHg) is in the same range as the raised portal pressure in our patients with NCPH (median portal pressure of 25 mmHg; range: 15-51 mmHg). We suggest that the pathological changes that we report in splenic vasculature in PH are the result of a raised portal pressure and HC, similar to the effect of raised pulmonary artery pressure on pulmonary vasculature.

Splenic artery in the presence of PH also shows pathological abnormalities. Microscopic examination of splenic arterial walls in cirrhotics is reported to undergo considerable thickening with disrupted endothelial cells. Disturbed smooth muscle cell layers with disrupted internal elastic lamina were also noted[3]. This injury is perhaps a result of increased pressure and flow, as well as increased cytokines, growth factors, shearing force and oxygen stress. In our study, 96% of patients with NCPH had abnormal splenic arteries upon histopathological examination (103/116; 89% had medial hypertrophy while 8/116; 7% had intimal thickening).

The similarity of the pathological features in the vasculature of patients with cirrhosis, NCPH with PHV and pulmonary hypertension leads us to conclude that the features we observe in NCPH are caused by raised pressure and HC, and not due to any degenerative disease of the veins. The same is true for splenic veins of patients with splenomegaly and hemolytic anemia who also have HC. Venous thrombosis has been reported to be the terminal event of all pathological changes in the venous wall of cirrhotics with PHV[5]. The raised pressure in the PSMS in both cirrhotic and non-cirrhotic PH could thus potentially result in the development of mesenteric venous thrombosis and intestinal gangrene. A reduction in portal pressure can prevent the development of this condition. The role of non-selective beta blockers in this context should be reassessed. Since the lifespan of patients with NCPH is compared to that of cirrhotics, compliance to lifelong drug therapy is unlikely. It is difficult to predict the clinical value and cost effectiveness of such treatment in preventing deaths from variceal bleeding, as well as preventing complications related to mesenteric venous thrombosis[12]. According to a meta-analysis, haemodynamic response rate to non-selective beta blockers is only 46%[13]. In view of these, a prophylactic shunt may be

justified to reduce portal pressure and prevent complications.

We observed that the proportion of patients with pathological abnormalities in the splenic vein were significantly greater in the delayed presentation group as compared to the early presentation group. On this basis, we propose that interventions to reduce portal pressure must be initiated at the diagnosis of NCPH instead of waiting for the patient to be symptomatic before the initiation of therapy. The damage to the vasculature starts early and can be prevented from progressing to venous thrombosis and its sequelae if early surgical intervention is initiated to reduce portal pressure. The complete reversibility of the pathological changes in the veins, once established, is uncertain.

CONCLUSION

Pathological changes in splenic vein similar to those in cirrhotic patients have been observed in patients with NCPH. They reflect the effect of HC and increased pressure in the PSMS, and are not primarily due to any venous degenerative changes. These changes are similar to those observed in pulmonary vasculature in pulmonary hypertension. We recommend that PH in NCPH be treated as systemic and pulmonary hypertension equivalent in the gastrointestinal tract. We show that these pathological venous changes in NCPH are observed in a greater proportion of patients in the delayed presentation group ($P < 0.003$). It would therefore be interesting to further explore the utility of early aggressive intervention to reduce portal pressure and hemodynamic stress to avoid potential lethal effects of mesenteric venous thrombosis and its sequelae on the intestine, liver and pancreas.

ARTICLE HIGHLIGHTS

Research background

Portal hypertension (PH) is known to be associated with changes in vascular structure and function of the portosplenomesenteric system (PSMS, portal hypertensive vasculopathy). Pathological abnormalities of PSMS has been described in the literature only for cirrhotic patients. This vasculopathy is believed to be related to raised portal pressure and hyperdynamic circulation (HC).

Research motivation

In view of similar circulatory changes in PSMS, it is anticipated that pathological changes in the splenic and portal veins, which are similar to those reported in cirrhotic patients with PH, may also be present in patients with non-cirrhotic PH (NCPH). Venous thrombosis is the terminal event of this vasculopathy. Early shunt surgery in NCPH may prevent the development of mesenteric venous thrombosis and its sequelae.

Research objectives

In this study, we aimed to study the possible association of long-term exposure of PSMS to raised pressure and HC, portal hypertensive vasculopathy (PHV) and resultant mesenteric venous thrombosis and its sequelae.

Research methods

A prospective observational study was performed on 116 patients with NCPH (extrahepatic portal vein obstruction: 53 and non-cirrhotic portal fibrosis: 63) who underwent proximal splenorenal shunt, interposition shunt or splenectomy with devascularization in JIPMER, Pondicherry, India, a tertiary level referral center, between 2011-2016. All patients were evaluated by Doppler study of PSMS, computed tomography porto-venogram and upper gastrointestinal endoscopy. Acoustic resonance forced impulse scans and abdomen ultrasounds were done for all cases to exclude cirrhosis. Intraoperative and histopathological assessment of the harvested splenic vein was performed in all. The study group was divided into delayed and early presentation based on the median duration of symptoms (*i.e.* 108 mo).

Research results

Upon histopathological examination of veins, splenic veins in all patients with NCPH

were found to be abnormal (based on the presence of one or more pathological characteristics studied).

Research conclusions

There is no report in the literature on PHV in NCPH. PHV involving the splenic vein is similar in cirrhotic as well as non-cirrhotic portal hypertensive patients. They reflect the effect of HC and increased pressure in the PSMS. We show that these pathological venous changes in NCPH are observed in a greater proportion of patients in the delayed presentation group ($P < 0.003$). It would therefore be interesting to explore the utility of early aggressive intervention to reduce portal pressure and hemodynamic stress to avoid potential lethal effects of mesenteric venous thrombosis and its sequelae on the intestine, liver and pancreas.

Research perspectives

It would be significant to investigate the role of early shunt surgery in NCPH to prevent the worsening of PHV and the development of mesenteric venous thrombosis and its sequelae in these patients.

REFERENCES

1 **Li T**, Ni JY, Qi YW, Li HY, Zhang T, Yang Z. Splenic vasculopathy in portal hypertension patients. *World J Gastroenterol* 2006; **12**: 2737-2741 [PMID: 16718761 DOI: 10.3748/wjg.v12.i17.2737]

2 **Li T**, Yang Z. Research progress of vasculopathy in portal hypertension. *World J Gastroenterol* 2005; **11**: 6079-6084 [PMID: 16273630 DOI: 10.3748/wjg.v11.i39.6079]

3 **Yang Z**, Zhang L, Li D, Qiu F. Pathological morphology alteration of the splanchnic vascular wall in portal hypertensive patients. *Chin Med J (Engl)* 2002; **115**: 559-562 [PMID: 12133298 DOI: 10.1097/00000441-200204000-00011]

4 **Wilson JB**. Changes in the portal and splenic veins in portal hypertension and their relation to splenomegaly. *Gut* 1961; **2**: 310-315 [PMID: 14007362 DOI: 10.1136/gut.2.4.310]

5 **Li PL**. Adaptation in veins to increased intravenous pressure, with special reference to the portal system and inferior vena cava. *J Path Bact* 1940; **50**: 121-136 [DOI: 10.1002/path.1700500115]

6 **McCarthy AL**, Woolfson RG, Raju SK, Poston L. Abnormal endothelial cell function of resistance arteries from women with preeclampsia. *Am J Obstet Gynecol* 1993; **168**: 1323-1330 [PMID: 7682754 DOI: 10.1016/0002-9378(93)90389-Z]

7 **Hosokawa H**, Aiuchi S, Kambe T, Hagiwara Y, Kubo T. Mechanical stretch-induced mitogen-activated protein kinase activation is mediated *via* angiotensin and endothelin systems in vascular smooth muscle cells. *Biol Pharm Bull* 2002; **25**: 1588-1592 [PMID: 12499645 DOI: 10.1248/bpb.25.1588]

8 **Rosenkranz S**, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016; **37**: 942-954 [PMID: 26508169 DOI: 10.1093/eurheartj/ehv512]

9 **Tuder RM**, Marecki JC, Richter A, Fijalkowska I, Flores S. Pathology of pulmonary hypertension. *Clin Chest Med* 2007; **28**: 23-42, vii [PMID: 17338926 DOI: 10.1016/j.ccm.2006.11.010]

10 **Yi ES**, Kim H, Ahn H, Strother J, Morris T, Masliah E, Hansen LA, Park K, Friedman PJ. Distribution of obstructive intimal lesions and their cellular phenotypes in chronic pulmonary hypertension. A morphometric and immunohistochemical study. *Am J Respir Crit Care Med* 2000; **162**: 1577-1586 [PMID: 11029379 DOI: 10.1164/ajrccm.162.4.9912131]

11 **Palevsky HI**, Schloo BL, Pietra GG, Weber KT, Janicki JS, Rubin E, Fishman AP. Primary pulmonary hypertension. Vascular structure, morphometry, and responsiveness to vasodilator agents. *Circulation* 1989; **80**: 1207-1221 [PMID: 2805259 DOI: 10.1161/01.CIR.80.5.1207]

12 **Sarin SK**, Kapoor D. Non-cirrhotic portal fibrosis: current concepts and management. *J Gastroenterol Hepatol* 2002; **17**: 526-534 [PMID: 12084024 DOI: 10.1046/j.1440-1746.2002.02764.x]

13 **Albillos A**, Bañares R, González M, Ripoll C, Gonzalez R, Catalina MV, Molinero LM. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis. *Am J Gastroenterol* 2007; **102**: 1116-1126 [PMID: 17391317 DOI: 10.1111/j.1572-0241.2007.01191.x]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2020 January 27; 12(1): 9-16

DOI: 10.4240/wjgs.v12.i1.9

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Bile leakage after loop closure *vs* clip closure of the cystic duct during laparoscopic cholecystectomy: A retrospective analysis of a prospective cohort

Sandra C Donkervoort, Lea M Dijksman, Aafke H van Dijk, Emile A Clous, Marja A Boermeester, Bert van Ramshorst, Djamila Boerma

ORCID number: Sandra C Donkervoort 0000-0003-1088-0761; Lea M Dijksman 0000-0001-9227-1390; Aafke H van Dijk 0000-0001-9758-3609; Emile A Clous 0000-0002-5544-6136; Marja A Boermeester 0000-0001-5941-5444; Bert van Ramshorst 0000-0003-0865-0983; Djamila Boerma 0000-0001-9212-1317.

Author contributions: Donkervoort SC designed the study and wrote the manuscript; Dijksman LM performed the statistical analysis and deducted a risk score; van Dijk AH collected the data and reference articles; Clous EA collected the data; Boermeester MA helped write the manuscript with emphasis on how to present the findings; van Ramshorst B critically reviewed the presented data; Boerma D co-designed the study and helped write the manuscript.

Institutional review board statement: The subject of this study concerns usual care without an intervention. The study was reviewed and approved by the MEC OLVG Institutional Review Board.

Informed consent statement: The

Sandra C Donkervoort, Emile A Clous, Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam 1090 HM, Netherlands

Lea M Dijksman, Bert van Ramshorst, Djamila Boerma, Department of Research and Epidemiology, St. Antonius Hospital, Nieuwegein 3435 CM, Netherlands

Aafke H van Dijk, Marja A Boermeester, Department of Surgery, Academic Medical Centre, Amsterdam 1105 AZ, Netherlands

Corresponding author: Sandra C Donkervoort, MD, PhD, Surgeon, Department of Surgery, Onze Lieve Vrouwe Gasthuis, PO-box 95500, Amsterdam 1090 HM, Netherlands. s.c.donkervoort@olvg.nl

Abstract

BACKGROUND

Laparoscopic cholecystectomy (LC) is one of the most frequently performed surgical procedures. Cystic stump leakage is an underestimated, potentially life threatening complication that occurs in 1%-6% of the patients. With a secure cystic duct occlusion technique during LC, bile leakage becomes a preventable complication.

AIM

To investigate the effect of polydioxanone (PDS) loop closure of the cystic duct on bile leakage rate in LC patients.

METHODS

In this retrospective analysis of a prospective cohort, the effect of PDS loop closure of the cystic duct on bile leakage complication was compared to patients with conventional clip closure. Logistic regression analysis was used to develop a risk score to identify bile leakage risk. Leakage rate was assessed for categories of patients with increasing levels of bile leakage risk.

RESULTS

Of the 4359 patients who underwent LC, 136 (3%) underwent cystic duct closure by a PDS loop. Preoperatively, loop closure patients had significantly more

subject of this study concerns usual care without an intervention. An informed consent was not applicable to our study.

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

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.

Specialty type: Gastroenterology and hepatology

Received: June 16, 2019
Peer-review started: June 19, 2019
First decision: August 2, 2019
Revised: October 19, 2019
Accepted: November 20, 2019
Article in press: November 20, 2019
Published online: January 27, 2020

P-Reviewer: Vagholkar K
S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Ma YJ

complicated biliary disease compared to the clipped closure patients. In the loop closure cohort, zero (0%) bile leakage occurred compared to 59 of 4223 (1.4%) clip closure patients. For patients at increased bile leakage risk (risk score ≥ 1) rates were 1.6% and up to 13% (4/30) for clip closure patients with a risk score ≥ 4. This risk increase paralleled a stepwise increase of actual bile leakage complication for clip closure patients, which was not observed for loop closure patients.

