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Colonic Crohn's disease – decision is more important than incision: A surgical dilemma

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Abstract

The most common localization for intestinal Crohn's disease (CD) is the terminal ileum and ileocecal area. It is estimated that patients with CD have one in four chance of undergoing surgery during their life. As surgery in ulcerative colitis ultimately cures the disease, in CD, regardless of the extent of bowel removed, the risk of disease recurrence is as high as 40%. In elective surgery, management of isolated Crohn's colitis continues to evolve. Depending on the type of surgery performed, colonic CD patients often require further medical or surgical therapy to prevent or treat recurrence. The elective surgical treatment of colonic CD is strictly dependent on the localization of disease, and the choice of the procedure is dependent of the extent of colonic involvement and previous resection. The most common surgical options in colonic CD are total proctocolectomy (TPC) with permanent ileostomy, segmental bowel resection, subtotal colectomy. TPC completely removes all colonic and rectal disease and avoids the use of a potentially diseased anus. We will review current options for the elective surgical treatment of colonic CD, based on the current literature and our own personal experience.

Key Words: Crohn's disease; Colonic Crohn's disease; Surgery; Surgical treatment; Colonic resection; Segmental colectomy; Total colectomy

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Core Tip: The most common localization for intestinal Crohn's disease (CD) is the terminal ileum and ileocecal area. In elective surgery, management of isolated Crohn's colitis continues to evolve. As surgery in ulcerative colitis ultimately cures the disease, in CD, regardless of the extent of bowel removed, the risk of disease recurrence is as high as 40%. Depending on the type of surgery performed, colonic CD patients often require further medical or surgical therapy to prevent or treat recurrence. The elective surgical treatment of colonic CD is strictly dependent on the localization of disease, and the choice of the procedure is dependent of the extent of colonic involvement and previous resection.

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INTRODUCTION

The most common localization for intestinal Crohn's disease (CD) is the terminal ileum and ileocecal area. CD can involve the entirety of the gastrointestinal tract and can be multifocal^[1]. Incidence of isolated colonic CD varies from 25% to 60% of all comers^[2]. In up to 40% of colonic CD, the rectum is spared from inflammation, a prerequisite for restoration of intestinal continuity in favorable cases, in contrast with ulcerative colitis (UC), where rectal involvement is the norm^[2,3]. On the other hand, severe perianal fistulizing CD is a contraindication to restorative procedures.

COLONIC CROHN'S DISEASE

Colonic CD has clinical and phenotypical features that are different from the more common ileitis (Table 1). Colonic CD without perianal fistulizing involvement is often associated with a less aggressive phenotype and lower indication to surgery than ileal or ileocolonic CD^[4]. Extraintestinal symptoms are statistically more frequent in colonic CD^[5].

It is estimated that patients with CD have one in four chance of undergoing surgery during their life, but as surgery in UC ultimately cures the disease, in CD, regardless of the extent of bowel removed, the risk of disease recurrence is as high as 40%^[6]. Depending on the type of surgery performed, colonic CD patients often require further medical or surgical therapy to prevent or treat recurrence.

Up to 31% of all colonic CD patients will require an end ileostomy in their lifetime. Restoration of intestinal continuity and preservation of adequate function and quality of life are of paramount importance.

The indication for operative management of CD include acute disease complications (*i.e.*, toxic colitis with or without associated megacolon, hemorrhage, and perforation), chronic disease complications, such as neoplasia, growth retardation, and extra-intestinal manifestations, or failed medical therapy^[2]. Failed medical therapy can take several forms including unresponsive disease, incomplete response, medication-related complications, and non-compliance with pharmacological therapies.

The surgical treatment of colonic CD is strictly dependent on the localization of disease, disease phenotype and patient's physiologic characteristics. Timing of surgery is critical to avoid an urgent operation often associated with postoperative complications and a temporary or permanent fecal diversion. The most common post-operative complications, such as leakage, abscess and peritonitis, occur in 13%-17% of all procedures, mostly when carried in emergency setting^[7].

Patients suffering intraabdominal septic complications have statistically significantly higher 1-, 2-, 5-, and 10-year surgical recurrence rates (25%, 29%, 50%, and 57%) than patients without such complications (4%, 7%, 19%, and 38%, $P = 0.0003$)^[8].

Patients undergoing emergency surgery for CD are at high risk for surgical site infections (SSI), due to severe malnutrition, anemia, immunosuppression secondary to medical therapy (especially with steroids) and chronic illness^[7,9]. Previous studies have

Table 1 Features of ileal/ileocolonic Crohn's disease, isolated colonic Crohn's disease, and ulcerative colitis

Characteristics	Ileal and ileocolonic CD	Isolated colonic CD	Ulcerative colitis
Sex	Slight female predominance (55%)	Female predominance (65%)	Equal or slight male predominance
Genetics	Crohn's-associated genotype including NOD2/CARD15	Genotype midway between CD and UC	UC-associated genotype including HLA-DRB1*01:03
Serology	ASCA commonly positive; pANCA usually negative	ASCA less commonly positive than ileal CD; pANCA positive	ASCA usually negative; pANCA commonly positive
Mucosa-associated microbiota	Marked changes commonly including increased proteobacteria (<i>e.g.</i> , <i>E. coli</i>) and fusobacteria	Intermediate changes similar to ileal/ileocolonic CD but less consistent	Modest changes, including slight increase in <i>E. coli</i>
Response to mesalazine	No efficacy	No efficacy	Good efficacy
Response to anti-TNF	Good efficacy	Good efficacy, probably better than for ileal/ileocolonic CD	Good efficacy
Response to exclusive enteral nutrition	Good efficacy	Probably good efficacy	No efficacy
Surgery rate and type	Required in majority	Required in minority. High failure for pouch-anal reconstruction	Required in minority. Low failure for pouch-anal reconstruction

CD: Crohn's disease; ASCA: Anti-*Saccharomyces cerevisiae*; HLA: Human leucocyte antigen; pANCA: Perinuclear antineutrophil cytoplasmic antibodies; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

looked at the efficacy of oral antimicrobial prophylaxis with mechanical preparation during inflammatory bowel disease surgery, with a reduction in SSI of 10% when CD patients are treated with oral and intravenous antimicrobial prophylaxis^[9]. However, surgery for Crohn is often complicated by the presence active intraabdominal infection and strictures precluding effective bowel preparation. This results in a higher risk of SSI in CD patients when compared to other elective colorectal operations^[10].

In severe fulminant isolated CD or indeterminate colitis the surgical approach of choice is a subtotal colectomy (SC) with end ileostomy. The procedure can often be performed laparoscopically and it is usually well tolerated if properly timed. Moreover, it leaves a chance to restore the sphincter function.

In elective surgery, management of isolated Crohn's colitis continues to evolve^[11-13]. In this article, we will review current options for the elective surgical treatment of colonic CD, based on the current literature and our own personal experience.

Accurate preoperative assessment of the disease and patient's characteristics are mandatory, especially in terms of location and natural history of the disease, previous resections, current therapy and general medical conditions. Since preoperative anemia, such as hemoglobin level of < 10 g/dL, is associated with an increased postoperative anastomotic leakage rate, an adequate treatment of anemia is mandatory before surgery. Nutrition and drug therapy optimization are advised in the elective setting^[7]. In presence of abscess or signs of sepsis, surgery should be postponed after percutaneous or laparoscopic drainage and antibiotic treatment. Parenteral nutrition is also advised and liberally used in these patients.

The elective surgical treatment of colonic CD is strictly dependent on the localization of disease, and the choice of the procedure is dependent of the extent of colonic involvement and previous resection (Figure 1). The most common surgical options in colonic CD are total proctocolectomy (TPC) with permanent ileostomy, segmental bowel resection (SBR), SC. TPC completely removes all colonic and rectal disease and avoids the use of a potentially diseased anus.

Perianal manifestations are linked to increased progression to complicated colonic CD.

The fecal stream plays an important role on the genesis of CD. Fistulizing disease in CD has a poor outcome if not properly treated. The fistulas can be treated through traditional surgery as seton drainage and long-term antibiotics, but exclusion of anal function, even temporary, can help in refractory perianal CD. Most recently the use of monoclonal antibodies to tumor necrosis factor alfa has been described to enhance healing of fistula, including perianal, in CD and allow to make a safe anastomosis in 80% of patient primarily treated with resection and terminal ileostomy, while allowing the healing of perianal disease when administered preoperatively in a number of patients.

In spite of new therapies, severe rectal and perianal involvement remains a contraindication to primary anastomosis, due to a high incidence (50%) of

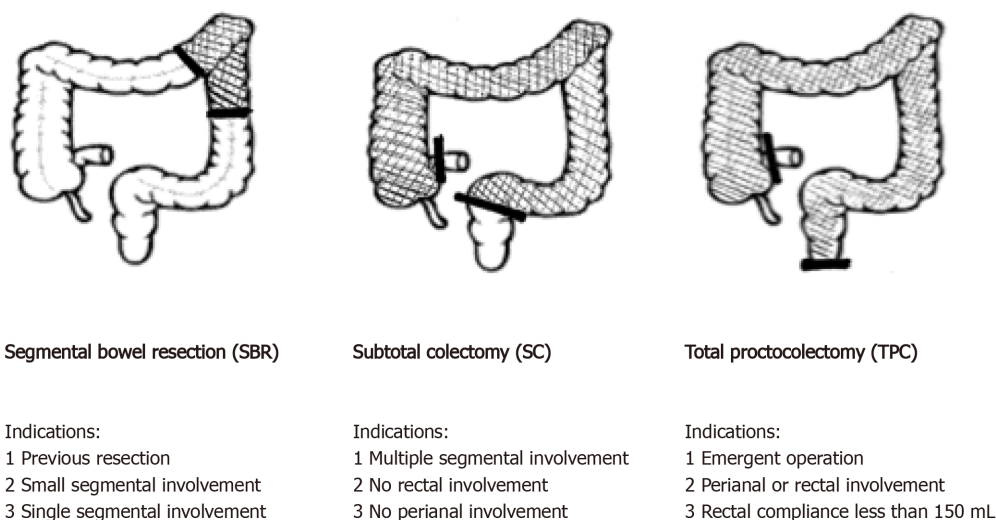


Figure 1 Surgical procedures and indications in isolated colonic Crohn's disease.

complications, such as leakage and refractory complex rectal fistula. Consequently, in the presence of perianal or rectal disease and colitis, TPC should be preferred.

Patients with proctocolitis that warrant operative treatment usually require a TPC with creation of a permanent ileostomy, especially those persons with colitis whose proctitis, anorectal sphincter dysfunction, or anoperineal sepsis is too severe for rectal preservation. In patients with CD recurrence in the small bowel after TPC is the lowest of all surgical options (around 30%).

TPC with permanent stoma is the safest option to avoid further operations in high-risk patients. On the other hand, TPC carries significant risks of perineal wound and stoma complications^[6] and many patients prefer to avoid a permanent stoma. This has led to the adoption of sphincter preserving surgical strategies including segmental colectomy for limited disease and SC with anastomosis when the rectum is healthy.

SBR for CD colitis may offer improved function and a lower risk of a permanent stoma in the short term, but in the long-term recurrence rates as high as 50% (from 32% to 62% in different series)^[6,13-19] can affect the anastomosis and other sites in the colon (Table 2). This technique showed an increased risk of postoperative complications^[6]. Time to recurrence is faster following SBR compared to other surgical procedures; these patients require immunosuppressive medications and develop drug refractory distal disease.

However, segmental colectomy allows a good colonic function and a perceived postoperative quality of life that is the highest of the three procedures.

Indication to SBR are a single colonic CD localization (< 20 cm of macroscopic involvement)^[20].

Patients with extensive colonic involvement, or multiple segmental involvement, relative rectal sparing, and adequate ano-rectal continence are candidates to SC and ileo-rectal anastomosis. The recurrence rate for this approach varies from 41% to 74% in different series^[6,14]. Both SC and SBR are equally effective treatment options for colonic CD with limited colonic involvement. Segmental colectomy is associated with earlier recurrences than subtotal/total procedure.

It should be emphasized that a recurrence can be treated medically and can take place years after the index surgery. Therefore, segmental or SC with ileorectal anastomosis allow a reasonable quality of life in young patients for a number of years, delaying the need for permanent fecal diversion.

Despite the increasing experience with laparoscopy in CD, one-fifth of selected cases still need conversion^[12,21,22]. Several conditions, such as recurrent CD with dense adhesions, abdominopelvic sepsis, fistulizing CD, inflammatory mass, are at risk of a laparotomy, and when the severity of these condition is preoperatively known, a primary open approach should be considered. As far as laparoscopic techniques in colonic CD, even in high volume centers for Crohn surgery the conversion rates are higher than 25%^[23]. Laparoscopy is the gold standard for ileocecal resection in CD^[12], and several studies have demonstrated the superiority of laparoscopy over laparotomy in this setting, but the learning curve of colonic CD is steeper^[24].

Table 2 Recurrence after segmental bowel resection and after total colectomy in patients with isolated colonic Crohn's disease

Ref.	Patient/type of surgery	Recurrence rate (%)
Longo <i>et al</i> ^[16] , 1988	18 segmental bowel resection	62
	131 total colectomy	65
Allan <i>et al</i> ^[15] , 1989	36 segmental bowel resection	66
	63 total colectomy	53
Bernell <i>et al</i> ^[18] , 2001	134 segmental bowel resection	49
	106 total colectomy	53
Andersson <i>et al</i> ^[19] , 2002	31 segmental bowel resection	39
	26 total colectomy	46
Martel <i>et al</i> ^[17] , 2002	84 segmental bowel resection	43
	39 total colectomy	41
Fichera <i>et al</i> ^[13] , 2005	55 segmental bowel resection	38.8
	49 total colectomy	22.9
	75 total proctocolectomy	9.3

CONCLUSION

In conclusion the surgeon must remember that CD cannot be cured with surgery only. Instead, surgery is used in conjunction with maximal medical therapy to treat symptoms of the disease and improve the patient's quality of life. Surgical interventions should be limited in scope.

The management of isolated CD colitis continues to evolve. A surgical approach appears mandatory when the disease is no longer responsive to medical therapies, or when the complications of medical therapies become debilitating. Preoperative treatment with antibiotics, nutritional support, percutaneous drains, optimization of the medical treatment should be considered before colonic resection with a planned anastomosis. In CD colitis, a planned surgery avoids an emergency operation and the need for ileostomy. SBR were associated with the increased likelihood of developing postoperative SSI as opposed to extended colectomies. Segmental resections were performed mostly for strictures or fistulae/abscesses in the descending or sigmoid colon, and, in addition, more of these procedures were safely completed by an anastomosis. Extended colectomies were performed for non-stricturing/non-penetrating disease and were more often completed by stoma formation.

Elective surgery is strictly dependent on the localization of the disease. The choice of procedure is dependent of the extent of colonic involvement and previous resection of the small bowel. The presence and extent of proctitis should be taken into account especially when planning left-sided resections.

Isolated colonic CD patients tend to have better outcomes if treated in high-volume centers, and in the absence of local expertise, patients requiring elective surgery should be referred to a specialist unit.

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Role of artificial intelligence in hepatobiliary and pancreatic surgery

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Abstract

Over the past decade, enhanced preoperative imaging and visualization, improved delineation of the complex anatomical structures of the liver and pancreas, and intra-operative technological advances have helped deliver the liver and pancreatic surgery with increased safety and better postoperative outcomes. Artificial intelligence (AI) has a major role to play in 3D visualization, virtual simulation, augmented reality that helps in the training of surgeons and the future delivery of conventional, laparoscopic, and robotic hepatobiliary and pancreatic (HPB) surgery; artificial neural networks and machine learning has the potential to revolutionize individualized patient care during the preoperative imaging, and postoperative surveillance. In this paper, we reviewed the existing evidence and outlined the potential for applying AI in the perioperative care of patients undergoing HPB surgery.

Key Words: Artificial intelligence; Liver surgery; Pancreatic surgery; Augmented reality; Virtual reality; Intra-operative

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Core Tip: The use of artificial intelligence (AI) increases hepatobiliary surgeons' capability in the timely selection of appropriate patients for precise, personalized delivery of complex surgical procedures with increased safety and ease. Published studies have mainly concentrated on assessing the technical feasibility of utilizing AI, and future research needs to focus on delivering and assessing the clinical impact of these promising techniques.

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INTRODUCTION

Outcomes of hepatobiliary and pancreatic (HPB) surgery have improved tremendously over the past decade with reduced postoperative mortality from 20% to less than 3% and 5%-6% for major liver and pancreatic surgery, respectively^[1,2]. Such an improvement has been attributed to more sophisticated preoperative imaging and improved perioperative care, progressive surgical techniques with a better anatomical understanding of anatomy, technological advancement of intra-operative instrumentation, early identification, and management of complications^[3,4]. However, procedures remain technically complex, requiring careful preoperative planning, intra-operative execution from experienced surgeons, anesthetists, nursing staff, and longer operative hours. The postoperative morbidity remains high at 20%-30%, and mortality rates for some of the more complex resections is reported to be as high as 10%^[5-8]. There is a need to continue to explore and integrate the novel and innovative technological tools into the clinical practice to improve these outcomes.

Artificial Intelligence (AI) has been investigated for its role in predictive population risk stratification, clinical decision support systems, promoting it into the new era of digital medicine, and precise surgery^[9-12]. Most of the uses of AI are based on machine learning, which is a technique that can automatically learn, recognize specific patterns, and make useful decisions based on the available data^[13]. Deep learning is part of the same technique, which replicates the neural network of the human brain for data analysis. The most representative characteristic of deep learning is that it is based on actual data, and the decision process is accomplished with minimal human interventions^[14,15]. Integration of such processes into the various aspects of delivery of HPB surgery will allow improving oncological and post-operative outcomes.

In this article, we review the existing and the future role of AI in HPB surgery by focusing on (1) preoperative planning [three-dimensional (3D) visualization and printing]; (2) intra-operative care; integrated use of augmented reality in open and minimally invasive (laparoscopic and robotic) surgery; and (3) finally its application in postoperative care and radiomics (Table 1).

AI-BASED PREOPERATIVE IMAGING

3D visualisation and virtual simulation

Currently, most HPB surgeons use two-dimensional (2D) images from computed tomography (CT), magnetic resonance imaging (MRI) scans to evaluate the position of a lesion, and its relationship to the surrounding structures in the preoperative planning. However, the 3D cognitive interpretation of spatial structure of the tumor and its relation with surrounding structures can be misjudged at times. Professor Marescaux^[16] was the first to use 3D visualization to delineate the complex liver anatomy in 1998. 3D reconstruction of 2D images from CT scan and MRI helps the surgeon to visualize the spatial relationship of the tumor and surrounding intrahepatic structures, identify the normal vascular and biliary anatomy and its variations, and ultimately improves preoperative planning and at times to be able to consider surgical resection based on 3D imaging in patients considered unresectable on 2D images or vice versa^[17-19]. Fang *et al*^[18,20] demonstrated that patients who underwent surgery based on a 3D operation plan had lesser operation time ($P = 0.028$), lower hepatic inflow occlusion ($P = 0.029$), and reduced high grade (Clavien-Dindo grade III-V) postoperative complications ($P = 0.048$) as compared to patients who underwent surgery without any 3D planning^[18,20].

Hilar cholangiocarcinoma usually presents in an advanced stage when the caudate lobe and hilar structures are already invaded^[21]. These patients require radical resection with hepatectomy, associated with significantly increased mortality of 10%-15% and a significantly higher postoperative morbidity of up to 40%^[22,23]. Zhang *et al*^[24] in a study of 23 patients with hilar cholangiocarcinoma of Bismuth grades III and IV, showed that preoperative 3D reconstruction could accurately determine the presence of tumor invasion into hilar vessels, variant hilar anatomy, and future liver volumes

Table 1 Summary of the studies included in the review evaluating the role of artificial intelligence in hepatobiliary and pancreatic surgery

Ref.	Aim	No. of patients	Outcome
Preoperative imaging			
Fang <i>et al</i> ^[18]	To compare the surgical outcomes of pre-operative planning based on 3D assisted surgery for HCC	116	Shorter operation time ($P = 0.028$), and reduced complications ($P = 0.048$) among surgeries performed based on 3D planning
Mise <i>et al</i> ^[30]	To assess how pre-operative VH influences the outcomes of liver surgery	1194	Better post-operative oncological outcomes for those in the VH group ($P = 0.04$)
Fang <i>et al</i> ^[33]	To assess the resectability of pancreatic and periampullary tumours by 3D visualization system	80	PPV, NPV, sensitivity, specificity, accuracy for resectability was 100% and was better than CT angiography ($P < 0.05$)
Intra-operative use			
Okamoto <i>et al</i> ^[46]	To evaluate the utility of AR-based navigation surgery for pancreatotomy	19	Surface-rendering image corresponded to that of the actual organ Allowed safe dissection while preserving the adjacent vessels or organs
Ntourakis <i>et al</i> ^[49]	To investigate the potential of AR-based navigation to help locate and resect colorectal liver metastases	03	Allowed detection of all the lesions
Buchs <i>et al</i> ^[65]	To evaluate Stereotactic navigation technology for targeting hepatic tumors during robotic liver surgery	02	The augmented endoscopic view allows accurate assessment of resection margin and allowed better identification of vascular and biliary structures during parenchymal transection
Post-operative management and follow-up			
Merath <i>et al</i> ^[71]	To assess ML algorithm to predict patient risk of developing complications following liver, pancreatic or colorectal surgery	15, 657	Good predictability of post-operative complication with C-statistic of 0.74, outperforming the ASA (0.58) and ACS-surgical risk (0.71) calculators
Mai <i>et al</i> ^[73]	To establish and validate an ANN model to predict severe PHLF in patients with HCC following hemi hepatectomy	357	The ANN model resulted in AUROC of 0.880 for the development set of and 0.876 for the validation set in predicting severe PHLF
Zhou <i>et al</i> ^[80]	To develop a CT-based radiomic signature and assess its ability to preoperatively predict the early recurrence of HCC	215	Adding a radiomics signature into conventional clinical variables can significantly improve the accuracy of the preoperative model in predicting early recurrence ($P = 0.01$)
Banerjee <i>et al</i> ^[82]	RVI was assessed for its ability to predict MVI and outcomes in patients with HCC who underwent surgical resection or liver transplant		The diagnostic accuracy, sensitivity, and specificity of RVI in predicting MVI was 89%, 76% and 94%, respectively. Positive RVI score was associated with lower OS ($P < 0.001$) and RFS ($P = 0.001$)

3D: 3-dimensional; HCC: Hepatocellular carcinoma; VH: Virtual hepatectomy; PPV: Positive predictive value; NPV: Negative predictive value; AR: augmented reality; ML: Machine learning; ANN: Artificial neural network; RVI: Radio genomic venous imaging; MVI: Microvascular invasion; PHLF: Post-hepatectomy liver failure; ASA: American Society of Anaesthesiologists; ACS: American College of Surgeons.

that helped to develop an individualized operative plan for a patient^[24]. Similar benefits were reported by Okuda *et al*^[25] along with higher negative resection margins for biliary malignancies for patients who underwent preoperative surgical planning with 3D reconstruction^[25]. Another benefit of 3D reconstruction is the accurate stereoscopic assessment of portal vein anatomy and determining the line of parenchymal transection and planning portal vein reconstruction^[26]. Other studies also reported similar benefits including reduced amount of intraoperative bleeding with the use of preoperative 3D reconstruction^[27-29].