CONCLUSION
Cystic duct closure with a PDS loop during LC may reduce bile leakage in patients at increased risk for bile leakage.

Key Words: Laparoscopic cholecystectomy; Cystic duct occlusion; Bile leak; Endo-loop

Core tip: Laparoscopic cholecystectomy is one of the most frequently performed surgical procedures. Cystic duct leakage is an underestimated, potentially life threatening complication. With a secure cystic duct occlusion technique, bile leakage becomes a preventable complication. Assessing leakage rates for both clipped and looped patients, we found that in clip closure patients, leakage rates increased from 0.9% up to 13% depending upon their bile leakage risk, whereas loop closure patients leakage rates remained 0%, even for patients at highest risk. Cystic duct closure with a polydioxanone loop may well be a secure occlusion technique.

Citation: Donkervoort SC, Dijksman LM, van Dijk AH, Clous EA, Boermeester MA, van Ramshorst B, Boerma D. Bile leakage after loop closure *vs* clip closure of the cystic duct during laparoscopic cholecystectomy: A retrospective analysis of a prospective cohort. *World J Gastrointest Surg* 2020; 12(1): 9-16
URL: https://www.wjgnet.com/1948-9366/full/v12/i1/9.htm
DOI: https://dx.doi.org/10.4240/wjgs.v12.i1.9

INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most frequently performed surgical procedures. Bile duct injury is a postoperative complication associated with significant morbidity[1,2]. Reports on the rate of bile duct injury as a complication of LC have consistently varied from 0.5% to 1%[3,4]. Recently, it has been reported that cystic stump leakage rates (type A bile duct injury) are underestimated, especially in a subpopulation of patients with complex biliary disease[5]. Patients with previous biliary events [history of cholecystitis, cholangitis, pre-operative endoscopic retrograde cholangiopancreatography (ERCP) for suspected choledocholithiasis] or acute cholecystitis are at increased risk (4%-7%) for cystic stump leakage[6,7]. These patients often require percutaneous drainage of the biloma, endoscopic sphincterotomy, stent placement, or even re-laparoscopy or re-laparotomy[5,8].

Bile leakage from the cystic stump can be regarded a preventable complication, if during LC the cystic duct is correctly and securely occluded. To date, the application of non-absorbable metal clips for cystic duct closure is the standard of care in most hospitals and countries[8]. As an alternative for metal clips, we introduced the use of absorbable polydioxanone ligature (loops) for which few reports in literature can be found[1,9-15].

This technique is now the standard for appendix stump closure in appendectomy and has been widely reported. A decrease in bile leakage rate after LC may well be achieved using loop cystic duct closure, especially in the subpopulation of patients with complicated biliary disease. If so, this technique will lead to important improvements in patient safety for patients undergoing LC. However, there is little high quality evidence to support the hypothesis that looping the cystic duct during LC is safer than clipping.

In the present study, we analysed the effect of closure of the cystic duct using polydioxanone loops on overall bile leakage rate from the cystic duct in patients

undergoing LC. Leakage rates were additionally assessed for patients identified as being at risk for postoperative bile leakage complication.

MATERIALS AND METHODS

Data source

The study cohort was part of a database created for all consecutive patients who underwent LC for symptomatic cholecystolithiasis over a 10-year period (2002-2012) in two large teaching hospitals. Details on data retrieval of both cohorts until 2009 have been previously described in more detail[16,17]. Data entry of patients with loop cystic duct closure into this database ran thereafter until June 2012.

Study population

The looped cystic duct closure was introduced after our previous studies on timing of LC after ERCP showed cystic stump leakage rates to be 3%-5% for patient who had undergone ERCP prior to LC[17,18].

The technique used to close the cystic duct has been recorded in all patients from the original operative reports. The standard of care in that period was the use of three parallel clips, two proximal and one distal, with transection of the cystic duct leaving two parallel clips in situ. In the loop closure group patients underwent an LC in which the cystic stump was closed after transection by a polydioxanone ligature (loop). In September 2010 loop-closure of the cystic stump was introduced in patients who underwent LC for complicated gallstone disease or when confronted with a wide or inflamed cystic duct during LC. After more experience was gained in the use of loops, the use of loop closure in patients with less evidently inflamed cystic ducts became more naturally, and use expanded. When polydioxanone ligature (loop) was used, the cystic duct was transected between two non-resorbable clips. The loop was then placed over de cystic duct stump behind the clip that initially secured the cystic stump.

Patient characteristics and outcome variables

Patient age, gender, co-morbidity as well as disease characteristics were noted. The primary end point of this study was the occurrence of bile leakage from the cystic duct stump. Post-operative bile leakage complications were identified by chart review. Identification of bile leakage complications was done by meticulous screening of postoperative charts, blood results, radiology reports, and readmission notes. To search for all bile leakage complications (predominantly type A bile leaks), the occurrence of post-operative re-interventions by ERCP, percutaneous drainage procedures or re-laparoscopy, and re-laparotomy were checked. In addition, complication data were compared with hospital complication registration systems.

The effect of a loop on bile leakage complication was analysed by determining overall bile leakage rates for both clipped and looped patients. We also assessed the bile leakage rate in the period before the introduction of loop closure in clinical practice (clip closure only period, 2002-2010) in comparison with the period after the introduction of loop closure (mixed closure period, 2010-2012).

Statistical analysis

Statistical analysis was performed using SPSS version 19.0. Statistical significance is expressed as $P < 0.05$. Categorical data were shown as number (%) and compared using the Pearson χ^2 or Fisher's Exact test (where appropriate). Continuous data were shown as median with interquartile range (25%-75%) and compared using the Mann-Whitney *U* test. In this study we did not use comparative statistics analysis, when describing groups with one or more zero–cell counts as calculation of *P* value is less reliable in such cases and regular statistical tests are not designed for data with zero events.

From our database, independent risk variables predicting for a bile leakage complication were extracted. Risk variables included patient characteristics such as gender, age, American Society of Anaesthesiology (ASA) classification and body mass index. Furthermore, disease events such as previous choledocholithiasis, acute cholecystitis, pancreatitis and previous cholecystitis operated on in delayed setting were taken into account. With these variables a risk score was created as a tool to identify and define patients at increased risk for a bile leakage complication. Therefore, we used univariate and multivariate analyses with binomial logistic regression. All factors with a univariate *P* value < 0.1 were used in multivariate analysis. A risk score

was created using the beta-coefficient from factors contributing to the multivariate analysis, for which variables with $P < 0.1$ were taken into account because of the small sample size of the loop closure group. Scores were calculated by dividing the beta of each variable by the lowest beta and then rounded. The sum of these values was expressed in a final risk score. For this retrospective study, the Medical Ethical Committee at the OLVG reviewed the study protocol and a waiver was granted.

RESULTS

A total of 4359 patients underwent LC in one of the two hospitals. The median age was 50 years (interquartile range 39-62). About half of the patients were female (54%). A total of 136 of 4359 (3%) patients underwent cystic duct closure by a loop (loop closure group) instead of traditional closure by clips only (clip closure group).

Table 1 shows the demographic data of patients in the clip closure and loop closure groups. Loop closure was significantly more often used in older patients ($P = 0.038$), co-morbid patients ($P = 0.021$), and patients with complicated biliary disease: Pre-operative ERCP ($P = 0.001$), previous cholecystitis ($P < 0.001$) and acute cholecystitis ($P < 0.001$).

The overall bile leakage rate was 1.4% (59 of 4359 patients). Stratification for bile leakage risk of patients was done by developing a risk score based on logistic regression analysis (Table 2). Patients at risk for bile leakage in our population were patients with a higher (3 or 4) ASA classification (odds ratio [OR]: 1.7, 95% confidence interval [CI]: 0.9-3.3, $P = 0.09$), pre-operative ERCP (OR: 1.9, 95%CI: 1.5-2.5, $P = 0.037$), acute cholecystitis (OR: 2.7, 95%CI: 1.4-5.0, $P = 0.002$) and/or previous cholecystitis (OR: 5.1, 95%CI: 2.3-11.4, $P < 0.001$). The risk score, which was deducted from the beta values, showed patients with a previous cholecystitis to be at highest risk for a post-cholecystectomy bile leakage complication. Male gender, age, and pre-operative pancreatitis were not independent predictors for bile leakage complication.

Figure 1 displays the bile leakage rates for both groups as a function of predicted bile leakage risks. The clip closure patients without a predicted bile leakage risk were shown to have a 0.9% bile leakage rate (27 of 3154) *vs* 0% (0 of 60) for the low risk loop closure patients. For patients in the clip closure group with a bile risk score ≥ 1, leakage rate was 3.1% (33/1069), whereas 0% (0/76) in the intermediate-high risk loop closure patients had bile leakage. Leakage rates increased up to 13% (4/30) for patients with a risk score ≥ 4 or higher in the clip closure group *vs* 0% (0/3) for the loop closure group. No comparative statistics analysis was done because the loop closure group had zero events.

When comparing the time period with clip closure only to the time period in which clip closure as well as loop closure were used, overall bile leakage rates were 1.6% (41/2633) and 1.1% (19/1726; $P = 0.2$) respectively. No significant differences between observed bile leakage were found between the two time periods when stratifying for predicted risk of bile leakage; 0.9% (9/1307) *vs* 0.7% (18/1907; $P = 0.44$), respectively for the low risk patients, and 3.2% (23/726) *vs* 2.4% (10/419; $P = 0.45$), respectively for the high-risk patients (Figure 2).

DISCUSSION

In this prospective consecutive series, no bile leakage complications occurred in patients with loop closure of the cystic duct during LC, whereas after clip closure bile leakage rates varied from 2% to 13% depending on patients' bile leakage risk profile. This result stands out in particular, because loop closure was used more frequently in patients with an increased bile leakage risk.

Recently we showed that bile leakage risk is underestimated in the literature[6]. Postoperative bile leakage can occur from cystic duct stump leakage due to unsecured closure of the cystic duct, leakage from an accessory duct on the liver bed (Luska) and injury to the common bile duct. The focus in our study was cystic duct stump leakage (type A bile leaks) due to unsecured closure. If a secure technique can be identified improvements can be pursued, avoiding a potentially life threatening complication.

Leakage rates are consistently reported to be 1%-2%[3,4,19,20]. Patients with uncomplicated symptomatic biliary disease have a 1% bile leakage rate, but a subgroup of patients with complicated biliary disease due to pre-operative ERCP for suspected choledocholithiasis, patients with an acute cholecystitis, and patients with a delayed cholecystectomy have a cystic duct leakage rate up to 6%[6]. The risk score

Table 1 Demographics and baseline data

	Total, *n* = 4359	Clipped cystic duct, *n* = 4223	PDS loop cystic duct, *n* = 136	*P* value
Patient characteristics				
Age, median (IQR)	50 (39-62)	58 (43-71)	49 (38-61)	
> 65 yr, *n* (%)	869	832 (20)	37 (27)	0.038
Male, *n* (%)	2012	1945 (46)	67 (49)	NS
ASA 3-4, *n* (%)	239	225 (7)	14 (13)	0.021
History prior to LC				
Pre-operative ERCP	612	580 (14)	32 (24)	0.001
Pancreatitis	258	254 (6)	13 (10)	0.065
Previous cholecystitis	132	116 (3)	16 (12)	< 0.001
Indication for surgery				< 0.001
Sympt. biliary disease, *n* (%)	3737	3652 (87)	85 (62)	
Acute cholecystitis, *n* (%)	622	571 (13)	51 (38)	

All variables are in median. A total of 949 (22%) missing cases for American Society of Anaesthesiology (ASA) classification. NS: Not significant; IQR: Interquartile range (25%-75%) or in number (%); ASA 3-4: American Society of Anaesthesiology of 3 and 4; ERCP: Endoscopic retrograde cholangiopancreatography; LC: Laparoscopic cholecystectomy; PDS: Polydioxanone.

Table 2 Stratification of 4359 patients after laparoscopic cholecystectomy, according to risk score prediction of bile leakage based on a logistic regression model

	Multivariable		Beta	Risk score
	OR (95%CI)	*P* value		
Male gender	-	-	-	-
Age > 65 yr	-	-	-	-
ASA 3-4	2.0 (0.9-4.1)	0.074	0.68	1
Pre-op ERCP	1.7 (0.9-3.3)	0.094	0.54	1
Pre-op pancreatitis	-	-	-	-
Acute cholecystitis	2.7 (1.4-5.0)	0.002	0.98	2
Delayed surgery for previous cholecystitis	5.1 (2.3-11.4)	< 0.001	1.63	3
Maximum score				5

OR and CI with multivariable logistic regression analysis. CI: Confidence interval; OR: Odds ratio; ASA 3-4: American Society of Anaesthesiology of 3 and 4; ERCP: Endoscopic retrograde cholangiopancreatography; ASA: American Society of Anaesthesiology; pre-op ERCP: Pre-operative endoscopic retrograde cholangiopancreatography; Delayed surgery: Patients treated after a previous cholecystitis in a delayed setting; Maximum score: Delayed and acute cholecystitis exclude each other.

provided the possibility to stratify for pre-operative risk for bile leakage and thus more complex procedures. Present data showed that the loop closure group had a very low leakage rate, even in the more difficult cases.