3D visualization techniques are also used to perform virtual liver resection before actual surgery to assess the resectability of the lesion and calculate future liver remnant. In patients with hepatocellular carcinoma (HCC), virtual hepatectomy allowed more aggressive surgery based on portal territory-oriented resection with a higher disease-free 5-year survival. Similarly, patients with colorectal liver metastasis (CRLM) who underwent virtual hepatectomy had equivalent long term outcomes to patients who did not have a virtual resection, despite the larger tumor load in the virtual hepatectomy group^[30]. Virtual hepatectomy is also of great use in living donor liver transplantation procedures. The donor selection can be further optimized based on the information available from 3D imaging, including the need for venous reconstruction based on the donor vascular anatomy resulting in improved safety of operation^[30].

3D visualization of peri-pancreatic vessels before surgery is reported to have

reduced the operative time, blood loss, and hospital stay significantly compared to patients who underwent surgery based on 2D image planning prior to pancreaticoduodenectomy ($P = 0.024$) and distal pancreatectomy ($P = 0.026$)^[31,32]. Fang *et al*^[33] reported sensitivity and sensitivity of 100% for resectability assessment of pancreatic cancer by 3D reconstruction^[33]. It also helps determine the size and location of the main pancreatic duct before surgery, which may help select optimal anastomotic technique^[31]. Assessment of resectability of the borderline resectable tumors (with involvement of surrounding vessels) is vital as 25% of the patients explored surgically are considered unresectable at laparotomy. It is likely that the benefits of 3D reconstruction be translated to improve the resection rates in this group.

3D printed models

Although 3D images and reconstruction can significantly benefit the understanding the surgical anatomy, the display is still on 2D screen, limiting its use. This limitation can be overcome by converting 3D reconstructed images into real physical models with 3D printing technology. The first use of 3D printing was reported in 2013 by Zein *et al*^[34]. Since then, 3D printing has been reported to be useful in treating liver tumors and also in liver transplants^[35-39]. One substantial benefit of the 3D printed model is that they can be brought into the operating room and compared with the real liver during surgery and adjusted in the optimal anatomical position to identify intrahepatic structures. This advantage of navigating on a real physical liver model is that it can locate small, disappearing CRLM and perform precise segmentectomies. 3D-printed models allow visualization and planning of the exact line of transection^[36,39]. Xiang *et al*^[26] reported the ability to precisely identify and manage the replaced hepatic arteries, segment IV portal vein branch coming from the right anterior portal vein to plan a right hemihepatectomy with extreme precision and prevent segment IV ischemia in a patient with HCC and avoided post hepatectomy decompensation of the liver function^[26]. Burdall *et al*^[38] reported using a hybrid 3D model containing hepatic, pancreatic, and choledochal components and used it to simulate laparoscopic choledochal surgery^[38]. In living donor liver transplantation for small infants and neonates, 3D printed liver models have shown promising results in assessing the size discrepancies between recipient and graft^[39]. Such information is useful for an adequate plan to reduce the graft volume and complex vascular and biliary structures of the liver than traditional CT imaging and help avoid unexpected surgical complications while preserving the vital vascular structures^[39]. However, such a comparison of the real-time and printed models will need 1:1 size matching increasing the production cost of each model.

Low-cost 3D liver printed models were used for trainees' medical education and to help them practice hepatectomy operations with a positive impact on the understanding of liver anatomy, better visualization, and higher learning efficacy^[40,41]. The recent 3D Bio-printed models consist of new-generation bio-inks and hepatic cells, which are biocompatible, scalable, convenient, and low-cost^[42]. These models have a vital role in developing liver tissue engineering and even artificial liver, which may expand their therapeutic role in managing patients with liver failure^[42].

AI can reduce the complexity of a traditionally manual process of 3D printing. The main application of AI in 3D printing comes from automation of workflow. This comprises various steps, from the creation of the model as a Computer Aided Design file, to its preparation for printing in a slicing software, to its final printing. AI can also help improve the 3D printing process by assessing the printability before starting any process. The quality of the final product can also be predicted and the process be controlled to avoid printing errors, effectively saving time.

Intraoperative use of AI in HPB surgery

The major drawback of 3D reconstruction and printing techniques lies in associating the 3D reconstructed images or physical models to the actual surgery due to inadequate synchronization between the two modalities^[43]. These limitations could be overcome using computer guiding software, which combines preoperative 3D reconstructive images with intraoperative information in real-time. It can be done by Augmented Virtuality (AV) that displays a virtual environment that is controlled by real information or by Augmented Reality (AR) that displays virtual information based on real images of the patient. It is a relatively new and unused tool to improve oncological safety in the field of HPB surgery. It can confirm the ideal dissection plane and anatomical landmarks in real-time and help achieve safe margins with maximum functional preservation^[44]. AV, AR, and mixed reality (MR) offer a safe and reliable surgical navigation method, which reduces the chances of misinterpretation between the 3D reconstruction model and actual operating space^[30,44].

For locally advanced pancreatic cancers, intraoperative computer-based navigation can be used to assess the spatial relationship of the tumor with the involved vessels and the possibility of venous reconstruction or arterial involvement depending on tumor invasion, increasing the safety, and effectiveness of the procedure^[45]. Okamoto *et al*^[46] reported 19 patients who underwent AR-based navigation surgery for pancreatectomy^[46]. In this study, reconstructed preoperative images were superimposed on the real organs on the monitor display during surgery, and it corresponded to that of the actual organs^[46]. Such information is most useful in patients with small pancreatic neuroendocrine tumours, liver lesions deep in the parenchyma that are challenging to navigate at minimally invasive surgery, and planning of microwave coagulation therapy^[47-49]. Modern chemotherapy for CRLM can cause shrinkage of tumors to the extent that they may disappear on post-chemotherapy scans. In a pilot study, Ntourakis *et al*^[49] reported that AR helped in detecting those missing lesions and achieving a negative margin with no local recurrence at a median follow up of 22 mo^[49].

AI in minimally invasive HPB surgery

Laparoscopic cholecystectomy is one of the most common general and specialist surgical procedures performed worldwide. Injury to common bile duct is considered one of the avoidable complications that is otherwise associated with the need for further interventions and adds a considerable burden of medico-legal litigation. The risk of bile duct injury can be reduced by correctly identifying the standard anatomical landmarks at surgery (the common bile duct, cystic duct, lower edge of the left medial liver segment, Rouviere's sulcus). Tokuyasu *et al*^[50] developed an AI-based learning model to detect these four anatomical landmarks using real-time object detection algorithms on using a training set of over 2000 endoscopic camera images^[50]. These landmarks were successfully identified with adequate precision intra-operatively by the validation cohort, and such novel systems can reduce bile duct injury during laparoscopic cholecystectomy and other iatrogenic injuries^[50].

Minimally invasive surgery for major laparoscopic hepatectomies is being practiced routinely in specialist units with reported benefits of reduced scar size, postoperative morbidity, and shorter hospital stay^[51]. Donor hepatectomy, pancreaticoduodenectomy are also increasingly performed by experienced specialist surgeons by minimally invasive means. However, in addition to the long learning curve for the surgeons to be able to perform these procedures, one of the main issues is the loss of the tactile sensation, which is replaced by force feedback through a laparoscopic instrument to differentiate between the tissues of varying consistency, making it challenging to appreciate tumor margins and be able to identify the smaller but vital vascular structures.

For minimally invasive surgeries, it seems appropriate to use AR techniques to superimpose in the endoscopic view structures which are not visible by direct camera view but are visible in the preoperative images^[52,53]. AR technology uses CT and MRI data to reconstruct a 3D image of the liver and detailed intrahepatic vasculature, and the virtual image is superimposed on the liver surface in a 1:1 ratio, to assist the operating surgeon during surgery^[53,54]. Phutane *et al*^[55] showed that AR-based hepatectomy for HCC could help detect intrahepatic tumors, the transection plane, and locating the hepatic veins before parenchymal transection, which can reduce bleeding and duration of surgery^[55]. Similar findings were reported by Hallet *et al*^[56] who used trans-thoracic minimally invasive liver resection guided by AR^[56].

Loss of depth perception with monocular cameras is also another disadvantage contributing to the longer operative times^[57,58]. These limitations could potentially be overcome with the help of AR and MR technology, which will not only aid in finding the position the intra-parenchymal lesions but also provides a better field of vision. This facilitates the oncological resection and limits the risk of operative bleeding^[30,59]. It also provides a solution to reduce the gap between the three-dimensional reconstruction model and the actual operating space, which helps overcome uncoordinated hand and eye maneuvering during surgery^[43,54].

AR also has a vital role in laparoscopic surgical education of trainees. For surgeons in the earlier part of the career, this could reduce the duration of learning curves. A recent randomized controlled trial showed that AR-based training could improve the necessary skills of laparoscopic cholecystectomy in surgical residents and overcome the learning curve^[60]. It has distinct advantages and broad prospects in many aspects, such as preoperative planning, intraoperative navigation, surgical education, and doctor-patient communication^[54]. Although 3D visualization and AR allow further navigation, there is still a need to develop more on the haptics to replace the palpation, and tactile sensation in minimally invasive HPB surgery, may it be to determine the

boundaries between normal and cancer tissue.

The limitations include that the patient-specific 3D reconstructed images need to be prepared using complex algorithms requiring a lot of time and effort. This problem can be overcome by real-time acquisition of high-resolution preoperative scans and 3D reconstructions. Secondly, preparing the whole system to achieve the desired navigation during surgery and required registrations; the process itself can significantly increase the overall duration of surgery and anesthesia time for patients. It varies on the type of procedure and the complexity of the AR system as well. The solution to this problem is to develop fully automated systems, which would reduce the total time required for completion. However, to date, most of the registration is performed manually.

Robotic HPB surgery

The use of AI techniques in HPB robotic surgery helps achieve exceptional performance with increased ability to perform the fine skills in delineating complex *in vivo* hilar and pancreatic anatomy, helping the operating surgeon make accurate decisions and perform the desired task with increased meticulousness and efficiency^[12]. 3D imaging, multi-fold magnification, and significantly improved dexterity are the most noticeable features of currently available robotic systems that allow precise tumor localization, dissection, reduce blood loss, and potentially higher success rates for certain types of hepatobiliary procedures like spleen-preserving distal pancreatectomies compared to a traditional open approach^[61]. 10-fold magnified 3D intra-operative views of robotic surgery overcome the limitation of depth perception associated with the laparoscopic technique. It helps in the dissection of delicate tissue like liver parenchyma, and the increased dexterity, even in narrow spaces, allows for intra-corporeal suturing at the same time^[62]. This was highlighted in a matched comparative study in which higher rates of successful, purely minimally invasive approaches were reported with the robotic technique compared with conventional laparoscopy for major hepatectomies^[63]. As with laparoscopy, the surgeon operating with the help of a robot cannot use the "sense of touch" to identify blood vessels or differentiate between healthy and scar tissue by manual palpation.

AR has been used to overcome this limitation^[58]. Pessaux *et al*^[64] reported the use of the see-through visualization feature of AR for port placement, one of the most crucial steps in robotic surgery. Each robotic port was placed according to the patient's anatomy, variations, and target lesions. AR allowed for the accurate and safe identification of intrahepatic vascular structures throughout the surgery. Hepatic pedicle clamping was not used in any of the cases, and none of the patients required perioperative transfusion^[64]. In another study, Buchs *et al*^[65] reported the benefits of AR-based robotic resection in patients who had resection of HCC. The augmented endoscopic view delineated an accurate resection margin around the tumor. The overlay of reconstructed 3D models also helped during parenchymal transection to identify vascular and biliary structures, and safe tumor margin widths of 0.5 cm and 1 cm were achieved, with no complications^[65]. Constant research and development have also enabled robots to automatically perform some *in vitro* simple surgical errands, such as suturing and knot tying^[66]. However, the current equipment and technology are still far from attaining complete autonomy to robots in surgery, and human control would continue for safety and complex decision-making.