Focus on bile leakage complications after LC is important as there is a lot to gain. It is an unwanted complication with potential high morbidity inducing high healthcare costs as patients often require endoscopic intervention depending upon the nature of the leakage, with or without a percutaneous drainage procedure, re-laparoscopy, or even re-laparotomy[21-24]. Although the reported success rate of an initial treatment of bile leakage is high (96%), it is still a potentially life threatening situation, possibly leading to sepsis and multiple organ failure due to biliary peritonitis[2].

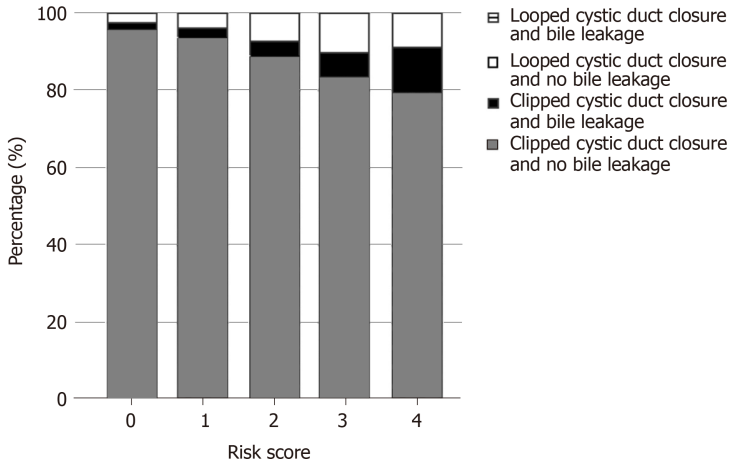

Figure 1 Identified risk for a bile leakage complication and bile leakage rate for clip closure and loop closure patients. X-axis: Summarised risk score for bile leakage complication; Y-axis: Percentage of patients with and without bile leakage in loop closure patients and cystic duct closure patients.

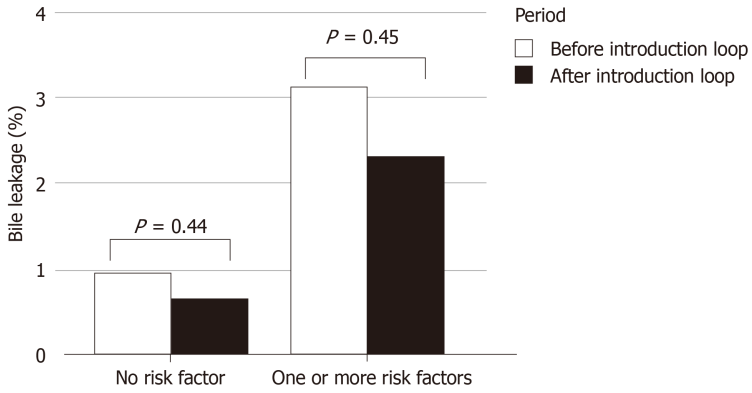

Figure 2 Bile leakage complication rate in patients after laparoscopic cholecystectomy for the period with only clip closure of the cystic duct (clip closure only period) and the period after loop cystic duct closure had been introduced (mixed closure period). No risk score: No bile leakage risk according to risk score prediction of Table 2; Risk score ≥ 1: Bile leakage risk score ≥ 1 according to risk score prediction of Table 2.

Bile leakage after LC due to the failure of a closed cystic stump (1%) is preventable if a secure closing technique is used during cholecystectomy[3,25]. Different techniques for cystic duct closure exist, of which the placement of non-resorbable metal clips has been the standard of care to date. Clipped closure is reportedly complicated by post-operative bile leakage due to laceration of the duct[26], through the conduction of electricity[27], necrosis of the clamped tissue[28], or migration of the clips[6,11,29,30], especially when placed on inflamed tissue.

Other techniques of cystic duct closure, such as absorbable clips, ligatures, and vessel sealants, have been proposed. Gurusamy *et al*[31] reported a systematic review of three trials including a total of 255 patients. Duct occlusion with absorbable clips, non-absorbable clips, and absorbable ligatures were compared. All three trials consisted of no more than 75 patients per group and were at high risk for bias. No difference in bile leakage complication between the groups was found.

Since the widespread use of harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH, United States) and vessel sealants (LigaSure™) in laparoscopic surgery, these techniques have also been explored for closure of the cystic duct. Although studies have shown that these techniques are deemed safe and efficient, they have at least comparable bile leakage rates (1.75%) as clips[32,33].

Reports on other techniques of cystic stump closure (*i.e.* metal clips, locking clips, ligatures) are limited. There is not enough high quality evidence to either encourage or discourage a specific technique of closure during LC. As the overall bile leakage rate (1%) is low in LC, studies with a large number of patients are necessary to deliver evidence for superior cystic duct closure. When searching for a superior cystic duct closure technique, a study design with a subpopulation of high-risk patients will give

the best insight. None of the aforementioned studies used a subpopulation with an increased risk for bile leakage complication for analysis. We are the first to analyse bile leakage complication in a subpopulation of patients with multiple risk factors for leakage. Previously we found that LC is technically more difficult in "complicated" biliary disease compared to patients with "uncomplicated" biliary disease[7,14]. Here, we show that bile leakage outcome is different for these subgroups and advocate to recognise that patients with gallstone disease consist of two different disease entities, "uncomplicated" and "complicated" disease.

Present data should be regarded with caution. A few limitations of the present study have to be highlighted: First, the low number of looped patients; the looped cohort consisted of only 3% of the total population. No events/bile leakage occurred in the looped cystic duct group, which made statistical analysis difficult. The lack of events may have been caused by chance rather than an effect of the loop closure. No formal sample size calculation was done in this retrospective setup. Larger patient populations are needed to be able for a more accurate estimation of the effect. However, with all limitations in mind, loop closure of the cystic duct performed far better than the clip closure group, and foremost, better than expected based on predicted risk of postoperative bile leakage.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic cholecystectomy (LC) is one of the most frequently performed surgical procedures. Cystic stump leakage is an underestimated, potentially life threatening complication and still occurs in 1%-6% of the patients. If a secure cystic duct occlusion technique can be found bile leakage becomes a preventable complication and morbidity from LC significantly reduced. With our study we believe to contribute to a reduction in bile leakage rates.

Research motivation

The main topic is cystic stump leakage complication after LC. The key problem is that this complication is underestimated and still occurs in 1%-6% of patients. We can solve this unnecessary complication by finding a secure cystic duct closure technique. As yet data on cystic duct closure technique is scars, using a polydioxanone (PDS) loop has not been described in a significant cohort yet. We find the use of a loop very promising and an interesting topic for future research.

Research objectives

To investigate the effect of PDS loop closure of the cystic duct on bile leakage rate in LC patients and compare bile leakage complication with the conventional clipped closure technique in patients with and without increased bile leakage risk. We show that PDS loop closure is a safe closure technique, as 0% bile leakage complications occurred even in high risk patients; whereas, in clipped closure patients the bile leakage rate increased from 0.9 up to 13%, dependent upon the bile leakage risk. PDS loop closure technique deserves more attention.

Research methods

In this retrospective analysis of a prospective cohort, the effect of PDS loop closure of the cystic duct on bile leakage complication was compared to patients with conventional clip closure. Logistic regression analysis was used to develop a risk score to identify bile leakage risk. Leakage rate was assessed for categories of patients with increasing levels of bile leakage risk. This is a novel approach to the problem.

Research results

We show that PDS loop closure is a safe closure technique, as 0% bile leakage complications occurred even in high risk patients; whereas, in clipped closure patients bile the leakage rate increased from 0.9% up to 13%, dependent upon the bile leakage risk. PDS loop closure technique deserves more attention. This study contributes to a more secure cystic duct closure technique during LC and can motivate to further investigate this closure technique to increase the level of evidence.

Research conclusions

Cystic duct closure with a PDS loop during LC may reduce bile leakage in patients at increased risk for bile leakage.

Research perspectives

PDS loop is a potential secure cystic duct closure technique with no bile leakage complication risk even in high-risk patients. A change in cystic duct closure technique has already been implemented in our institution. The conventional clipped closure technique is not used in patients at risk for bile leakage complication. Randomised controlled trial or large prospective multicentre cohort.

ACKNOWLEDGEMENTS

We would like to thank Joep. E.E.M Maeijer from the AVD of Teaching Hospital at OLVG for his creative support in creating figures.

REFERENCES

1 **Shea JA**, Healey MJ, Berlin JA, Clarke JR, Malet PF, Staroscik RN, Schwartz JS, Williams SV. Mortality and complications associated with laparoscopic cholecystectomy. A meta-analysis. *Ann Surg* 1996; **224**: 609-620 [PMID: 8916876 DOI: 10.1097/00000658-199611000-00005]

2 **Booij KA**, de Reuver PR, Yap K, van Dieren S, van Delden OM, Rauws EA, Gouma DJ. Morbidity and mortality after minor bile duct injury following laparoscopic cholecystectomy. *Endoscopy* 2015; **47**: 40-46 [PMID: 25532112 DOI: 10.1055/s-0034-1390908]

3 **Massoumi H**, Kiyici N, Hertan H. Bile leak after laparoscopic cholecystectomy. *J Clin Gastroenterol* 2007; **41**: 301-305 [PMID: 17426471 DOI: 10.1097/MCG.0b013e31802c29f2]

4 **Strasberg SM**, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg* 1995; **180**: 101-125 [PMID: 8000648 DOI: 10.1006/jsre.1995.1018]

5 **Bergman JJ**, van den Brink GR, Rauws EA, de Wit L, Obertop H, Huibregtse K, Tytgat GN, Gouma DJ. Treatment of bile duct lesions after laparoscopic cholecystectomy. *Gut* 1996; **38**: 141-147 [PMID: 8566842 DOI: 10.1136/gut.38.1.141]

6 **Donkervoort SC**, Kortram K, Dijksman LM, Boermeester MA, van Ramshorst B, Boerma D. Anticipation of complications after laparoscopic cholecystectomy: prediction of individual outcome. *Surg Endosc* 2016; **30**: 5388-5394 [PMID: 27129543 DOI: 10.1007/s00464-016-4895-9]

7 **Reinders JS**, Gouma DJ, Heisterkamp J, Tromp E, van Ramshorst B, Boerma D. Laparoscopic cholecystectomy is more difficult after a previous endoscopic retrograde cholangiography. *HPB (Oxford)* 2013; **15**: 230-234 [PMID: 23374364 DOI: 10.1111/j.1477-2574.2012.00582.x]

8 **Bektas H**, Schrem H, Winny M, Klempnauer J. Surgical treatment and outcome of iatrogenic bile duct lesions after cholecystectomy and the impact of different clinical classification systems. *Br J Surg* 2007; **94**: 1119-1127 [PMID: 17497652 DOI: 10.1002/bjs.5752]

9 **Fullum TM**, Kim S, Dan D, Turner PL. Laparoscopic "Dome-down" cholecystectomy with the LCS-5 Harmonic scalpel. *JSLS* 2005; **9**: 51-57 [PMID: 15791971 DOI: 10.1016/S0149-7944(01)00530-X]

10 **Nowzaradan Y**, Meador J, Westmoreland J. Laparoscopic management of enlarged cystic duct. *Surg Laparosc Endosc* 1992; **2**: 323-326 [PMID: 1341555]

11 **Hanazaki K**, Igarashi J, Sodeyama H, Matsuda Y. Bile leakage resulting from clip displacement of the cystic duct stump: a potential pitfall of laparoscopic cholecystectomy. *Surg Endosc* 1999; **13**: 168-171 [PMID: 9918624 DOI: 10.1007/s004649900932]

12 **Swanstrom LL**. "Clipless" cholecystectomy: evolution marches on, even for lap chole. *World J Surg* 2011; **35**: 824-825 [PMID: 21327604 DOI: 10.1007/s00268-011-0974-1]

13 **Saha SK**. Ligating the cystic duct in laparoscopic cholecystectomy. *Am J Surg* 2000; **179**: 494-496 [PMID: 11004339 DOI: 10.1016/s0002-9610(00)00391-3]

14 **Donkervoort SC**, Dijksman LM, de Nes LC, Versluis PG, Derksen J, Gerhards MF. Outcome of laparoscopic cholecystectomy conversion: is the surgeon's selection needed? *Surg Endosc* 2012; **26**: 2360-2366 [PMID: 22398961 DOI: 10.1007/s00464-012-2189-4]

15 **Kortram K**, Reinders JS, van Ramshorst B, Wiezer MJ, Go PM, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. *Surg Endosc* 2010; **24**: 2206-2209 [PMID: 20174934 DOI: 10.1007/s00464-010-0928-y]

16 **Danzinger R**, Nauta R, Park J. Biliary tract. In: Essentials of General Surgery. 4th ed. Philadelphia: Lippincott Williams and Wilkins. Essentials of General Surgery. 2006; 348-350

17 **Reinders JS**, Goud A, Timmer R, Kruyt PM, Witteman BJ, Smakman N, Breumelhof R, Donkervoort SC, Jansen JM, Heisterkamp J, Grubben M, van Ramshorst B, Boerma D. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. *Gastroenterology* 2010; **138**: 2315-2320 [PMID: 20206179 DOI: 10.1053/j.gastro.2010.02.052]

18 **Donkervoort SC**, van Ruler O, Dijksman LM, van Geloven AA, Pierik EG. Identification of risk

factors for an unfavorable laparoscopic cholecystectomy course after endoscopic retrograde cholangiography in the treatment of choledocholithiasis. *Surg Endosc* 2010; **24**: 798-804 [PMID: 19707824 DOI: 10.1007/s00464-009-0659-0]

19 **Matsui Y**, Yamaki S, Yamamoto T, Isizaki M, Matsui K, Yanagimoto H, Toyokawa H, Kaibori M, Satoi S, Kwon AH. Absence of cystic duct leakage using locking clips in 1017 cases of laparoscopic cholecystectomy. *Am Surg* 2012; **78**: 1228-1231 [PMID: 23089440]

20 **Yang TF**, Guo L, Wang Q. Evaluation of Preoperative Risk Factor for Converting Laparoscopic to Open Cholecystectomy: A Meta-Analysis. *Hepatogastroenterology* 2014; **61**: 958-965 [PMID: 26158149]

21 **Rustagi T**, Aslanian HR. Endoscopic management of biliary leaks after laparoscopic cholecystectomy. *J Clin Gastroenterol* 2014; **48**: 674-678 [PMID: 24296422 DOI: 10.1097/MCG.0000000000000044]

22 **de Reuver PR**, Rauws EA, Bruno MJ, Lameris JS, Busch OR, van Gulik TM, Gouma DJ. Survival in bile duct injury patients after laparoscopic cholecystectomy: a multidisciplinary approach of gastroenterologists, radiologists, and surgeons. *Surgery* 2007; **142**: 1-9 [PMID: 17629994 DOI: 10.1016/j.surg.2007.03.004]

23 **Pitt HA**, Sherman S, Johnson MS, Hollenbeck AN, Lee J, Daum MR, Lillemoe KD, Lehman GA. Improved outcomes of bile duct injuries in the 21st century. *Ann Surg* 2013; **258**: 490-499 [PMID: 24022441 DOI: 10.1097/SLA.0b013e3182a1b25b]

24 **Donkervoort SC**, Dijksman LM, Versluis PG, Clous EA, Vahl AC. Surgeon's volume is not associated with complication outcome after laparoscopic cholecystectomy. *Dig Dis Sci* 2014; **59**: 39-45 [PMID: 24081642 DOI: 10.1007/s10620-013-2885-5]

25 **Paajanen H**, Suuronen S, Eskelinen M, Hytonen S, Juvonen P. Frequency of bile leak after laparoscopic cholecystectomy: audit of a surgical residency program. *Am Surg* 2014; **80**: 91-94 [PMID: 24401523]

26 **Hamer DB**. Cystic duct laceration by metallic clips: a cautionary note. *Br J Surg* 1996; **83**: 708 [PMID: 8689218 DOI: 10.1002/bjs.1800830530]

27 **Hawasli A**. The use of absorbable clips in laparoscopic cholecystectomy. *J Laparoendosc Surg* 1994; **4**: 333-338 [PMID: 7833518 DOI: 10.1089/lps.1994.4.333]

28 **Kennedy RJ**, Clements WD, Diamond T. Cystic duct laceration by metallic clips: a cautionary note. *Br J Surg* 1995; **82**: 1543 [PMID: 8535814 DOI: 10.1002/bjs.1800821128]

29 **Goshi T**, Okamura S, Takeuchi H, Kimura T, Kitamura S, Tamaki K, Okamoto K, Kaji M, Muguruma N, Okahisa T, Shunto J, Takayama T. Migrated endoclip and stone formation after cholecystectomy: a case treated by endoscopic sphincterotomy. *Intern Med* 2009; **48**: 2015-2017 [PMID: 19952484 DOI: 10.2169/internalmedicine.48.2634]

30 **Ray S**, Bhattacharya SP. Endoclip migration into the common bile duct with stone formation: a rare complication after laparoscopic cholecystectomy. *JSLS* 2013; **17**: 330-332 [PMID: 23925031 DOI: 10.4293/108680813X13654754534350]

31 **Gurusamy KS**, Bong JJ, Fusai G, Davidson BR. Methods of cystic duct occlusion during laparoscopic cholecystectomy. *Cochrane Database Syst Rev* 2010; CD006807 [PMID: 20927751 DOI: 10.1002/14651858.CD006807.pub2]

32 **Westervelt J**. Clipless cholecystectomy: broadening the role of the harmonic scalpel. *JSLS* 2004; **8**: 283-285 [PMID: 15347120]

33 **Redwan AA**. Single-working-instrument, double-trocar, clipless cholecystectomy using harmonic scalpel: a feasible, safe, and less invasive technique. *J Laparoendosc Adv Surg Tech A* 2010; **20**: 597-603 [PMID: 20629516 DOI: 10.1089/lap.2009.0375]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2020 January 27; 12(1): 17-27

DOI: 10.4240/wjgs.v12.i1.17

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Outcomes associated with the intention of loco-regional therapy prior to living donor liver transplantation for hepatocellular carcinoma

Tsung-Han Wu, Yu-Chao Wang, Chih-Hsien Cheng, Chen-Fang Lee, Ting-Jung Wu, Hong-Shiue Chou, Kun-Ming Chan, Wei-Chen Lee

ORCID number: Tsung-Han Wu 0000-0002-5083-8851; Yu-Chao Wang 0000-0002-9236-5001; Chih-Hsien Cheng 0000-0001-8176-0631; Chen-Fang Lee 0000-0001-6292-7694; Ting-Jung Wu 0000-0001-8911-8758; Hong-Shiue Chou 0000-0002-3583-2048; Kun-Ming Chan 0000-0002-7566-0113; Wei-Chen Lee 0000-0002-8627-1324.

Author contributions: Wu TH drafted the manuscript; Chan KM, Wu TH, Cheng CH, Wu TJ, Chou HS, and Lee WC contributed to the acquisition of data; Chan KM and Lee WC contributed to the critical revision of the manuscript for important intellectual content; all authors contributed to the work.

Institutional review board statement: This study was fully approved by the internal review board of Chang Gung Memorial Hospital at Linkou (Approval No.: 99-3089B), and informed consent from patient was waived due to its retrospective nature.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed

Tsung-Han Wu, Yu-Chao Wang, Chih-Hsien Cheng, Chen-Fang Lee, Ting-Jung Wu, Hong-Shiue Chou, Kun-Ming Chan, Wei-Chen Lee, Department of General Surgery and Chang Gung Transplantation Institute, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan 33305, Taiwan

Kun-Ming Chan, Department of Organs Transplantation Institute, Chang Gung University College of Medicine, Taoyun 33305, Taiwan

Corresponding author: Kun-Ming Chan, MD, Associate Professor, Chief Doctor, Surgeon, Department of General Surgery and Chang Gung Transplantation Institute, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, 5 Fu-Hsing Street, Gui-Shan District, Taoyuan 33305, Taiwan. chankunming@cgmh.org.tw

Abstract

BACKGROUND

Loco-regional therapy for hepatocellular carcinoma (HCC) during the period awaiting liver transplantation (LT) appears to be a logical approach to reduce the risk of tumor progression and dropout in the waitlist. Living donor LT (LDLT) offers a flexible timing for transplantation providing timeframe for well preparation of transplantation.

AIM

To investigate outcomes in relation to the intention of pre-transplantation loco-regional therapy in LDLT for HCC patients.

METHODS

A total of 308 consecutive patients undergoing LDLTs for HCC between August 2004 and December 2018 were retrospectively analyzed. Patients were grouped according to the intention of loco-regional therapy prior to LT, and outcomes of patients were analyzed and compared between groups.

RESULTS

Overall, 38 patients (12.3%) were detected with HCC recurrence during the follow-up period after LDLT. Patients who were radiologically beyond the University of California at San Francisco criteria and received loco-regional

therapy as down-staging therapy had significant inferior outcomes to other groups for both recurrence-free survival (RFS, $P < 0.0005$) and overall survival ($P = 0.046$). Moreover, patients with defined profound tumor necrosis (TN) by loco-regional therapy had a superior RFS (5-year of 93.8%) as compared with others ($P = 0.010$).

CONCLUSION

LDLT features a flexible timely transplantation for patient with HCC. However, the loco-regional therapy prior to LDLT does not seem to provide benefit unless a certain effect in terms of profound TN is noted.

Key Words: Hepatocellular carcinoma; Loco-regional therapy; Living donor liver transplantation; Outcomes; Tumor necrosis; Liver transplantation

Core tip: Liver transplantation (LT) has become an ideal treatment for liver cirrhosis associated with hepatocellular carcinoma (HCC) as it simultaneously removes the tumors and cures the underlying liver cirrhosis. Living donor LT (LDLT) offers a flexible timing for transplantation providing timeframe for well preparation of transplantation. The study investigates the outcome in relation to the intention of pre-transplantation loco-regional therapy in LDLT for HCC. Although the study is still unable to establish a definitive therapeutic protocol to achieve a beneficial outcome of HCC after LDLT, achieving profound tumor necrosis by loco-regional therapy could also offer better outcomes for patients undergoing LDLT for HCC.

Citation: Wu TH, Wang YC, Cheng CH, Lee CF, Wu TJ, Chou HS, Chan KM, Lee WC. Outcomes associated with the intention of loco-regional therapy prior to living donor liver transplantation for hepatocellular carcinoma. *World J Gastrointest Surg* 2020; 12(1): 17-27
URL: https://www.wjgnet.com/1948-9366/full/v12/i1/17.htm
DOI: https://dx.doi.org/10.4240/wjgs.v12.i1.17

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause for cancer-related death worldwide, and its management is rapidly evolving during the last decade[1]. However, the selection of appropriate treatment for patients with HCC remains a challenge because of the clinical complexity of patients and the variability of treatment efficacy. As such, the concept of HCC treatment has currently embraced a multidisciplinary approach, which remarkably improved the long-term patients' outcome.

Surgical treatments including liver resection (LR) and liver transplantation (LT), currently provide the greatest opportunity for the potential cure of HCC. Moreover, LT is regarded as the best choice for patients who have liver cirrhosis associated with HCC but ineligible for primary LR, as the transplantation cures the underlying cirrhosis and provides the lowest cancer recurrence rate. Although the Milan Criteria set a gold standard for LT to treat HCC with favorable overall and recurrence-free survival (RFS), the strict criteria also limits the range of patients who can receive LT [2]. Therefore, numerous alternative expanded criteria have been introduced, showing comparable clinical outcomes than the Milan criteria[3-7].

However, the expansion of selection criteria should be taken cautiously, because HCC recurrence remains a great concern, leading to a poor outcome after LT. By contrast, loco-regional therapy prior to LT might be considered for the purpose of down-staging the tumor, to reduce the risk of progression and dropout of patients on the waiting list, or to improve the possibility of a favorable outcome after LT[8-11]. Previous studies had shown that loco-regional therapy is effective to improve the outcome after LT, but these results seems to be biased by the robust pathological response to the treatment in certain patients[12-16]. Nonetheless, a consensus has not been reached for the timing and the modality of treatment. Additionally, living donor LT (LDLT) account for the majority of LT events, due to the scarcity of organ from

to treatment by written consent.

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

Data sharing statement: No additional data are available. All data generated or analyzed during this study are included in this published article.

Specialty type: Gastroenterology and hepatology

Received: October 3, 2019
Peer-review started: October 3, 2019
First decision: October 24, 2019
Revised: November 6, 2019
Accepted: November 28, 2019
Article in press: November 28, 2019
Published online: January 27, 2020

P-Reviewer: Chen Z, Guo JS, Niu ZS
S-Editor: Yan JP
L-Editor: A
P-Editor: Ma YJ

deceased donors in most of the Asian countries. Therefore, further investigation of LDLT remains important to optimize therapeutic strategies for patients with HCC. This study enrolled patients who had undergone LDLT for HCC, and further investigated the impact of pre-transplantation loco-regional therapy after LT. Apart from that, loco-regional therapy prior to LDLT based on the intention of treatment were also examined.

MATERIAL AND METHODS

Patients

All patients who had undergone LDLT for HCC at the Organ Transplantation Institute of Chang Gung Memorial Hospital at Linkou, Taiwan, were retrospectively analysed after the approval of the Institutional Review Board (99-3089B). As a result, a total of 308 consecutive patients undergone LDLTs for HCC between August 2004 and December 2018 at the transplantation center were included in this study, in which all patients were pathologically proven of HCC through histological examination of the explant liver. Subsequently, patients were grouped according to the intention of loco-regional therapy prior to LT, and outcomes of patients were analyzed and compared between groups.

HCC evaluation and management before transplantation

The diagnosis of HCC was based on the European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines[17,18]. The treatment of HCC is mainly based on the algorithm of the Barcelona Clinic Liver Cancer (BCLC) staging system. In line with the current practices for HCC, the treatment modality options were multidisciplinary and depended on patient's performance, cirrhotic status of the liver, and the tumor characteristics[1]. In particular, LR is always considered the preferred treatment for HCC. Patients with HCC ineligible to LR and willing to undergo transplantation were evaluated for LT eligibility. The transplantation criteria for HCC were based on the University of California at San Francisco (UCSF) criteria, that use radiological imaging evidence in terms of tumor number and size[7].