Regarding intraoperative limitations, inattentional blindness, an event when an unexpected object suddenly appears in the surgeons' field of view, is one of the biggest concerns that need to be addressed while using 3D overlays^[67]. AR provides a vast amount of data and information to surgeons, which may be distracting^[68]. Therefore, it is of utmost importance to project only relevant data or develop a method to display different sets of information depending on surgeons' needs. The latency of the whole system of AR is also a concern. Currently, the latency for laparoscopic procedures is reported to be 144 ± 19 milliseconds^[69], and any prolonged latency in robotic surgery is best avoided to maintain the accuracy and the surgeon's comfort.

PREDICTIVE MODEL GUIDED POSTOPERATIVE MANAGEMENT

Predictive models for postoperative morbidity

HPB surgery is associated with high postoperative morbidity and mortality rates. The reported morbidity rate for major hepatectomy is 25%, and for pancreaticoduodenectomy, it is nearly 40%^[5-8,70]. Early prediction of morbidity with detailed attention and thorough postoperative management of complications can positively

impact the overall outcomes of complex HPB procedures. The perioperative imaging information can be combined with clinical data to establish corresponding diagnostic and predictive models. For instance, a machine learning technique was applied to develop an algorithm after extracting data of 15657 patients was used to predict the postoperative morbidity after HPB and colorectal surgery^[71]. This algorithm had a better predictive (C-statistic of 0.74) ability than other established methods like the American College of Surgery-risk calculator (C-statistic 0.71) and American Society of Anaesthesiologists levels (C-statistic 0.58). The algorithm had excellent performance in predicting postoperative stroke, wound dehiscence (superficial SSI, organ space SSI), cardiac arrest, and progressive renal failure (C-statistic 0.96-0.98). The algorithm also showed a good predictive ability for sepsis and perioperative hemorrhage^[71]. Similarly, algorithms are being used to predict the risk of liver failure after hepatectomy^[72,73]. Patients at risk of liver failure may avoid major hepatectomy and undergo adjuvant or an alternative treatment.

Predictive models for a liver transplant

In liver transplant, data that predicts the expected survival with a specific graft is crucial in selecting the best recipient for each graft. Wingfield *et al*^[74] in a systematic review suggested that AI based predictive model can be used to determine graft outcomes after deceased donor liver transplant. These models were based on multiple factors from donor, recipient, and graft. The AI-based models proved to be superior in predicting graft survival than the traditional log regression model and other classic scores (MELD, SOFT)^[74]. Similar findings were reported by Liu *et al*^[75] when they developed a machine learning-based algorithm to predict short term survival after liver transplant^[75]. These models can be used to assign the graft to appropriate recipients and improve survival and the outcomes after liver transplant.

Radiomics in HPB surgery and models for cancer surveillance

Radiomics presents a new horizon to generate new understanding and concepts within specific areas of pathology. It is based on the techniques which mines quantitative data from patients imaging (Ultrasound, CT, MRI, and PET/CT) and analyses it to retrieve clinically relevant information that can be used for diagnosis and prognostication^[76]. For example, Park *et al*^[77] recently developed a radiomics fibrosis index to assess liver cirrhosis^[77]. The model was based on data extracted from MRI images of the liver. This radiomics index demonstrated to be considerably better than routine normalized liver enhancement and serum fibrosis indices^[77]. A similar CT based radiomic model was used for the diagnosis and severity of portal hypertension. This model was significantly better in diagnosing portal hypertension than clinical indices and other methods like liver stiffness^[78].

The role of radiomics is getting significantly crucial in the field of hepatobiliary oncology. The role is postulated on the theory that a radiologic phenotype can imitate genetic variations of carcinogenesis and help determine the expected tumour behavior. These radiomics based models are being used to substantiate clinical decision making and practice precision medicine. Hepatocellular carcinoma is associated with a high recurrence rate. Early recurrence after resection is itself a poor prognostic factor, reducing 5-year survival rates from 70% to 30%^[79]. Almost 50% of patients develop recurrence within five years of surgery. If patients at increased risk of recurrence are identified using accurate algorithms, the physician can arrange more close surveillance. Zhou *et al*^[80] developed a model based on 21 radiomic features from 300 patients^[80]. This model proved that combining conventional clinical factors and radiomics feature can perform better in accurately predicting early recurrence than with Barcelona Clinic Liver Cancer (BCLC) staging, Childs classification, and other clinical features alone^[80]. Microvascular invasion is one of the indicators of early recurrence in patients with HCC^[81]. This information is often available only on post-resection histological analysis. Banerjee *et al*^[82] developed a model based on a cluster of preoperative radiomic features for predicting the presence of microvascular invasion^[82]. Its accuracy can reach up to 94%, which is better than the results based on imaging only^[82]. Zheng *et al*^[83] developed a CT-based radiomic nomogram to predict recurrence-free survival rates for HCC after resection, ablation, and transplant. These nomograms predicted the prognosis and recurrence much more effectively than the traditional staging^[83].

Elarre *et al*^[84] evaluated the 2-year relapse risk for pancreatic cancer patients based on a machine-learning algorithm^[84]. The main goal was to provide prognostic information to patients who underwent pancreatic resection. This model showed an accuracy of more than 60% for disease recurrence within two years of surgery^[84]. It proved to be a valuable tool, especially for high-risk patients. Intensive surveillance

and extended use of adjuvant treatment for such patients can be considered based on this model^[84].

CONCLUSION

The ultimate goal of AI is to achieve a better and individualized healthcare plan for each patient. Integrating the genomic and molecular targeting information and clinic-pathological features of the individual liver and pancreatic cancer patients will enable surgeons to provide precise and personalized surgery with the aid of surgical technology enhanced with 3D imaging, AR, VR and MR modalities.

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Retrospective Cohort Study

Laparoscopic hepatectomy reduces postoperative complications and hospital stay in overweight and obese patients

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Abstract**BACKGROUND**

Laparoscopic liver surgery is currently considered the standard of care for various liver malignancies. However, studies focusing on perioperative outcome after laparoscopic hepatectomy (LH) in overweight patients are still sparse and its benefit compared to open hepatectomy (OH) is a matter of debate.

AIM

To analyze postoperative outcomes in overweight [body mass index (BMI) over 25 kg/m²] and obese (BMI over 30 kg/m²) patients undergoing LH and compare postoperative outcome with patients undergoing OH.

METHODS

Perioperative data of 68 overweight (BMI over 25 kg/m²) including a subcohort of obese (BMI over 30 kg/m²) patients ($n = 27$) who underwent LH at our institution between 2015 and 2019 were retrospectively analyzed regarding surgical outcome and compared to an equal number of patients undergoing OH.

RESULTS

The mean BMI was 29.8 ± 4.9 kg/m² in the LH group and 29.7 ± 3.6 kg/m² in the OH group with major resections performed in 20.6% (LH) and 26.5% (OH) of cases, respectively. Operative time (194 ± 88 min *vs* 275 ± 131 min; $P < 0.001$) as well as intensive care (0.8 ± 0.7 d *vs* 1.1 ± 0.8 d; $P = 0.031$) and hospital stay (7.3 ± 3.6 d *vs* 15.7 ± 13.5 d; $P < 0.001$) were significant shorter in the LH group. Also, overall complications (20.6% *vs* 45.6%; $P = 0.005$) and major complications (1.5% *vs* 14.7%, $P = 0.002$) were observed less frequently after LH. An additional

authors report that there is no conflict of interest.

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investigation analyzing the subgroup of obese patients who underwent LH ($n = 27$) and OH ($n = 29$) showed a shorter operative time (194 ± 81 min vs 260 ± 137 min; $P = 0.009$) and a reduced length of hospitalization (7.7 ± 4.3 d vs 17.2 ± 17 d; $P < 0.001$) but no difference in postoperative complications or overall cost.

CONCLUSION

LH is safe and cost-effective in overweight and obese patients. Furthermore, LH is significantly associated with fewer postoperative complications and reduced hospital stay compared to OH in these patients.

Key Words: Laparoscopic hepatectomy; Obesity; Overweight; Morbidity; Postoperative outcome; Cost

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Core Tip: Laparoscopic liver resection has emerged as a considerable alternative to conventional liver surgery. However, studies focusing on perioperative outcome after laparoscopic hepatectomy in overweight patients are still sparse and its benefit compared to open hepatectomy is a matter of debate. Our comparative analysis demonstrated that the laparoscopic approach is significantly associated with fewer postoperative complications and reduced hospital stay compared to conventional open hepatectomy in these patients.

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INTRODUCTION

Overweight and obesity in Germany has been identified as a major health problem and its prevalence has been continuously growing over the last decades. According to the German DEGS1 study (2013), 67.1% of men and 53.0% of women are overweight. Also, the prevalence of obesity has risen substantially, as 23.3% of men and 23.9% women are currently considered to be obese^[1]. Overweight is associated with multiple comorbidities which can influence postoperative outcome after minor and major liver resection^[2]. Furthermore, several studies have reported an increased risk of technical difficulties during surgery and frequent occurrence of postoperative complications^[3-5]. In addition, obesity may be associated with chronic liver disease, such as steatosis and nonalcoholic steatohepatitis, which can further increase surgical morbidity^[6,7].

Laparoscopic surgery has several advantages compared to conventional surgery, such as less abdominal wall trauma, early postoperative regeneration and less postoperative morbidity^[8,9]. About thirty years ago, obesity was generally considered a contraindication for laparoscopic surgery due to the associated technical difficulties. Around fifteen years ago, multiple studies had indicated obesity as a risk factor for conversion. However, recent studies have shown that laparoscopic surgery can be considered a standard procedure in obese patients, with good results after cholecystectomy, gastrectomy, and colectomy^[10-12]. However, studies focusing on the perioperative outcomes after laparoscopic hepatectomy (LH) in overweight patients are still sparse and its benefit compared to open hepatectomy (OH) is a matter of debate^[13-15]. Thus, the aim of this study was to analyze postoperative outcomes in overweight (BMI ≥ 25 kg/m²) and obese (BMI ≥ 30 kg/m²) patients undergoing LH and compare postoperative outcome with patients undergoing OH.



MATERIALS AND METHODS

We report a single-center retrospective analysis evaluating postoperative outcome after liver resection in overweight and obese patients with malignant liver tumors. Therefore, we compared short-term outcome and postoperative complications of patients with a BMI ≥ 25 kg/m² who underwent LH ($n = 68$) or OH ($n = 68$). The Institutional Review Board approval was obtained before analysis of the data (EK 423/19).

A total of 226 patients underwent LH between January 2015 and August 2019 at the Department of Surgery and Transplantation of the RWTH Aachen University Hospital of which 68 patients were overweight and presented with a malignant tumor. In the comparison group, 68 overweight patients (BMI ≥ 25 kg/m²) were selected from 497 individuals who underwent OH during the above-mentioned period at our institution. Selection was performed by matching for gender, age, BMI, diagnosis, ASA classification, previous abdominal surgery, and resection extent by two independent authors. Furthermore, a subset of 27 patients undergoing LH and 29 patients undergoing OH were considered to be obese (BMI ≥ 30 kg/m²) and were further analyzed separately. The indication for surgery was approved by a multidisciplinary tumor board including surgeons, hepatologists, oncologists and radiologists. The resection extent was defined according to segmental anatomic description by Couinaud and type of hepatectomy was classified according to Brisbane 2000 terminology^[16]. Resections of more than three liver segments were categorized as a major liver resection.