Based on the clinical context, we divided patients with HCC waiting to receive LT in three groups. Group I comprised patients who had not received any loco-regional therapy for HCC before LDLT. Group II comprised patients who had unresectable HCC and met the UCSF radiological criteria (rUCSF), but were unable to receive LT immediately due to the availability of donors or hesitation about LT surgery. These patients would thus be recommended for loco-regional therapy in order to reduce the risk of tumor progression. Group III comprised patients who had an HCC beyond rUCSF criteria, and loco-regional therapy was performed for the purpose of down-staging.

Liver transplantation and follow-up

All LDLT procedures were performed using standard techniques and without venous bypass. The immunosuppressant regimen consisted of calcineurin inhibitors, antimetabolites, and steroid as previous described[13]. After transplantation, the explanted livers were subjected to a thorough histological examination to determine the HCC pathological characteristics. Patients who had received loco-regional therapy were further pathologically examined for effectiveness in relation to the degree of tumor necrosis (TN) as previous described[13], and a mean TN higher than 60% was defined as profound TN. Additionally, all patients were re-assessed for HCC in terms of tumor number and size for the transplantation criteria based on pathological results that termed as pathologic UCSF (pUCSF).

After LDLT, patients were regularly followed-up for graft function and tumor recurrence in the department. Generally, liver ultrasonography was performed in a minimum of 3-mo intervals. Radiological imaging including computed tomography and/or magnetic resonance imaging was routinely performed at 1, 3, 6, and 12 mo of the first year and annually afterward or whenever there was suspicion of HCC recurrence.

Outcome and statistical analysis

The outcome assessments included HCC RFS and the patients overall survival (OS). RFS was measured from the date of LDLT to the detection of HCC recurrence, while

OS was calculated from the date of LDLT to the death of patient or until the end of this study. The survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The categorical clinic-pathological variables were analyzed using the χ^2 or Fisher exact test as appropriate. Continuous variables are presented as median and range followed by comparison using the Kruskal–Wallis test. All statistical analyses were performed using the SPSS statistical software package version 25.0 (SPSS, Inc., Chicago, IL, United States) for Windows. A *P* value of less than 0.05 was considered statistically significant. The statistical review of the study was performed by a biomedical statistician.

RESULTS

General outcomes of patients

Among 738 LDLTs, 308 patients (41.7%) including 249 males and 59 females were confirmed to have HCC and were included in this study. Based on the aforementioned grouping criteria, 52 patients (16.9%) were in Group I, 228 patients (74.0%) were in Group II, and the remaining 28 patients (9.1%) were in Group III. During the follow-up, 38 patients (12.3%) were detected with HCC recurrence in a period from 1.2 to 92.5 mo after LT (median, 15.0 mo). Overall, 103 patients (33.4%) died during the study, of which 17 were hospital mortalities (5.5%) within 3 mo, and 30 patients (9.7%) died of HCC recurrence after LDLT. The remaining 205 alive patients included 6 patients with recurrent HCC and 199 HCC-free patients at the end of this study.

Group comparison

The clinical features of the patient groups are summarized in Table 1. Generally, the majority of clinical features were similar between groups. As group III represented HCC beyond rUCSF criteria for transplantation, their tumor characteristics in terms of number and size were significantly more aggressive than the other two groups. However, the severity of liver cirrhosis and the Model for End-Stage Liver Disease (MELD) score was significantly higher in group I. Specifically, 21.2% and 24.6% of patients in group I and group II, respectively, were beyond pUCSF criteria, which did not correlate with radiological criteria before LDLT. Similarly, after pathological examination, 21.4% of patients within group III were within UCSF criteria.

The comparison of survival curves showed that both RFS (Figure 1, $P < 0.0005$) and OS (Figure 2, $P = 0.046$) were significantly different between the 3 groups. Moreover, the subgroup analysis showed that group III had significant poorer outcomes (5-years RFS and OS of 54.7% and 56.2%, respectively) compared with group I (90.0%, and 62.7%) and group II (88.2%, and 73.3%), However, RFS and OS outcomes between group I and II were statistically similar.

Outcome associated with loco-regional therapy

Subsequently, patients who had received loco-regional therapy were further pathologically examined for effectiveness in relation to the degree of TN. Patients with loco-regional therapy were further compared based on the definition of profound TN. A total of 85 patients undergoing loco-regional therapy prior to LDLT, accounting for 33.2% of all patients, had profound TN.

The clinico-pathological features of patients regarding the TN status were compared in Table 2. The serum level of alpha-fetoprotein (AFP) was significantly higher in patients who were unable to get profound TN, as well as the size and number of the HCC features. However, loco-regional therapy related to the treatment timing and modality were both not significantly difference between the two patient groups. Among patients with a profound TN, we observed a higher percentage of patients who were within the radiological and pathological UCSF criteria.

We compared the RFS and OS curves of patients who had profound TN and patients who did not. The RFS of patients with profound TN at 1, 3, and 5 years were 98.7%, 97.4%, and 93.8%, respectively, whereas the RFS of patients without profound TN at the same time points were 90.7%, 81.5%, and 79.7% (Figure 3, $P = 0.01$). Moreover, the comparison of OS curves between these two groups were also not significant. The cumulative OS of patients with profound TN at 1, 3, and 5 years were 88.2%, 86.7%, and 82.0%, respectively, while the OS of patients without profound TN were 83.5%, 72.5%, and 66.4%, respectively (Figure 4, $P = 0.17$).

Table 1 The clinical features of patients based on the intention of loco-regional therapy before living donor liver transplantation

	Group I (*n* = 52)	Group II (*n* = 228)	Group III (*n* = 28)	*P* value
Age, median (range)	58 (13-70)	56 (33-69)	56 (38-69)	0.246
Sex				
Male	39 (75.0)	186 (81.6)	24 (85.7)	0.437
Female	13 (25.0)	42 (18.4)	4 (14.3)	
Hepatitis status, *n* (%)				
Hepatitis B positive	25 (48.1)	152 (66.7)	19 (67.9)	0.181
Hepatitis C positive	17 (32.7)	51 (22.4)	7 (25.0)	
HBV + HCV	6 (11.5)	10 (4.4)	1 (3.6)	
None	4 (7.7)	15 (6.6)	1 (3.6)	
MELD score, median (range)	15.5 (8-36)	10.0 (6-35)	9.5 (5-22)	< 0.0001
Child Class, *n* (%)				< 0.0001
A	9 (17.3)	116 (50.9)	16 (57.1)	
B	17 (32.7)	81 (35.5)	8 (28.6)	
C	26 (50.0)	31 (13.6)	4 (14.3)	
AFP, median (range)	9.2 (2.0-1552)	11.8 (1.3-18250)	53.4 (2.0-461)	0.098
Graft type, *n* (%)				0.578
Left liver	2 (3.8)	16 (7.0)	1 (3.6)	
Right liver	50 (96.2)	212 (93.0)	27 (96.4)	
GRWR (%), *n* (%)				0.037
≤ 0.8	7 (13.5)	64 (28.1)	4 (14.3)	
> 0.8	45 (86.5)	164 (71.9)	24 (85.7)	
Tumor Number, median (range)	1 (1-20)	2 (1-22)	4 (1-20)	< 0.0001
Maximum tumor size, median (range)	2.1 (1.0-7.5)	2.5 (1.0-9.2)	3.4 (1.5-11.2)	0.006
Pathologic UCSF, *n* (%)				< 0.0001
Within	41 (78.8)	172 (75.4)	6 (21.4)	
Beyond	11 (21.2)	56 (24.6)	22 (78.6)	
Histology grade, *n* (%)				0.382
1-2	43 (82.7)	169 (74.1)	20 (71.4)	
3-4	9 (17.3)	59 (25.9)	8 (28.6)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; MELD: Model for end-stage liver disease; AFP: Alpha-fetoprotein; GRWR: Graft recipient weight ratio; UCSF: University of California San Francisco.

DISCUSSION

Since the first successful LT performed by Thomas E Starzl half a century ago, LT has become a common and routine operation in many transplantation centers worldwide. Moreover, a flourishing LDLT practice has evolved in East Asia due to the scarcity of deceased donors[19]. Currently, LT has become the ideal curative treatment for liver cirrhosis associated with HCC, it simultaneously removes the tumors and cures the underlying liver cirrhosis. As such, LDLT offers a flexible timely transplantation possibility, providing a defining timeframe prepare the recipient before the operation. Theoretically, performing a pre-operative treatment might ameliorate the aggressiveness of HCC and improve the overall patient's outcome. Therefore, the present study analyzed patients who underwent LDLT for HCC to investigate the outcome in relation to the pre-transplantation loco-regional therapy. According to this study, the outcome of LDLT for patient with HCC was satisfactory, with a favorable RFS rate.

Table 2 Clinical characteristics of patients associated with pre-transplantation loco-regional therapy according to the presence of profound tumor necrosis (*n* = 256)

	Profound tumor necrosis (≥ 60%)		
	With (*n* = 85)	Without (*n* = 171)	*P* value
Age, median (range)	55 (33-67)	56 (33-69)	0.177
Sex, *n* (%)			0.198
Male	66 (77.6)	144 (84.2)	
Female	19 (22.4)	27 (15.8)	
Hepatitis status, *n* (%)			0.834
Hepatitis B positive	54 (63.5)	117 (68.4)	
Hepatitis C positive	22 (25.9)	36 (21.1)	
HBV + HCV	4 (4.7)	7 (4.1)	
None	5 (5.9)	11 (6.4)	
MELD score, median (range)	11 (6-27)	10 (5-35)	0236
Child Class, *n* (%)			0.460
A	46 (47.1)	92 (53.8)	
B	34 (40.0)	55 (32.2)	
C	11 (12.9)	24 (14.0)	
AFP, median (range)	9.0 (1.7-1300)	14.9 (1.3-18250)	0.018
Tumor Number, median (range)	1 (1-7)	3 (1-22)	< 0.0001
Maximum tumor size, median (range)	2.0 (0.7-7.0)	2.6 (0.5-11.2)	0.011
Loco-regional therapy, *n* (%)			0.756
Within 3 mo	45 (52.9)	87 (50.9)	
Beyond 3 mo	40 (47.1)	84 (49.1)	
Loco-regional therapy modality, *n* (%)			0.145
Local ablation	12 (14.1)	16 (9.4)	
TACE	63 (74.1)	144 (84.2)	
TACE + ablation	10 (11.8)	11 (6.4)	
Number of loco-regional therapy	1 (1-17)	1 (1-16)	0.084
Radiologic UCSF, *n* (%)			0.007
Within	82 (96.5)	146 (85.4)	
Beyond	3 (3.5)	25 (14.6)	
Pathologic UCSF, *n* (%)			< 0.0001
Within	75 (88.2)	103 (60.2)	
Beyond	10 (11.8)	68 (39.8)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; TACE: Transcatheter arterial chemoembolization; UCSF: University of California San Francisco.

However, loco-regional therapy prior to LDLT seems to not provide beneficial outcome unless a certain effect of loco-regional therapy before LT is achieved.

Although the treatment algorithm based on BCLC staging is very clear, the optimal treatment modality selection for patient with unresectable HCC remains uncertain. Moreover, individual patient may have their own choice of treatment after general consideration. Information about therapeutic options, importance of benefits and harms, the uncertainties of available options, and a patient's values through the implementation of shared decision making process could also affect the therapeutic

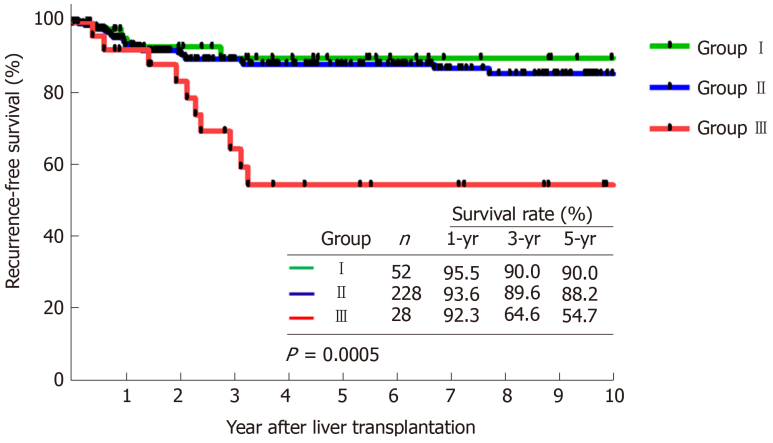

Figure 1 Comparison of recurrence-free survival curves between groups. Patients in group III have significant inferior survival curves compared with the other two groups. The 5-year recurrence-free survival rate was 54.7% ($P < 0.0005$).

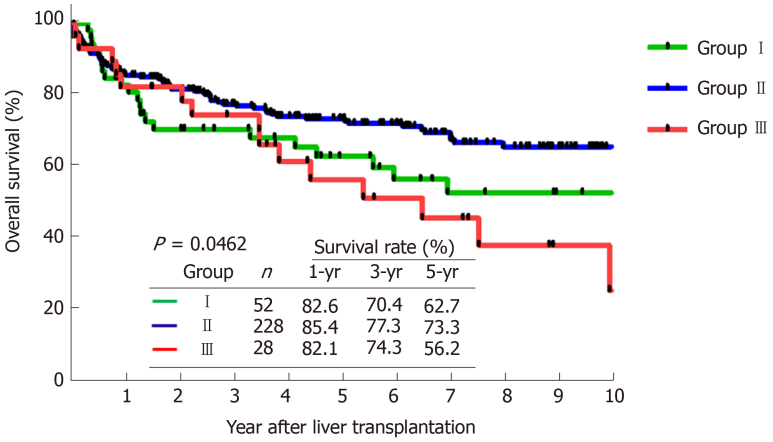

Figure 2 Comparison of overall survival curves between groups. Patients in group III have significant inferior survival curves compared with the other two groups. The 5-year overall survival rate was 56.2% ($P = 0.046$).

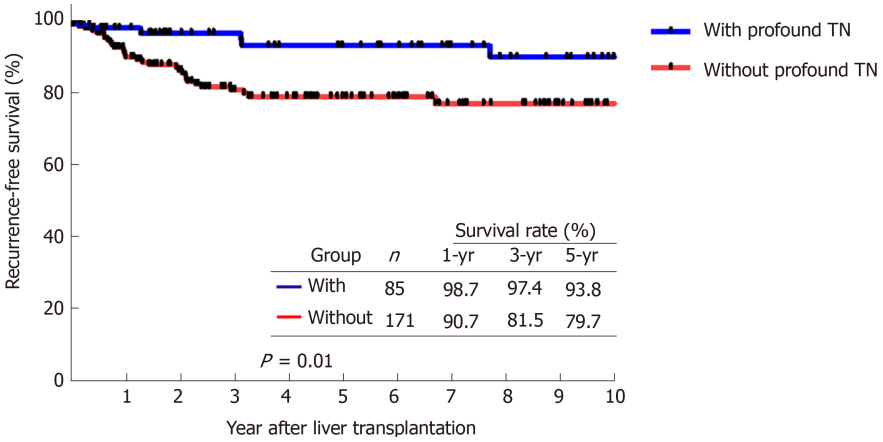

Figure 3 Comparison of recurrence-free survival curves based on the definition of profound tumor necrosis. The recurrence-free survival in patients with profound tumor necrosis (TN) was significantly better than those without profound TN ($P = 0.01$). TN: Tumor necrosis.

decision[20]. Clinically, a care provider should inform patients of all risks involved with a certain treatment instead of forcing a treatment for patient. Therefore, patients with unresectable HCC would be evaluated for LT only if the patient was willing to undergo transplantation in the institute. Additionally, the scarcity of donor remains the major concern for LT. Thus, the majority of patients received loco-regional therapy

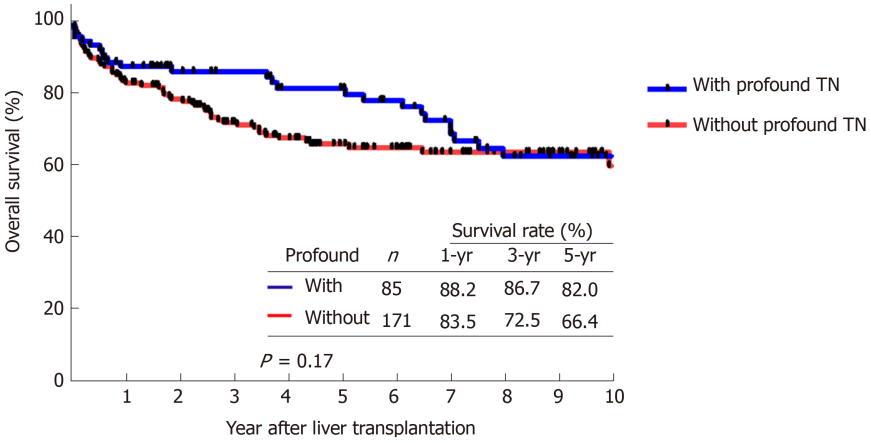

Figure 4 Comparison of overall survival curves based on the definition of profound tumor necrosis. The comparison of overall survival curves was not significantly different in relation to the presence of profound tumor necrosis (P = 0.17).

prior to LDLT due to the lack of available donor for immediate transplantation. Apart from that, patients might be initially listed for a deceased donor liver transplant and turned to LDLT because of the long-time waiting and the fear of tumor progression. In those patients, loco-regional therapy was mostly performed in order to reduce the risk of tumor progression.

Generally, the living donor liver graft is a dedicated gift from a recipient's relative, not competing with other patients awaiting for LT. LDLT usually offers a flexible timing for transplantation depending on the clinical scenario, the disease severity, and the preparation of available donor. In particular, the majority of patients with HCC have a low MELD score, meaning a non-life-threatening physical condition without a LT in a few weeks. The timeframe between the initiation of donor survey and matchup to LDLT in the institute is no longer than 4 wk. Therefore, a planned loco-regional therapy with such a short-term treatment seems unnecessary nor giving beneficial effects.

In line with the previous studies, profound TN was observed in those patients who had less aggressive HCC, lower AFP, a lower tumor number, and smaller tumor size [13,14,21]. Generally, the aim of both transcatheter arterial chemoembolization and local ablation is intend to induce TN as well as eradication of cancer cells. Although each modality has different therapeutic effects in terms of TN, sequential treatment or a combination of multi-modalities can lead to marked or complete necrosis for a HCC of defined size[22,23]. As such, the viable tumor burden could also be diminished by loco-regional therapy that results in TN and downstage of HCC status at a certain degree. Besides, a long waiting period might lead to tumor progression and patient ineligible for LT. Therefore, loco-regional therapy could also prevent dropout because of tumor progression among patients awaiting transplantation. However, timing and frequency of loco-regional therapy to achieve a profound TN response remain uncertain in the current clinical setting.

Additionally, it is difficult to assess TN through radiological imaging scan, and it could only be confirmed with thoroughly examination of the explanted liver after LT. Hence, it is unpractical to adjust the treatment strategy for LDLT on the basis of loco-regional therapy efficacy in terms of TN. Apart from that, radiological imaging scan could be mis-staging HCC. In this study, radiological images of nearly 20% of all the patients did not correlate to pathological staging. Moreover, interpret the radiological image of a cirrhotic liver is more difficult after loco-regional therapy. Nonetheless, loco-regional therapy for patient awaiting LT remains an international consensus for the management of HCC patients during the waiting time[8,24]. Hence, loco-regional therapy prior to LT might be insufficient for achieving a better outcome, but still encouraged as long as the patient is suitable for such treatment.

However, the outcomes related to the use of pre-transplantation loco-regional therapy were not statistically different in this study. Currently, the UCSF criteria are widely accepted to justify LT for HCC, in which the low incidence of HCC recurrence might be unable to reflect significance difference in this study. Additionally, the majority of group II patients only received one round of loco-regional therapy, and thus therapeutic effect in terms of profound or complete TN seems unachievable. Generally, loco-regional therapy before LT is mostly performed to prevent tumor progression in a long waiting time period. Therefore, the increased number of loco-

regional therapy could either reflect a long waiting time or a further tumor progression. However, a randomized controlled trial in terms of loco-regional therapy before LT may not be practical, in which the increased risk of tumor progression in certain study group might be a concern. Therefore, we are still unable to establish a definitive therapeutic protocol to achieve a beneficial outcome of HCC patients after LDLT.

In conclusions, although this study is limited by using a retrospective cohort, but few remarkable information might be helpful in planning therapeutic strategy for patients with HCC awaiting LDLT. A recent study showed that the use of loco-regional therapy could improve outcomes only in patients with a complete pathological response[14]. However, this study showed that achieving profound TN by loco-regional therapy could also offer better outcomes for patients undergoing LDLT for HCC. Therefore, loco-regional therapy for HCC prior to LDLT might be insufficient for achieving a better outcome but still encouraged as long as the patient is suitable for such treatment.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) has become an ideal curative treatment for liver cirrhosis associated with hepatocellular carcinoma (HCC) as it simultaneously removes the tumors and cures the underlying liver cirrhosis. Although the overall outcome of LT for HCC is favorable, tumor recurrence is still a great concern. Hence, there remain several unmet needs for improving the long-term outcome of LT for HCC.

Research motivation

Living donor LT (LDLT) account for the majority of LT in most of Asian region because of the scarcity of organ from deceased donors. LDLT offers a flexible timing for transplantation providing timeframe for well preparation of transplantation. Theoretically, a pre-operative treatment might mitigate the tumor burden and improve the overall outcome of HCC patients. Therefore, further investigation of LDLT in terms of pre-transplantation loco-regional therapy remains important to optimize therapeutic strategies for patients with HCC.

Research objectives

The main objectives of this study were to analyze patients who underwent LDLT for HCC to investigate the outcome in relation to the intention of pre-transplantation loco-regional therapy.

Research methods

All patients who had undergone LDLT for HCC between August 2004 and December 2018 were retrospectively analyzed. Subsequently, patients were grouped according to the intention of loco-regional therapy prior to LDLT, and outcomes of patients were analyzed and compared between groups. Group I comprised patients who had not received any loco-regional therapy before LDLT. Group II comprised patients who had HCC within the University of California at San Francisco (UCSF) radiological criteria (rUCSF), but had loco-regional before LDLT. Group III comprised patients who had an HCC beyond rUCSF criteria, and loco-regional therapy was performed for the purpose of down-staging.

Research results

Of 308 patients who underwent LDLT for HCC during the study period were divided into Group I (n = 52), Group II (n = 228) and Group III (n = 28) based on aforementioned definition. Overall, 38 patients (12.3%) were detected with HCC recurrence during the follow-up period after LDLT. Group III patients had significant inferior outcomes to other two groups for both recurrence-free survival (RFS, $P < 0.0005$) and overall survival (OS, $P = 0.046$). However, RFS and OS outcomes between group I and II were statistically similar. Moreover, patients with defined profound tumor necrosis by loco-regional therapy had a superior RFS as compared with others.

Research conclusions

The outcome of LDLT for patient with HCC was satisfactory with a favorable RFS rate in this study. Nonetheless, loco-regional therapy prior to LDLT seems to not provide

beneficial outcome unless a certain effect of loco-regional therapy prior to transplantation is achieved. Loco-regional therapy prior to LDLT might be insufficient for achieving a better outcome but still encouraged as long as the patient is suitable for such treatment.

Research perspectives

The study is still unable to establish a definitive therapeutic protocol to achieve a beneficial outcome of HCC patients after LDLT. Nonetheless, loco-regional therapy for HCC patient awaiting LT remains an international consensus for the management of HCC patients during the waiting time. The low incidence of HCC recurrence might be unable to reflect significance difference in this study. Therefore, additional loco-regional therapy studies in terms of high quality or larger prospective cohort studies could be undertaken in HCC patients listed for LDLT.

ACKNOWLEDGEMENTS

The authors would like to thank Ms. Shu-Fang Huang from Department of General Surgery, Chang Gung Memorial Hospital at Linkou for the statistical support and review.

REFERENCES

1 **Dhir M**, Melin AA, Douaiher J, Lin C, Zhen WK, Hussain SM, Geschwind JF, Doyle MB, Abou-Alfa GK, Are C. A Review and Update of Treatment Options and Controversies in the Management of Hepatocellular Carcinoma. *Ann Surg* 2016; **263**: 1112-1125 [PMID: 26813914 DOI: 10.1097/SLA.0000000000001556]

2 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

3 **DuBay D**, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, McGilvray I, Ghanekar A, Selzner M, Greig PD, Grant DR. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Ann Surg* 2011; **253**: 166-172 [PMID: 21294289 DOI: 10.1097/sla.0b013e31820508f1]

4 **Lee S**, Ahn C, Ha T, Moon D, Choi K, Song G, Chung D, Park G, Yu Y, Choi N, Kim K, Kim K, Hwang S. Liver transplantation for hepatocellular carcinoma: Korean experience. *J Hepatobiliary Pancreat Sci* 2010; **17**: 539-547 [PMID: 19727542 DOI: 10.1007/s00534-009-0167-6]

5 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

6 **Sugawara Y**, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007; **25**: 310-312 [PMID: 17960065 DOI: 10.1159/000106910]

7 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]

8 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]

9 **Lesurtel M**, Müllhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: an evidence-based analysis. *Am J Transplant* 2006; **6**: 2644-2650 [PMID: 16939518 DOI: 10.1111/j.1600-6143.2006.01509.x]

10 **Lu DS**, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, Saab S, Han S, Finn R, Hiatt JR, Busuttil RW. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005; **41**: 1130-1137 [PMID: 15841454 DOI: 10.1002/hep.20688]

11 **Cucchetti A**, Cescon M, Bigonzi E, Piscaglia F, Golfieri R, Ercolani G, Cristina Morelli M, Ravaioli M, Daniele Pinna A. Priority of candidates with hepatocellular carcinoma awaiting liver transplantation can be reduced after successful bridge therapy. *Liver Transpl* 2011; **17**: 1344-1354 [PMID: 21837731 DOI: 10.1002/lt.22397]