Staging and surgical technique

All assigned patients were preoperatively examined in detail. For staging, a gadolinium-based magnetic resonance imaging and/or contrast-material enhanced computed tomography were performed to assess the number, size and location of liver tumors and to exclude distant metastases. The general laparoscopic approach as well as number and size of trocars were selected depending on tumor entity, size and localization of the hepatic lesions. All resections were performed fully laparoscopic without the use of any hybrid techniques. By default, the first 12 mm trocar was placed in the direction or next to the resection plane to ensure optimal triangulation after placement of two additional 5 or 12 mm trocars. Additional trocars were inserted if needed. Resection specimens were extracted through a suprapubic Pfannenstiel incision in a plastic recovery bag or *via* an extended 12 mm trocar incision. The attending surgeon stood between the patient's legs (French position) and the patient was positioned in a left tilted supine position. The pneumoperitoneum was maintained at 12 mmHg intra-peritoneal pressure. Intrahepatic lesions were routinely located by laparoscopic ultrasound. Parenchymal transection was commonly performed by Thunderbeat® (Olympus K.K., Tokyo, Japan) or Harmonic Ace® (Ethicon Inc., Somerville, NJ, United States). If necessary, a laparoscopic ultrasonic surgical aspirator (CUSA, Integra Life Sciences, New Jersey, United States) was chosen for deeper parenchymal transection in close proximity to major vascular structures or bile ducts. Vascular staplers (Echelon, Ethicon, Somerville, NJ, United States) or polymer clips (Teleflex Inc., Pennsylvania, United States) were used for the dissection of large vessels and bile ducts. Open hepatectomy was usually performed *via* a midline incision with rightward extension. Open parenchymal transection was carried out using the CUSA and titanium clips or sutures.

Data collection

All study data including demographics, tumor characteristics, clinical chemistry, and operative and postoperative data of every patient was prospectively collected within an institutional database. The postoperative course was reviewed for complications and rated according to the Clavien-Dindo classification and quantified using the Comprehensive Complication Index (CCI), which is based on the complication grading by Clavien-Dindo classification and implements every complication after an intervention. The overall morbidity is reflected on a scale from 0 (no complication) to 100 (death)^[17,18]. Every patient's individual postoperative course was also assessed for specific surgical complications, *e.g.*, biliary leakage, liver failure, wound infection, and pneumonia. Additionally, overall cost evaluation was performed based on patients age and CCI score according to Staiger *et al*^[19], using a validated online cost-assessment tool, which estimates the total cost for 90 d after complex operations with a very high correlation^[19]. A correction factor according to the cost analysis of the OSLO-COMET Trial was applied to compensate the increased intra-operative costs of LH compared to

OH^[20]. In that particular study, the total intraoperative costs for laparoscopic surgery were \$1926 compared to \$1158 for the open operation, so a significant difference of \$710 was included in our cost calculation.

Statistical analysis

The primary endpoint of this study was the occurrence of postoperative complications in overweight and obese patients undergoing laparoscopic or open hepatectomy. The secondary endpoints were in-house mortality, duration of hospitalization, ICU stay, and estimated costs. Categorical data are presented as counts and percentages and compared using the chi-squared test, Fisher's exact test, or linear-by-linear association according to the scale and number of cases. Data derived from continuous variables are presented as mean and standard deviation and are analyzed by the Mann-Whitney *U* test. The level of significance was set to $P < 0.05$, and *P* values are given for two-sided testing. Analyses were performed using SPSS Statistics 24 (IBM Corp., Armonk, NY, United States).

RESULTS

We here analyzed a cohort of 136 overweight patients ($\text{BMI} \geq 25 \text{ kg/m}^2$) with a malignant tumor diagnosis who underwent hepatectomy at our institution between 2015 and 2019 with 68 individuals undergoing LH and 68 individuals undergoing OH. The patients' characteristics of the overall cohort are summarized in [Table 1](#).

Overweight patients

There were no significant differences between the LH and OH group in terms of patient sex ($P = 0.116$), age ($P = 0.812$), BMI ($P = 0.463$), tumor diagnosis ($P = 0.777$), ASA ($P = 0.328$) or previous abdominal surgery ($P = 0.592$). Mean BMI was $29.8 \pm 4.9 \text{ kg/m}^2$ in the LH group and $29.7 \pm 3.6 \text{ kg/m}^2$ in the OH group as shown in [Table 1](#). Common diagnoses in both groups were liver metastasis (LH: 60.3% *vs* OH: 61.8%) followed by hepatocellular carcinoma (LH: 29.4% *vs* OH: 25.0%) and intrahepatic cholangiocellular carcinoma (LH: 10.3% *vs* OH: 13.2%). 59.1% of patients in the LH group and 64.7% of patients in the OH group were classified as ASA III or higher. With regard to clinical characteristics, we observed statistically significant differences in the presence of liver fibrosis (LH: 30.9% *vs* OH: 11.8%; $P = 0.006$), preoperative albumin (LH: $4.4 \pm 0.4 \text{ g/dL}$ *vs* OH: $3.6 \pm 0.7 \text{ g/dL}$; $P < 0.001$), total bilirubin (LH: $0.4 \pm 0.3 \text{ mg/dL}$ *vs* OH: $0.9 \pm 0.6 \text{ mg/dL}$; $P < 0.001$) and INR (LH: 0.98 ± 0.08 *vs* OH: 1.06 ± 0.07 ; $P < 0.001$). Perioperative characteristics are shown in [Table 2](#). The mean operative time was significantly shorter in the LH group (LH: $194 \pm 88 \text{ min}$ *vs* OH: $275 \pm 131 \text{ min}$; $P < 0.001$). We performed major resections in 20.6% of patients who underwent LH and in 26.5% of patients who underwent OH, respectively ($P = 0.419$). Intensive care stay was significantly shorter after LH (LH: $0.8 \pm 0.7 \text{ d}$ *vs* OH: $1.1 \pm 0.8 \text{ d}$; $P = 0.031$) with an also significantly shorter hospitalization time (LH: $7.3 \pm 3.6 \text{ d}$ *vs* OH: $15.7 \pm 13.5 \text{ d}$; $P < 0.001$). A total of 3 (4.4%) patients in the OH group died during the hospital stay, while no postoperative mortality was reported in the LH cohort. Overall complications (LH: 20.6% *vs* OH: 45.6%; $P = 0.005$) as well as major complications defined as Clavien-Dindo \geq IIIb (LH: 1.5% *vs* OH: 14.7%, $P = 0.002$) occurred significantly less frequently in the LH group. A further detailed analysis of the complication types showed a significantly increased incidence of biliary leakage (LH: 1.5% *vs* OH: 14.7%; $P = 0.005$), postoperative liver failure (LH: 0.0% *vs* OH: 5.9%; $P = 0.042$) and pneumonia (LH: 0.0% *vs* OH: 8.8%; $P = 0.012$) after OH. CCI was also significantly higher in the OH group (LH: 3.9 ± 9.1 *vs* OH: 15.4 ± 23.6 ; $P < 0.001$), while estimated cost did not differ between the groups (LH: $10060 \pm 1537 \text{ €}$ *vs* OH: $11789 \pm 5973 \text{ €}$; $P = 0.779$).

Obese patients

An additional investigation analyzed a subset of obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$) who underwent laparoscopic ($n = 27$) or open hepatectomy ($n = 29$). A review of patients' demographics showed a slightly older OH cohort (LH: $61.3 \pm 10.4 \text{ years}$ *vs* OH: $67.5 \pm 11.0 \text{ years}$; $P = 0.036$), while we found no significant differences between the groups in terms of patient sex ($P = 0.116$), BMI ($P = 0.623$), diagnosis ($P = 0.628$), ASA score ($P = 0.835$) or previous abdominal surgery ($P = 0.512$). No significant differences in the presence of liver steatosis ($P = 0.186$), fibrosis ($P = 0.084$) or cirrhosis ($P = 0.329$) were observed. Preoperative albumin level was higher (LH: $4.3 \pm 0.3 \text{ g/dL}$ *vs* OH: $3.6 \pm 0.5 \text{ g/dL}$; $P < 0.001$) while total bilirubin (LH: $0.4 \pm 0.3 \text{ mg/dL}$ *vs* OH: $0.9 \pm 0.5 \text{ mg/dL}$; $P <$

Table 1 Patients' characteristics in the overweight and obese group (body mass index ≥ 25 kg/m²)

	LH vs OH		
	LH cohort (<i>n</i> = 68)	OH cohort (<i>n</i> = 68)	<i>P</i> value
Demographics			
Sex, <i>n</i> (%)			0.116
Male	36 (52.9)	45 (66.2)	
Female	32 (47.1)	23 (33.8)	
Age (yr)	64.4 ± 10.2	64.5 ± 12.3	0.812
BMI (kg/m²)	29.8 ± 4.9	29.7 ± 3.6	0.463
Diagnosis, <i>n</i> (%)			0.777
LM	41 (60.3)	42 (61.8)	
HCC	20 (29.4)	17 (25.0)	
iCC	7 (10.3)	9 (13.2)	
ASA, <i>n</i> (%)			0.328
I	0	0	
II	28 (41.2)	24 (35.3)	
III	35 (51.5)	42 (61.8)	
IV	5 (7.4)	2 (2.9)	
V	0	0	
Previous abdominal surgery, <i>n</i> (%)	23 (33.8)	26 (38.2)	0.592
Clinical characteristics			
Steatosis, <i>n</i> (%)	20 (29.4)	21 (30.9)	0.852
Fibrosis, <i>n</i> (%)	21 (30.9)	8 (11.8)	0.006
Cirrhosis, <i>n</i> (%)	9 (13.2)	12 (17.6)	0.477
Albumin (g/dL)	4.4 ± 0.4	3.6 ± 0.7	< 0.001
GGT (U/L)	85.1 ± 104.2	119.2 ± 219.0	0.326
Total bilirubin (mg/dL)	0.4 ± 0.3	0.9 ± 0.6	< 0.001
Platelet count (/nL)	254.0 ± 85.4	230.9 ± 90.5	0.135
Alkaline phosphatase (U/L)	85.1 ± 34.2	93.8 ± 84.2	0.584
INR	0.98 ± 0.08	1.06 ± 0.07	< 0.001
Hemoglobin (g/dL)	13.3 ± 1.7	13.6 ± 4.1	0.984

LH: Laparoscopic hepatectomy; OH: Open hepatectomy; BMI: Body mass index; LM: Liver metastasis; HCC: Hepatocellular carcinoma; iCC: intrahepatic cholangiocellular carcinoma; GGT: Gamma-glutamyl transpeptidase.

0.001) and INR levels (LH: 0.99 ± 0.07 vs OH: 1.06 ± 0.07 ; $P < 0.001$) were lower in the LH compared to the OH group. Table 3 shows the results of the analysis of perioperative data and a significantly shorter operative time (194 ± 81 min vs 260 ± 137 min; $P = 0.009$) and reduced length of hospitalization (7.7 ± 4.3 d vs 17.2 ± 17 d; $P < 0.001$) were observed after LH. CCI, overall and major complications as well as the incidence of biliary leakage, postoperative liver failure, and pneumonia were not significantly different between the groups.