12 **Millonig G**, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, Margreiter R, Vogel W. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007; **13**: 272-279 [PMID: 17256758 DOI: 10.1002/lt.21033]

13 **Chan KM**, Yu MC, Chou HS, Wu TJ, Lee CF, Lee WC. Significance of tumor necrosis for outcome of patients with hepatocellular carcinoma receiving locoregional therapy prior to liver transplantation. *Ann Surg Oncol* 2011; **18**: 2638-2646 [PMID: 21584831 DOI: 10.1245/s10434-011-1779-z]

14 **Agopian VG**, Harlander-Locke MP, Ruiz RM, Klintmalm GB, Senguttuvan S, Florman SS, Haydel B, Hoteit M, Levine MH, Lee DD, Taner CB, Verna EC, Halazun KJ, Abdelmessih R, Tevar AD, Humar A, Aucejo F, Chapman WC, Vachharajani N, Nguyen MH, Melcher ML, Nydam TL, Mobley C, Ghobrial RM, Amundsen B, Markmann JF, Langnas AN, Carney CA, Berumen J, Hemming AW, Sudan DL, Hong JC, Kim J, Zimmerman MA, Rana A, Kueht ML, Jones CM, Fishbein TM, Busuttil RW. Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. *Ann Surg* 2017; **266**: 525-535 [PMID: 28654545 DOI: 10.1097/SLA.0000000000002381]

15 **Na GH**, Kim EY, Hong TH, You YK, Kim DG. Effects of loco regional treatments before living donor liver transplantation on overall survival and recurrence-free survival in South Korean patients with hepatocellular carcinoma. *HPB (Oxford)* 2016; **18**: 98-106 [PMID: 26776857 DOI: 10.1016/j.hpb.2015.08.008]

16 **Halazun KJ**, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, Samstein B, Brown RS Jr, Emond JC, Busuttil RW, Agopian VG. Is it Time to Abandon the Milan Criteria?: Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies. *Ann Surg* 2018; **268**: 690-699 [PMID: 30048307 DOI: 10.1097/SLA.0000000000002964]

17 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

18 European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

19 **Chen CL**, Kabiling CS, Concejero AM. Why does living donor liver transplantation flourish in Asia? *Nat Rev Gastroenterol Hepatol* 2013; **10**: 746-751 [PMID: 24100300 DOI: 10.1038/nrgastro.2013.194]

20 **Op den Dries S**, Annema C, Berg AP, Ranchor AV, Porte RJ. Shared decision making in transplantation: how patients see their role in the decision process of accepting a donor liver. *Liver Transpl* 2014; **20**: 1072-1080 [PMID: 24863055 DOI: 10.1002/lt.23921]

21 **Merani S**, Majno P, Kneteman NM, Berney T, Morel P, Mentha G, Toso C. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. *J Hepatol* 2011; **55**: 814-819 [PMID: 21334400 DOI: 10.1016/j.jhep.2010.12.040]

22 **Wong LL**, Tanaka K, Lau L, Komura S. Pre-transplant treatment of hepatocellular carcinoma: assessment of tumor necrosis in explanted livers. *Clin Transplant* 2004; **18**: 227-234 [PMID: 15142041 DOI: 10.1111/j.1399-0012.2004.00164.x]

23 **Zalinski S**, Scatton O, Randone B, Vignaux O, Dousset B. Complete hepatocellular carcinoma necrosis following sequential porto-arterial embolization. *World J Gastroenterol* 2008; **14**: 6869-6872 [PMID: 19058317 DOI: 10.3748/wjg.14.6869]

24 **Kim SH**, Lee EC, Park SJ. Pretransplant locoregional therapy for hepatocellular carcinoma: encouraging but insufficient. *Hepatobiliary Surg Nutr* 2018; **7**: 136-137 [PMID: 29744345 DOI: 10.21037/hbsn.2018.01.08]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2020 January 27; 12(1): 28-33

DOI: 10.4240/wjgs.v12.i1.28

ISSN 1948-9366 (online)

CASE REPORT

Isolated colonic neurofibroma in the setting of Lynch syndrome: A case report and review of literature

Warren YL Sun, Armaan Pandey, Mark Lee, Shawn Wasilenko, Shahzeer Karmali

ORCID number: Warren YL Sun 0000-0001-5745-5784; Armaan Pandey 0000-0001-7188-4091; Mark Lee 0000-0002-0669-2285; Shawn Wasilenko 0000-0003-4844-6493; Shahzeer Karmali 0000-0002-5083-7912.

Author contributions: Sun WYL and Pandey A contributed to manuscript drafting; Lee M completed the histopathological diagnosis; Wasilenko S was the patient's gastroenterologist and performed the colonoscopy; Karmali S was the patient's surgeon; all authors were responsible for the revision of the manuscript and final approval for submission.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

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

Specialty type: Gastroenterology and hepatology

Open-Access: This article is an

Warren YL Sun, Shahzeer Karmali, Division of General Surgery, University of Alberta, Edmonton T6G 2B7, Alberta, Canada

Armaan Pandey, Cumming School of Medicine, University of Calgary, Calgary T2N 4Z6, Alberta, Canada

Mark Lee, Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton T5H 3V9, Alberta, Canada

Shawn Wasilenko, Division of Gastroenterology, University of Alberta, Edmonton T5H 3V9, Canada

Corresponding author: Warren YL Sun, MD, Doctor, Division of General Surgery, University of Alberta, 2D, Walter C Mackenzie Health Sciences Centre, 8440 - 112 Street, Edmonton T6G 2B7, Canada. warrensun@ualberta.ca

Abstract

BACKGROUND

Gastrointestinal neurofibromas are commonly found in patients diagnosed with neurofibromatosis type 1. However, isolated gastrointestinal neurofibromas are a rare entity and only fourteen cases of isolated colorectal neurofibromas have been documented in literature. Isolated gastrointestinal neurofibromas have not been associated with Lynch syndrome (LS). Patients with LS are at an increased risk of colorectal cancer, and are recommended to undergo screening colonoscopy.

CASE SUMMARY

A 33-year-old healthy female with a family history of LS was found to have unresectable polyp in the ascending colon on screening colonoscopy suspicious for malignancy. The patient was asymptomatic and had no stigmata of neurofibromatosis. A staging workup for colorectal cancer revealed no evidence of metastatic disease. A discussion with the patient resulted in the decision to undergo a segmental resection with ongoing surveillance. The patient underwent a laparoscopic right hemicolectomy. Histopathology was consistent with a gastrointestinal neurofibroma. Post-operatively, the patient recovered well. She will not require further treatment with regards to her colonic neurofibroma, but will continue to follow-up for ongoing surveillance of her LS.

CONCLUSION

We present the first case of an isolated colonic neurofibroma in a patient with LS.

Received: August 3, 2019
Peer-review started: August 3, 2019
First decision: September 10, 2019
Revised: September 24, 2019
Accepted: November 26, 2019
Article in press: November 26, 2019
Published online: January 27, 2020

P-Reviewer: Hashimoto N, Seow-Choen F
S-Editor: Gong ZM
L-Editor: A
P-Editor: Ma YJ

This case explores considerations for the management of isolated gastrointestinal neurofibromas given the lack of guidelines in literature.

Key Words: Isolated gastrointestinal neurofibroma; Colonic neurofibroma; Gastrointestinal neurofibromatosis; Lynch syndrome; Case report

Core tip: Gastrointestinal neurofibromas are rarely found in isolation in the absence of systemic neurofibromatosis. We present herein, the first case of an isolated colonic neurofibroma in a patient with Lynch syndrome. There are currently no guidelines for the management of isolated gastrointestinal neurofibromas due to the lack of studies. We recommend considering establishing a diagnosis with endoscopic mucosal biopsy or ultrasound guided biopsy, reserving resection for patients with symptomatic disease or alternative indications, and continuing to follow patients for the surveillance of neurofibromatosis type 1 to reduce associated morbidity and mortality.

Citation: Sun WY, Pandey A, Lee M, Wasilenko S, Karmali S. Isolated colonic neurofibroma in the setting of Lynch syndrome: A case report and review of literature. *World J Gastrointest Surg* 2020; 12(1): 28-33
URL: https://www.wjgnet.com/1948-9366/full/v12/i1/28.htm
DOI: https://dx.doi.org/10.4240/wjgs.v12.i1.28

INTRODUCTION

Lynch syndrome (LS), or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder caused by a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, or PMS2) that predisposes patients to various malignancies, of which colorectal cancer (CRC) is the most common[1]. Given the increased risk, patients diagnosed with LS are recommended to undergo cancer screening, including screening colonoscopy for CRC every two years beginning at the age of 20 to 25[2]. LS has also been associated with an increased risk of endometrial, gastric, ovarian, hepatobiliary, urinary tract, small bowel, and other cancers[1]. Additionally, the association of LS with neurofibromatosis has been reported in literature[3].

Neurofibromas are benign nerve sheath tumours originating from the peripheral nervous system containing an amalgamation of Schwann cells and fibroblasts[4]. While rare, malignant transformation into neurofibrosarcoma, or malignant peripheral nerve sheath tumour (MPNST) can occur[5]. Neurofibromas are typically associated with neurofibromatosis Type 1 (NF1), also known as von Recklinghausen disease. NF1 is an autosomal dominant disorder due to a mutation in chromosome 17[4]. Classic features of NF1 include café-au-lait macules, Lisch nodules, and neurofibromas of the skin; however, the cardiovascular system, eyes, bones, and gastrointestinal system can also be affected[6].

In patients with NF1 or multiple endocrine neoplasia type 2B (MEN 2B), gastrointestinal neurofibromas is relatively common, affecting approximately 25% of patients[7]. Most gastrointestinal neurofibromas occur in the stomach and small intestine[8]. These manifestations are typically asymptomatic, but symptoms may include abdominal pain, gastrointestinal bleeding, obstruction, and palpable masses [6]. However, isolated gastrointestinal neurofibromas in patients without a history of NF1 or MEN 2B are extremely rare[7]. In this report, we will present a rare case of isolated colonic neurofibroma in a patient with a history of LS.

CASE PRESENTATION

Chief complaints

A 33-year-old female with LS diagnosed with positive MSH6 mutation presented for

routine screening gastroscopy and colonoscopy.

History of presenting illness

The patient was asymptomatic with no gastrointestinal issues or stigmata of neurofibromatosis.

Personal and family history

The patient had a family history significant for LS and colorectal cancer in multiple family members. The patient was also diagnosed with LS with positive MSH6 mutation. She was otherwise healthy. There was no family history of NF1.

Physical examination

Physical examination revealed a benign abdomen. Cutaneous examinations revealed no evidence of café-au-lait spots or neurofibromatosis.

Laboratory examinations

Complete blood count, comprehensive metabolic panel, liver panel, and coagulation studies were all within normal limits. The patient also had a normal carcinoembryonic antigen (CEA) level of 1.3 μg/L (normal range < 5.0 μg/L).

Imaging examinations

Initial screening gastroscopy was unremarkable. Random biopsies revealed no diagnostic abnormality. Initial screening colonoscopy demonstrated 2 to 2.5 cm of abnormal appearing mucosa in the ascending colon with central tethering. An attempt to lift the area of concern with methylene blue was unsuccessful. The area was tattooed and biopsied, which was non-diagnostic. The patient underwent a repeat colonoscopy after two months. The suspicious area was again appreciated appearing as sessile, serrated, polypoid tissue measuring approximately 2.5 cm wrapped around a haustral fold in the ascending colon (Figure 1). Biopsies were obtained again, but the polyp was unresectable. The biopsies revealed sessile serrated polyp, negative for dysplasia. A staging workup was completed, which included a negative computerized tomography (CT) scan of the chest, abdomen and pelvis.

TREATMENT

Following two non-diagnostic biopsies, a referral to general surgery was made for the management of the unresectable polyp in the setting of LS. A discussion with the patient regarding the management included the recommendation of a subtotal colectomy versus a segmental resection, for which the patient elected for the latter. The patient underwent a laparoscopic right hemicolectomy.

FINAL DIAGNOSIS

Gross pathological examination revealed a 2.2 cm × 1.8 cm × 0.4 cm ill-defined polypoid lesion adjacent to the cecum. Microscopic examination demonstrated an area of reactive serrated mucosa overlying an ill-defined submucosal mass extending into superficial muscularis propria and overlying mucosa. The mass consisted of short small monomorphic spindle cells within a collagenous background (Figure 2A). The spindle cells were intermixed with scattered mast cells (Figure 2B). Immunohistochemistry showed the spindle cells were positive for S100 (Figure 2C). Fifteen lymph nodes were identified and negative for malignancy. Overall, the histomorphology and phenotype by ancillary immunohistochemistry were consistent with a gastrointestinal neurofibroma.

OUTCOME AND FOLLOW-UP

The patient tolerated the procedure well and was discharged on postoperative day three. She was seen one month later in follow-up and had recovered well. She will not require any further treatment with regards to her isolated colonic neurofibroma, but will continue to follow-up for ongoing surveillance of her LS.