DISCUSSION

In this study, we compared the perioperative outcomes of LH and OH in overweight and obese patients in a large European monocentric cohort and provide evidence that

Table 2 Perioperative characteristics in the overweight and obese group (body mass index ≥ 25 kg/m²)

	LH vs OH		P value
	LH cohort (n = 68)	OH cohort (n = 68)	
Operative data			
Operative time (min)	194 \pm 88	275 \pm 131	< 0.001
Major resection, n (%)	14 (20.6)	18 (26.5)	0.419
Operative procedure, n (%)			0.064
Atypical	15 (22.1)	23 (33.8)	
Segmentectomy	11 (16.2)	10 (14.7)	
Bisegmentectomy	28 (41.2)	17 (25.0)	
Left hepatectomy	0 (0.0)	5 (7.4)	
Right hepatectomy	13 (19.1)	13 (19.1)	
Extended left hepatectomy	0 (0.0)	1 (1.5)	
Conversion	4 (5.9)	-	
Postoperative data			
Intensive care/d	0.8 \pm 0.7	1.1 \pm 0.8	0.031
Hospitalization/d	7.3 \pm 3.6	15.7 \pm 13.5	< 0.001
Blood transfusion	12 (17.6)	16 (23.5)	0.396
Hospital mortality, n (%)	0 (0.0)	3 (4.4)	0.080
Postoperative complications, n (%)			0.065
No complications	54 (79.4)	37 (54.4)	
Clavien-Dindo I	4 (5.9)	5 (7.4)	
Clavien-Dindo II	5 (7.4)	8 (11.8)	
Clavien-Dindo IIIa	4 (5.9)	8 (11.8)	
Clavien-Dindo IIIb	1 (1.5)	3 (4.4)	
Clavien-Dindo IVa	0 (0.0)	4 (5.9)	
Clavien-Dindo IVb	0 (0.0)	0 (0.0)	
Clavien-Dindo V	0 (0.0)	3 (4.4)	
Clavien \geq IIIb	1 (1.5)	10 (14.7)	
Clavien \geq I	14 (20.6)	31 (45.6)	
Biliary leakage	1 (1.5)	10 (14.7)	0.005
Liver failure	0 (0.0)	4 (5.9)	0.042
Surgical site infections	2 (2.9)	6 (8.8)	0.145
Pneumonia	0 (0.0)	6 (8.8)	0.012
CCI	3.9 \pm 9.1	15.4 \pm 23.6	0.000
Estimated cost (€)	10060 \pm 1537	11789 \pm 5973	0.779

LH: Laparoscopic hepatectomy; OH: Open hepatectomy; CCI: Comprehensive Complication Index.

overweight patients undergoing LH have significantly fewer postoperative complications and reduced intensive care stay as well as overall hospitalization without increased overall costs.

Conventional open surgery in obese patients is associated with an increased morbidity risk and has adverse effects on the procedure itself^[6,7]. Also, the influence of overweight and obesity on the results of laparoscopic surgery have already been reported for several indications. For example, BMI is a known predictor of

Table 3 Perioperative characteristics in the obese group (body mass index ≥ 30 kg/m²)

	LH vs OH		
	LH cohort (<i>n</i> = 27)	OH cohort (<i>n</i> = 29)	<i>P</i> value
Operative data			
Operative time (min)	194 ± 81	260 ± 137	0.009
Major resection, <i>n</i> (%)	5 (18.5)	5 (17.2)	0.901
Operative procedure, <i>n</i> (%)			0.257
Atypical	7 (25.9)	8 (27.6)	
Segmentectomy	4 (14.8)	7 (24.1)	
Bisegmentectomy	11 (40.7)	9 (31.0)	
Left hepatectomy	0 (0.0)	3 (10.3)	
Right hepatectomy	5 (18.5)	2 (6.9)	
Conversion	2 (7.4)	-	
Postoperative data			
Intensive care/d	0.7 ± 0.4	1.0 ± 0.8	0.240
Hospitalization/d	7.7 ± 4.3	17.2 ± 17	< 0.001
Blood transfusion	3 (11.1)	8 (27.6)	0.121
Hospital mortality, <i>n</i> (%)	0 (0.0)	0 (0.0)	0.080
Postoperative complications, <i>n</i> (%)			0.562
No complications	19 (70.4)	17 (58.6)	
Clavien-Dindo I	3 (11.1)	2 (6.9)	
Clavien-Dindo II	1 (3.7)	2 (6.9)	
Clavien-Dindo IIIa	3 (11.1)	3 (10.3)	
Clavien-Dindo IIIb	1 (3.7)	2 (6.9)	
Clavien-Dindo IVa	0 (0.0)	3 (10.3)	
Clavien-Dindo IVb	0 (0.0)	0 (0.0)	
Clavien-Dindo V	0 (0.0)	0 (0.0)	
Clavien ≥ IIIb	1 (3.7)	5 (17.2)	0.102
Clavien ≥ I	8 (29.6)	12 (41.4)	0.359
Biliary leakage	1 (3.7)	3 (10.3)	0.335
Liver failure	0 (0.0)	2 (6.9)	0.165
Surgical site infections	2 (7.4)	4 (13.8)	0.440
Pneumonia	0 (0.0)	0 (0.0)	-
CCI	5.4 ± 11.1	12.3 ± 16.8	0.132
Estimated cost (€)	10111 ± 1748	11021 ± 3133	0.710

LH: Laparoscopic hepatectomy; OH: Open hepatectomy; CCI: Comprehensive Complication Index.

perioperative results in laparoscopic colorectal surgery, as longer operation times, higher conversion rates, and increased morbidity, including anastomotic leakage and surgical site infection, were observed in obese patients^[21,22]. In comparison to open surgery, the minimal-invasive approach is associated with less postoperative abdominal wall complications in obese patients, although the procedure is typically more technically challenging to perform. Adjustments in surgical equipment, such as the use of longer trocars and other operating equipment, may be necessary to successfully conduct laparoscopic surgery.

In contrast, inconsistent data are available regarding the safety of liver resection in

obese patients. For example, a retrospective cohort study compared the impact of obesity on postoperative complications and 30-d mortality in 3960 patients undergoing liver resection using the NSQIP database of the American College of Surgeons. Here, it was reported that obesity is linked to increased perioperative complications without a substantial rise in 30-d mortality^[2]. In contrast, Utsunomiya *et al*^[23] reported no substantial difference between obese and non-obese patients with respect to postoperative complications following liver resection for hepatocellular carcinoma. They concluded that complications after OH in obese patients are mainly due to the access trauma, as most hepatectomies are performed *via* bilateral subcostal or J-shaped incisions and that obesity as a risk factor will be revised since the advent of laparoscopy in liver surgery. The latter was confirmed by Nomi *et al*^[24], who analyzed 228 patients undergoing laparoscopic liver resection and found that higher BMI does not negatively impact the short-term outcomes after LH.

However, most of the available data focuses on the comparison of obese and non-obese patients while only few reports have analyzed small cohorts with LH in contrast to OH in overweight patients. Uchida *et al*^[14] for example analyzed only 12 LH *vs* 10 OH cases. Nevertheless, they found a significantly shorter operation time and blood loss in patients with a BMI ≥ 25 kg/m² after LH, which is similar to our results. Another study by Toriguchi *et al*^[25] observed a reduction in intraoperative blood loss and shorter hospital stay after LH than after OH in overweight patients. Of note, only 13 cases with LH were reported in the mentioned study which limits validity of this particular report.

The largest available series was published by Ome *et al*^[26] and consists of 63 LH *vs* 79 OH in patients with a BMI ≥ 25 kg/m². The authors demonstrated a better short-term outcome with respect to the need for blood transfusion and length of postoperative hospital stay, but, as comparable to the other cited studies, only a small number of patients undergoing major liver resection (9%, 13/144) were included^[26]. In contrast, our cohort contained at least 19% in both groups, who underwent major laparoscopic liver resection.

In our study a more detailed analysis of the complications revealed less frequent bile leakage, liver failure and pneumonia after LH compared to OH. Significant differences in short-term outcome and complications were only observed in the analysis of overweight patients and not in the obese subgroup. This lack of statistical significance in the obese subgroup might be explained by the smaller number of cases in this subanalysis.

From our point of view, LH in obese patients is feasible and safe, but nevertheless of increased difficulty. Regarding this issue, a study by Hasegawa *et al*^[27] showed that the surgical difficulty of LH was influenced by obesity and prolonged the operation time. Additionally, Yu *et al*^[13] reported that obesity increased the conversion rate of LH to up to 31% in their cohort of 29 patients with a BMI ≥ 28 kg/m². In comparison, we observed a conversion rate of 5.9% (BMI ≥ 25 kg/m²) and 7.4% (BMI ≥ 30 kg/m²) in our study. Our results are further based on a high-risk cohort, since more than 60% of our patients were classified as ASA III or higher. In many studies, patients are selected and the proportion of ASA I/II is up to 80%^[28,29].

Analysis of the overall cost of our cohort was performed using a prediction tool with a correction factor according to the cost measurement of the OSLO Comet Trial for higher intraoperative material costs in LH and showed no significant difference in both overweight and obese patients between LH and OH. This confirms the results of a study by Wabitsch *et al*^[30] which showed that higher intraoperative costs for LH are compensated by lower complication rates and a shorter length of hospitalization in comparison to OH.

Our analysis has certain limitations that need to be discussed. First, the results are based on a single-center cohort analyzed in a retrospective fashion with a limited number of patients, especially in the obese group; therefore, it is underpowered to reach a definitive conclusion and warrants confirmation from other groups. Second, our data were not obtained in a clinical trial and the patients were therefore not randomly assigned to OH or LH which limits validity.

CONCLUSION

Despite the aforementioned limitations, our comparative study of LH and OH in overweight patients does importantly add valuable aspects to the current literature as it comprises a significant proportion of individuals who underwent major liver resection. We therefore conclude that LH is safe and cost-effective in overweight and

obese patients. Furthermore, LH is significantly associated with fewer postoperative complications and reduced hospital stay compared to OH in these patients.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic liver surgery is considered the standard of care for various liver malignancies. However, several studies have reported an increased risk of technical difficulties during surgery and the frequent occurrence of postoperative complications in overweight and obese patients.

Research motivation

Studies focusing on perioperative outcome after laparoscopic hepatectomy in overweight patients are still sparse and its benefit compared to open hepatectomy is a matter of debate.

Research objectives

The aim of this study was to analyze postoperative outcomes in overweight (BMI ≥ 25 kg/m²) and obese (BMI ≥ 30 kg/m²) patients undergoing laparoscopic hepatectomy and compare postoperative outcomes with patients undergoing conventional open resection.

Research methods

Perioperative data of 68 overweight and obese patients who underwent laparoscopic hepatectomy at our institution between 2015 and 2019 were retrospectively analyzed regarding surgical outcome and compared to an equal number of patients undergoing open hepatectomy. The postoperative course was reviewed for complications and rated according to the Clavien-Dindo classification and quantified using the Comprehensive Complication Index.

Research results

We provide evidence that overweight patients undergoing laparoscopic hepatectomy have significantly fewer postoperative complications and reduced intensive care stay as well as overall hospitalization without increased overall costs.

Research conclusions

We conclude that laparoscopic hepatectomy is safe and cost-effective in overweight and obese patients. Additionally, this technique is significantly associated with fewer postoperative complications and reduced hospital stay compared to open hepatectomy in these patients.

Research perspectives

Additional research is needed to prospectively confirm our results and to evaluate outcomes in a larger and more balanced cohort to reach a definitive conclusion. Particularly in obese patients with a BMI above 30 kg/m², technical difficulties could be a factor in larger cohorts, which then become apparent.

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Retrospective Study

Pancreas-preserving duodenal resections vs pancreatoduodenectomy for groove pancreatitis. Should we revisit treatment algorithm for groove pancreatitis?

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Abstract

BACKGROUND

The management of cystic dystrophy of the duodenal wall (CDDW), or groove pancreatitis (GP), remains controversial. Although pancreatoduodenectomy (PD) is considered the most suitable operation for CDDW, pancreas-preserving duodenal resection (PPDR) has also been suggested as an alternative for the pure form of GP (isolated CDDW). There are no studies comparing PD and PPDR for this disease.

AIM

Hospital, approval No. 03-01-SG/2020 of January 14, 2020.

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 to treatment by written consent.

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

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To compare the safety, efficacy, and short- and long-term results of PD and PPDR in patients with CDDW.

METHODS

A retrospective analysis of the clinical, radiologic, pathologic, and intra- and postoperative data of 84 patients with CDDW (2004-2020) and a comparison of the safety and efficacy of PD and PPDR.

RESULTS

Symptoms included abdominal pain (100%), weight loss (76%), vomiting (30%) and jaundice (18%) and data from computed tomography, magnetic resonance imaging, and endoUS led to the correct preoperative diagnosis in 98.8% of cases. Twelve patients were treated conservatively with pancreaticoenterostomy ($n = 8$), duodenum-preserving pancreatic head resection ($n = 6$), PD ($n = 44$) and PPDR ($n = 15$) without mortality. Weight gain was significantly higher after PD and PPDR and complete pain control was achieved significantly more often after PPDR (93%) and PD (84%) compared to the other treatment modalities (18%). New onset diabetes mellitus and severe exocrine insufficiency occurred after PD (31% and 14%), but not after PPDR.

CONCLUSION

PPDR has similar safety and better efficacy than PD in patients with CDDW and may be the optimal procedure for the isolated form of CDDW. The pure form of GP is a duodenal disease and PD may be an overtreatment for this disease. Early detection of CDDW provides an opportunity for pancreas-preserving surgery.

Key Words: Groove pancreatitis; Cystic dystrophy of the duodenal wall; Pancreas-preserving duodenectomy; Pancreas-preserving duodenal resection; Chronic pancreatitis; Pancreatoduodenectomy

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Core Tip: This is a retrospective study that compared the safety, efficacy, short- and long-term results of pancreatoduodenectomy (PD) and pancreas-preserving duodenal resections (PPDR) in patients with groove pancreatitis (GP). Although PD is a conventional option for GP management, PPDR has been suggested as a treatment alternative for the pure form of GP in the early stage of this disease. Evaluation of these two treatment modalities has shown that PPDR for the pure form of GP is similar in terms of safety and better in efficacy compared to PD performed for GP. The key aim of this study is to demonstrate that PPDR may be the treatment of choice for the pure form of GP, which is a disease of the duodenum; early detection of GP makes preservation of the pancreas possible, and prolonged conservative treatment in early GP may lead to the development of segmental and diffuse pancreatitis, which may deprive patients of the pancreas-preserving option; PD is an overtreatment for the pure form of GP, since it involves resection of undamaged pancreas, which means that PPDR may be an alternative treatment procedure for GP.

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INTRODUCTION

Cystic dystrophy of the duodenal wall (CDDW) is a relatively rare form of chronic pancreatitis (CP). It is mainly observed in middle-aged men and manifests with abdominal pain, weight loss, and occasionally vomiting and jaundice^[1-7]. In the

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literature, it has also been referred to as groove pancreatitis (GP)^[8-11], periampullary duodenal wall cyst^[12], adenomyoma^[13,14], paraduodenal pancreatitis (PP)^[15-17], and pancreatic hamartoma of the duodenum^[18-20]. All these terms refer to the same histology, each one putting the emphasis on one of its different manifestations: Fibrotic inflammatory changes of the duodenal wall, spread of fibrosis to the groove area (thin area between the pancreas, common bile duct and duodenum) and common bile duct opening, duodenum wall thickening accompanied by intramural cyst formation, Brunner's gland hyperplasia and fragments of ectopic pancreatic tissue with myoid cells infiltrating the duodenal wall^[1,2,8,9,15].

This entity was first described as "cystic dystrophy" of the duodenal wall in 1970 by Potet *et al*^[1]. Stolte *et al*^[8] in 1982 and Becker *et al*^[9] in 1991 used the term GP, dividing it into "pure" and "segmental" forms. The "pure" form of the disease (which correlates to the isolated form of CDDW in the original description^[1]) refers to the condition where only cicatricial changes occur in the duodenum and area of the groove between the duodenum and the pancreas, while the pancreatic parenchyma remains intact. The "segmental" form of the disease is characterized by both the fibrotic changes of the groove, as well as signs of CP (fibrosis, pancreatic calculi, cysts, and changes of the duct of Wirsung) in the head of the pancreas or in the whole gland. In 2004, Adsay *et al*^[15] introduced the notion of "paraduodenal pancreatitis," also discriminating two types of the disease: "Pure" and "Segmental"^[17]. When considering groove, or PP, some authors also divide it into solid and cystic forms, depending on whether only fibro-inflammatory thickening of the medial duodenal wall is present or whether this thickening is accompanied by cystic transformation^[15-17]. Therapeutic approaches to treatment remain controversial, as well as the opinions on its primary cause, but today pancreatoduodenectomy (PD) is considered preferable and even a first-line treatment option for CDDW^[4,6,10,11,17,21-24]. Pancreas-preserving duodenal resection (PPDR) was introduced into practice in 2009^[25], and the objectives of this study were a comparison of the safety and efficacy of PD and PPDR in patients with CDDW.

MATERIALS AND METHODS

Patients and methods

A retrospective analysis of pre- and post-treatment data of 84 consecutive patients with CDDW treated by our group between February 2004 and April 2020 was performed. Patients with the so-called "solid type" of groove or PP were not included, as thickening (*i.e.*, inflammatory infiltration) of the medial duodenal wall in such patients may be the consequence, rather than the cause of chronic or acute inflammation of the pancreas. Intraoperative and short- and long-term postoperative data of the patients who underwent PD ($n = 44$) and PPDR ($n = 15$) were compared.

Patient information included demographic data, medical history, history of alcohol consumption and smoking and information on pancreatic endocrine and exocrine insufficiency. All blood tests and imaging studies were performed according to standard protocols.

All the cases were discussed at multidisciplinary meetings, which included experts in gastroenterology, pancreas surgery, radiology, oncology and endocrinology. Primary operative procedures were all elective. In all patients, initial treatment was conservative, which included smoking and alcohol cessation, analgesics, proton pump inhibitors, short- or long-acting somatostatin analogues, nutritional support and pancreatic enzyme replacement therapy (PERT), along with endoscopic procedures, including endoscopic ultrasonography, stenting, fine-needle aspiration and/or core-needle biopsy^[4,6,10,16,17]. Indications for surgical intervention were conservative and/or endoscopic treatment failure manifested by persistence of pain, duodenal obstruction, jaundice and (in one case) suspected tumor^[4,6,16,17]. The choice of the type of surgery changed with time, as our insight into the nature of the disease evolved. Patient flow is shown in **Figure 1**.

The procedures performed have been described in detail in our previous publications^[6,25] and elsewhere. These included internal drainage of the main pancreatic duct^[7,16,17], duodenum-preserving pancreatic head resection (DPPHR)^[26,27], pylorus-preserving (ppPD) and classical PD (Whipple procedure), Nakao procedure (PD modification)^[24], and PPDR^[6,25].

The diagnosis in all 59 patients who underwent PD and PPDR was clinically, radiologically and histologically confirmed. Eighteen patients (37%) demonstrated symptoms and signs of the isolated form of CDDW, as shown by computed tomography (CT) (**Figure 2A and B**), magnetic resonance imaging (MRI) and/or

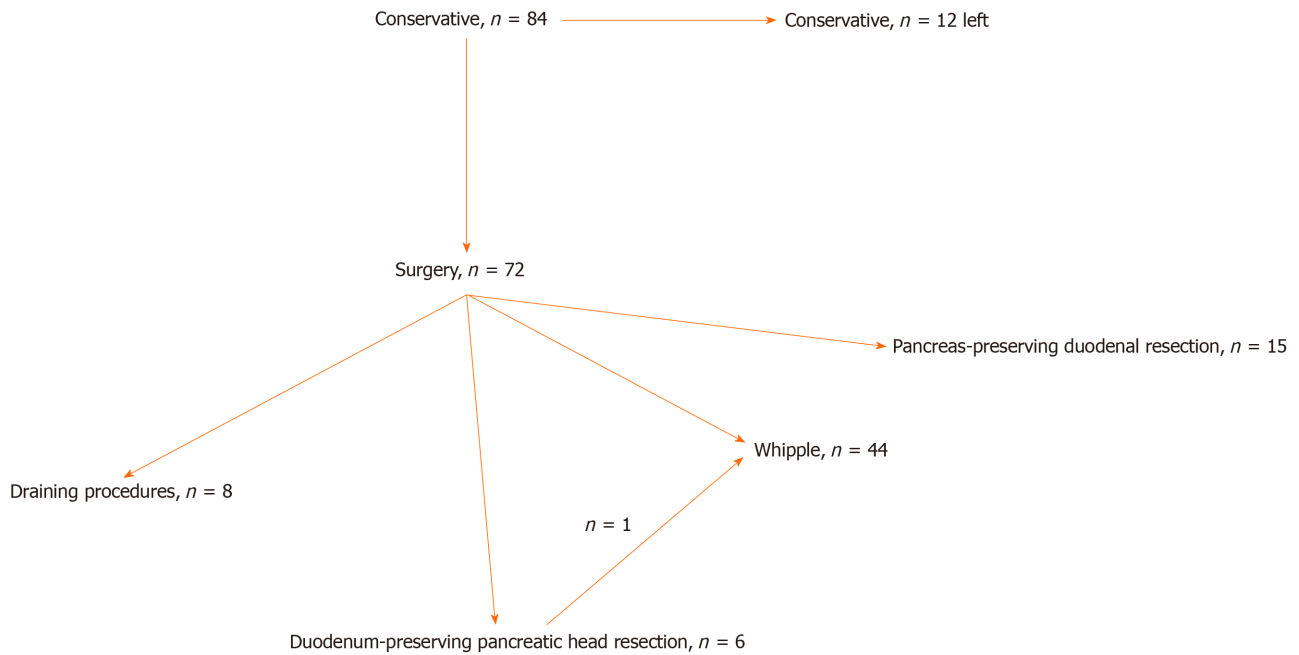


Figure 1 Patient flow chart.

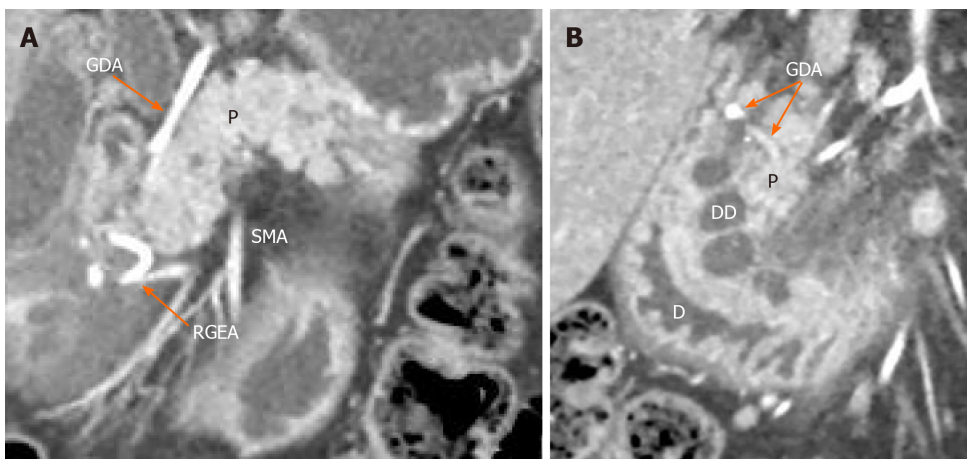


Figure 2 Isolated form of cystic dystrophy of the duodenal wall. Arterial phase. Coronal view. A: Deformation and thickening of the medial wall of the duodenum (D), major papilla surrounded by well-defined cysts located in the submucosa (DD). The gastroduodenal artery is shifted forward and to the left, lying in the groove between the unaffected pancreatic head (P) and duodenal wall; B: Unchanged orthotopic pancreas. Only the duodenum and the groove are involved. SMA: Superior mesenteric artery; GDA: Gastroduodenal artery; RGEA: Right gastro-epiploic artery.

endoscopic ultrasonography (Figure 3A and B) (*i.e.*, considerable (> 10 mm) thickening of the duodenal wall containing cystic cavities, separation of duodenal wall changes from the intact pancreas and antero-medial displacement of the gastroduodenal artery with respect to the pathological focus within the duodenum)^[3,28,29].