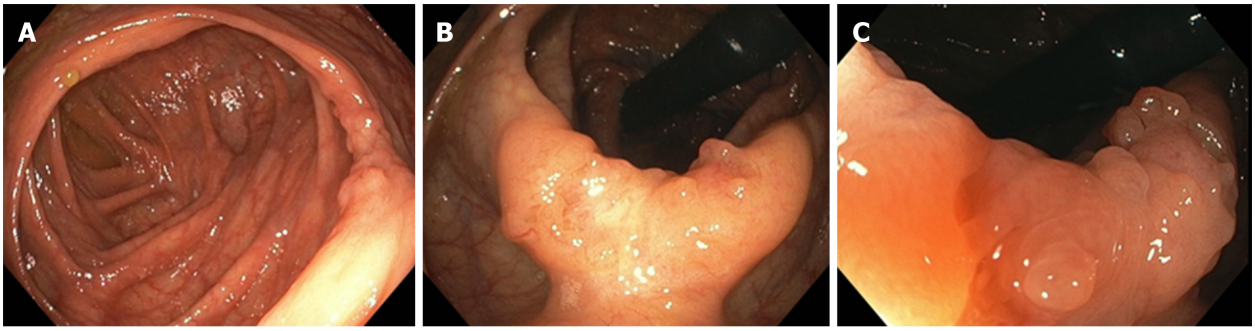

Figure 1 Endoscopic imaging of gastrointestinal neurofibroma. A: A 2.5 cm polypoid lesion was identified within a haustral fold adjacent to the cecum. B: The lesion demonstrated abnormal mucosa with central tethering suspicious for malignancy. C: Magnified view of polypoid lesion with abnormal mucosa concerning for adenocarcinoma.

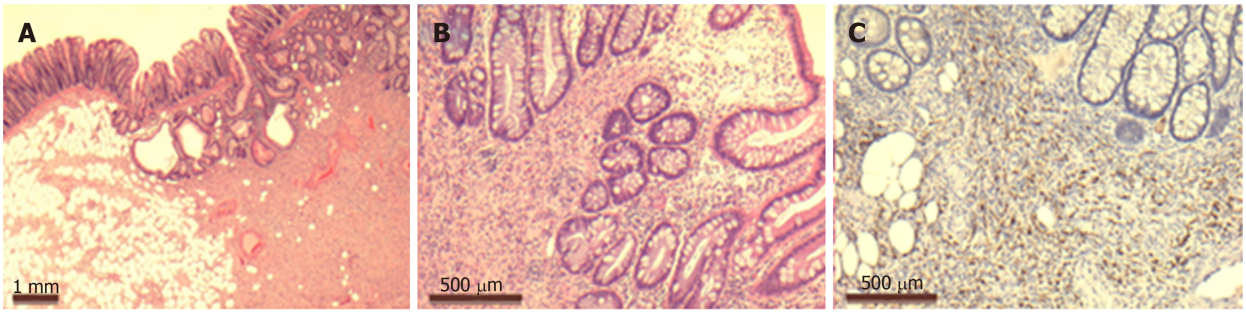

Figure 2 Pathologic examination of gastrointestinal neurofibroma. A: Low power view of submucosal spindle cell proliferation, (hematoxylin-eosin, 2.5 ×). B: Higher power view of monomorphic spindle cells with intermixed mast cells, (hematoxylin-eosin, 10 ×). C: Immunohistochemistry staining showing variable positivity of lesional cells for S100 protein (10 ×).

DISCUSSION

In this report, we presented the first case of isolated colonic neurofibroma in the setting of LS. Screening colonoscopy is routinely performed in patients with LS to diagnose colorectal cancers at an earlier stage. Commonly, clinicians and patients with non-diagnostic biopsies of suspicious colonic masses are faced with a dilemma: To resect or not resect. Given the patient in this study was at an increased risk of CRC due to LS, aggressive management of the mass with resection is appropriate. However, while submucosal aetiologies are more rare, it is also important to consider them in patients with non-diagnostic biopsies of colonic masses that may appear to have endoscopic features of submucosal origin. When conventional endoscopic mucosal biopsies fail to diagnose masses, the use of endoscopic ultrasound (EUS) guided biopsies may be considered to aid in the diagnosis[9].

Given the clinical context in this study, the patient was presented with the option of segmental resection versus subtotal colectomy. The patient expressed a desire for future pregnancy, and therefore, we elected for segmental resection to reduce the risk of infertility. However, total colectomy with ileoanal anastomosis would be the preferred primary treatment for patients with colon cancer or colon neoplasia unresectable by endoscopy[1]. The patient will require ongoing surveillance for CRC in the remainder of her colon. Furthermore, the patient would have required a completion proctocolectomy if her pathology confirmed a CRC.

Surprisingly, the final pathology revealed a gastrointestinal neurofibroma. Furthermore, the patient did not exhibit any features of NF1, thus, classifying this case as an isolated colonic neurofibroma. There have only been fourteen cases of isolated colorectal neurofibromas reported in the English literature (Table 1). The average age of presentation was 51 years. Nine patients (64%) were female, and four (29%) were asymptomatic.

While LS has not been associated with neurofibromas, MSH6 mutation has been associated with NF1 phenotype in literature[10]. Given that gastrointestinal neurofibromas are rarely found in isolation, some have recommended referring patients with isolated gastrointestinal neurofibromas for the workup and surveillance

Table 1 Cases of isolated colorectal neurofibromas reported in English literature (*n* = 14)

Ref.	Year of publication	Age (yr)	Sex	Presentation	Location of neurofibroma
Keith *et al*[15]	1937	50	F	Pain	Rectum
Woolf[16]	1938	70	M	Asymptomatic	Rectum
Butler *et al*[17]	1959	45	F	Pain, bleeding, tenesmus	Rectum
Geboes *et al*[18]	1978	NA	NA	NA	Rectum
Abramson *et al*[19]	1997	53	M	Bleeding	Transverse colon
Bononi *et al*[13]	2000	68	F	Tenesmus, bleeding	Sigmoid colon
Panteris *et al*[20]	2005	65	F	Bloody diarrhoea	Descending colon
Carter *et al*[7]	2008	52	F	Non-bloody diarrhoea, pain	Diffuse colonic involvement
Hindy *et al*[8]	2012	59	M	Asymptomatic	Transverse colon
Chelimilla *et al*[14]	2013	70	F	Asymptomatic	Ascending colon
Bilal *et al*[12]	2016	52	M	Pain	Proximal descending colon
Ahn *et al*[4]	2016	26	F	Asymptomatic	Sigmoid colon
Adioui *et al*[11]	2018	29	F	Pain, abdominal mass	Sigmoid colon
Miao *et al*[21]	2018	24	F	Pain, mass in stool	Ileocecal valve

F: Female; M: Male; NA: Not available.

of NF1[4,8,11-14]. We also agree with the need to screen patients with isolated gastrointestinal neurofibromas for NF1 given the associated morbidity and mortality with these conditions.

CONCLUSION

We present the first case of an isolated colonic neurofibroma in a patient with LS. Given the risk of colorectal cancer, the patient had a non-diagnostic polyp resected. There are currently no guidelines for the management of isolated gastrointestinal neurofibromas due to the lack of studies. We recommend considering establishing a diagnosis with endoscopic mucosal biopsy or ultrasound guided biopsy, reserving resection for patients with symptomatic disease or alternative indications, and continuing to follow patients for the surveillance of NF1 to reduce associated morbidity and mortality.

REFERENCES

1 **Giardiello FM**, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, Church JM, Dominitz JA, Johnson DA, Kaltenbach T, Levin TR, Lieberman DA, Robertson DJ, Syngal S, Rex DK; US Multi-Society Task Force on Colorectal Cancer. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Gastroenterology* 2014; **147**: 502-526 [PMID: 25043945 DOI: 10.1053/j.gastro.2014.04.001]

2 **Syngal S**, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**: 223-262; quiz 263 [PMID: 25645574 DOI: 10.1038/ajg.2014.435]

3 **Bandipalliam P**. Syndrome of early onset colon cancers, hematologic malignancies & features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations. *Fam Cancer* 2005; **4**: 323-333 [PMID: 16341812 DOI: 10.1007/s10689-005-8351-6]

4 **Ahn S**, Chung CS, Kim KM. Neurofibroma of the Colon: A Diagnostic Mimicker of Gastrointestinal Stromal Tumor. *Case Rep Gastroenterol* 2016; **10**: 674-678 [PMID: 27920660 DOI: 10.1159/000452202]

5 **Dunn GP**, Spiliopoulos K, Plotkin SR, Hornicek FJ, Harmon DC, Delaney TF, Williams Z. Role of resection of malignant peripheral nerve sheath tumors in patients with neurofibromatosis type 1. *J Neurosurg* 2013; **118**: 142-148 [PMID: 23101443 DOI: 10.3171/2012.9.JNS101610]

6 **Donk W**, Poyck P, Westenend P, Lesterhuis W, Hesp F. Recurrent abdominal complaints caused by a cecal neurofibroma: a case report. *World J Gastroenterol* 2011; **17**: 3953-3956 [PMID: 22025885 DOI: 10.3748/wjg.v17.i34.3953]

7 **Carter JE**, Laurini JA. Isolated intestinal neurofibromatous proliferations in the absence of associated systemic syndromes. *World J Gastroenterol* 2008; **14**: 6569-6571 [PMID: 19030214 DOI: 10.3748/wjg.14.6569]

8 **Hindy P**, Parvin R, Hanna K, Andrawes S, Gress F, Goodman A. An isolated neurofibromal polyp of the colon. *Case Rep Gastroenterol* 2012; **6**: 58-62 [PMID: 22423240 DOI: 10.1159/000336214]

9 **Vander Noot MR 3rd**, Eloubeidi MA, Chen VK, Eltoum I, Jhala D, Jhala N, Syed S, Chhieng DC. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. *Cancer* 2004; **102**: 157-163 [PMID: 15211474 DOI: 10.1002/cncr.20360]

10 **Pemov A**, Sung H, Hyland PL, Sloan JL, Ruppert SL, Baldwin AM, Boland JF, Bass SE, Lee HJ, Jones KM, Zhang X; NISC Comparative Sequencing Program, Mullikin JC, Widemann BC, Wilson AF, Stewart DR. Genetic modifiers of neurofibromatosis type 1-associated café-au-lait macule count identified using multi-platform analysis. *PLoS Genet* 2014; **10**: e1004575 [PMID: 25329635 DOI: 10.1371/journal.pgen.1004575]

11 **Adioui T**, Tamzaourte M, Nejjari F, Chakkor A, Elkaoui H, Boudhas A, Oukabli M, Rouibaa F, Aourarh A, Zentar A. Isolated Neurofibroma of the Sigmoid Colon: a Case Report and Review of the Literature. *J Gastrointest Cancer* 2018; **49**: 195-199 [PMID: 27577727 DOI: 10.1007/s12029-016-9864-y]

12 **Bilal M**, Bilimoria F, Clarke K. An isolated colonic neurofibroma. *Ann Gastroenterol* 2016; **29**: 381 [PMID: 27366045 DOI: 10.20524/aog.2016.0029]

13 **Bononi M**, De Cesare A, Stella MC, Fiori E, Galati G, Atella F, Angelini M, Cimitan A, Lemos A, Cangemi V. Isolated intestinal neurofibromatosis of colon. Single case report and review of the literature. *Dig Liver Dis* 2000; **32**: 737-742 [PMID: 11142587]

14 **Chelimilla H**, Chandrala CK, Niazi M, Kumbum K. Incidental finding of isolated colonic neurofibroma. *Case Rep Gastroenterol* 2013; **7**: 369-375 [PMID: 24163647 DOI: 10.1159/000355163]

15 **Keith A**, Albert R. A case of neurofibroma of the rectal wall. *Trans Am Proctol Soc* 1937; **38**: 68

16 **Woolf MS**. Neurofibroma of the Rectum. *Cal West Med* 1938; **49**: 463-464 [PMID: 18744831]

17 **Butler DB**, Hanna E. Neurogenic tumor of the rectum. *Dis Colon Rectum* 1959; **2**: 291-293 [PMID: 13663747]

18 **Geboes K**, De Wolf-Peeters C, Rutgeerts P, Vantrappen G, Desmet V. Submucosal tumors of the colon: experience with twenty-five cases. *Dis Colon Rectum* 1978; **21**: 420-425 [PMID: 212258]

19 **Abramson LP**, Orkin BA, Schwartz AM. Isolated colonic neurofibroma manifested by massive lower gastrointestinal bleeding and intussusception. *South Med J* 1997; **90**: 952-954 [PMID: 9305312]

20 **Panteris V**, Vassilakaki T, Vaitsis N, Elemenoglou I, Mylonakou I, Karamanolis DG. Solitary colonic neurofibroma in a patient with transient segmental colitis: case report. *World J Gastroenterol* 2005; **11**: 5573-5576 [PMID: 16222760 DOI: 10.3748/wjg.v11.i35.5573]

21 **Miao Y**, Wang JJ, Chen ZM, Zhu JL, Wang MB, Cai SQ. Neurofibroma discharged from the anus with stool: A case report and review of literature. *World J Clin Cases* 2018; **6**: 455-458 [PMID: 30294610 DOI: 10.12998/wjcc.v6.i11.455]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com