Histological diagnosis of CDDW was based on the detection of a cystic cavity or cavities in the duodenal wall, completely isolated from the pancreas, surrounded by areas of inflammation, fibrosis, and Brunner's gland hyperplasia. These cavities could contain fragments of ectopic pancreatic tissue, being postnecrotic cysts, or distended ectopic pancreatic ducts with preserved or desquamated epithelium (Figure 4A-D).

The diagnosis of CP in the orthotopic gland was based on the criteria presented elsewhere^[1,2,8,15]. When histologic examination of the duodenum and/or pancreas was not possible during the course of management of CDDW ($n = 25$), the diagnosis was based on pathognomonic findings of CT, MRI, and endoscopic ultrasonography according to the Cambridge and Rosemont criteria^[3,4,6,10,17,28,29-32]. PPDR was considered possible and indicated if only the duodenum was involved and in the absence of pancreatic duct calculi or calcification, cysts and fibrotic changes in the pancreatic parenchyma (Cambridge Class 0-1 and/or less than three Rosemont criteria)^[10,30-32].

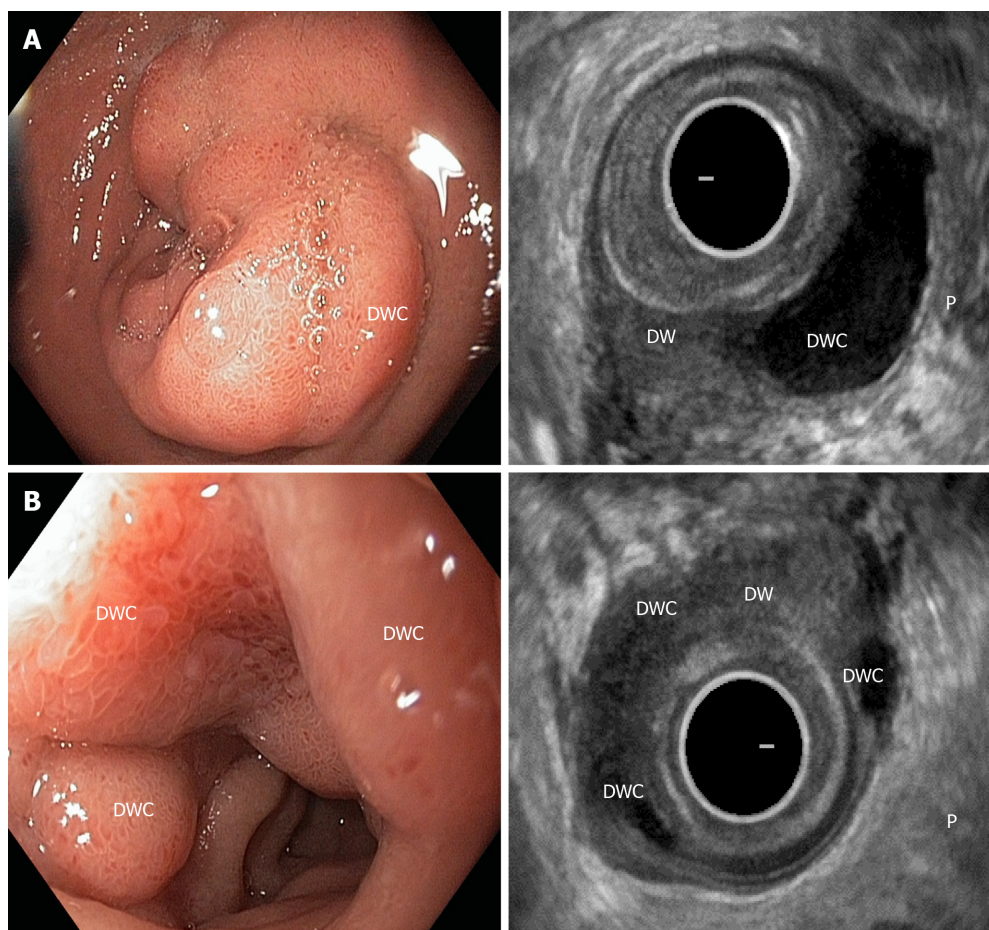


Figure 3 Duodenoscopy and endosonography. Isolated form of the cystic dystrophy of the duodenal wall with unchanged orthotopic pancreas (P). A: Duodenal wall cyst (DWC) within the submucosa and muscularis of the diffusely thickened duodenal wall (DW); B: Multiple DWCs in the submucosa and muscularis surrounding the major papilla in the diffusely thickened DW. DWC: Duodenal wall cyst; DW: Duodenal wall.

Pancreas-preserving surgery for CDDW was described previously^[6,25], and we want to note a few details (Figure 5A-D). If the affected area of the second duodenal portion does not exceed 4 cm, a segmental resection of this part of the duodenum followed by duodeno-duodenostomy is possible. However, tension may be a limitation for this type of reconstruction, especially if the inflammatory zone spreads wider. In this case, intestinal interposition can be an option (Figure 5B), as well as classical duodenectomy (Figure 5C) or Roux-en-Y reconstruction (Figure 5D).

If inflammatory and fibrotic changes around the duodenum are moderate, it is possible to remove all the walls of the duodenal cyst without causing damage to the pancreas (Figure 4C)^[25]. However, when significant fibrosis is present, it is preferable to keep the medial cystic wall intact to prevent possible damage to the pancreatic head^[6]. This does not predispose to relapse, since the cysts lack epithelium due to chronic inflammation. Intraoperative biopsy of the resected portion of the duodenum is essential to exclude malignancy^[33-35].

When inflammation and fibrosis extended beyond the second portion of the duodenum, we opted for the standard subtotal duodenectomy described by Chung *et al*^[36] (Figure 5A and B)^[37].

If the cyst extended to the first portion of the duodenum and/or stomach or if there was a peptic duodenal, pyloric or pre-pyloric ulcer, an antrectomy or pylorus resection with subsequent Roux-en-Y reconstruction was performed. Roux-en-Y reconstruction after ppPD PPDR is also an option if the surgeon sees reasons to separate the biliopancreatic tract from the food passage (Figure 5C).

All patients suffering from exocrine insufficiency received mini-microspheres of pancreatin (Creon®) at doses eliminating diarrhea, at least 200000 U/d before surgery. Pancreatin was continued for three months following the operation, at 240-320000 U/d. PERT was stopped if no signs of pancreatic insufficiency were observed after surgery.

The results of CDDW treatment were monitored for a period of 3 to 188 mo. The

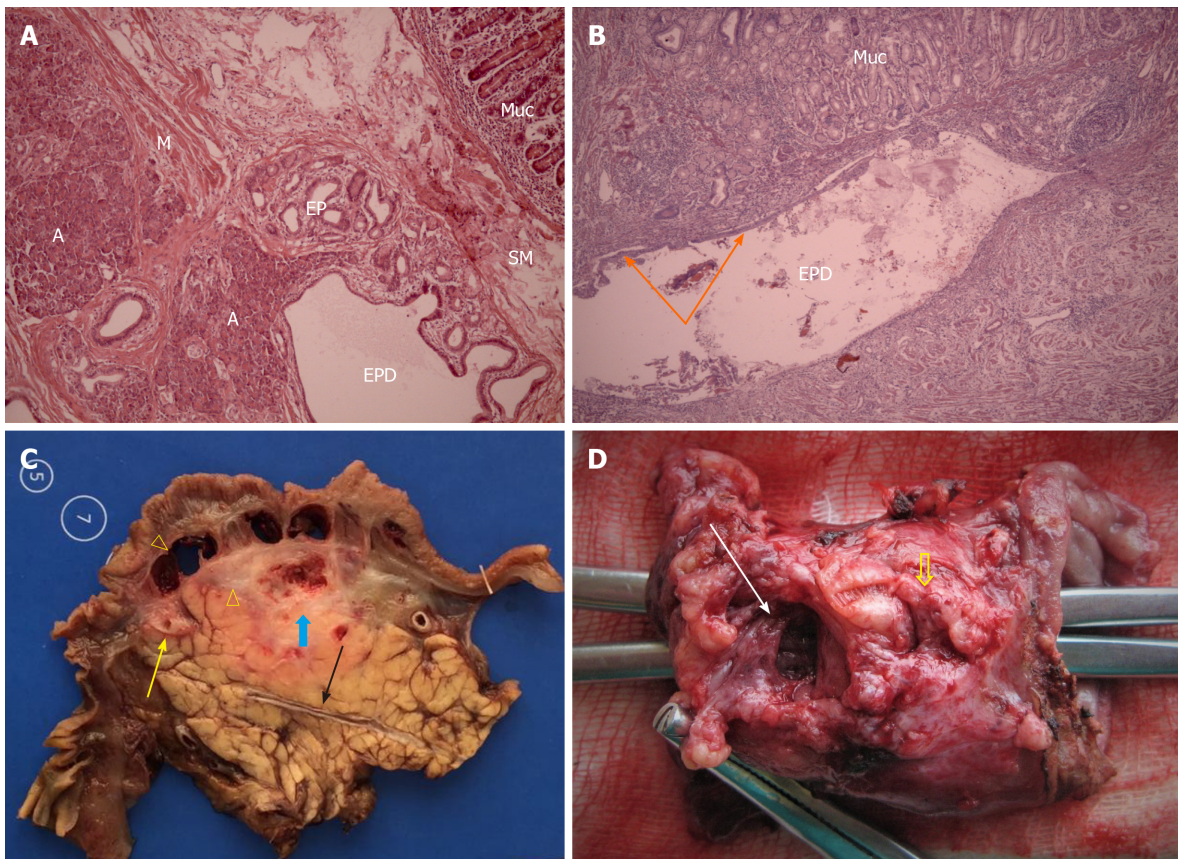


Figure 4 Microphotograph and resected specimen. A: Microphotograph of the isolated form of the cystic dystrophy of the duodenal wall. Heterotopia of the pancreatic tissue in the duodenal wall. Ectopic pancreatic tissue (EP), dilated ducts of the ectopic pancreas (EPD) and acini (A) in the duodenal wall, M: Duodenal muscle layer fibers; SM: Duodenal submucosa; Muc: Duodenal mucosa. Hematoxylin-eosin, $\times 100$; B: Microphotograph of the isolated form of the cystic dystrophy of the duodenal wall. Cyst in the duodenal wall formed by a dilated duct of the ectopic gland (EPD) with the foci of preserved epithelium (arrows). Hematoxylin-eosin, $\times 50$; C: Cystic dystrophy of the duodenal wall associated with chronic pancreatitis in the pancreatic head (segmental form of groove pancreatitis). Resected specimen after Whipple procedure in a 47-year-old male. There are multiple cysts within the thickened, chronically inflamed duodenal wall of the second portion of the duodenum (arrowheads) without dilation of the common hepatic (yellow arrow) and main pancreatic (black arrow) ducts. Chronic inflammation in the pancreatic head with necrotic mass (thick blue arrow) makes pancreas-preserving surgery unjustified and pancreatoduodenectomy the surgery of choice; D: Isolated form of the cystic dystrophy of the duodenal wall = pure form of groove pancreatitis. Due to unchanged orthotopic gland, pancreas-preserving duodenal resection was performed in a 53-year-old male. Resected 6-cm specimen of the second part of the duodenum with major papilla (thick yellow arrow) and large scar-sided cyst of the medial duodenal wall with the remainder of the ectopic pancreatic tissue inside. A forceps was introduced into the duodenum to show the absence of communication between the duodenal lumen and the lumen of the cyst (white arrow).

following information was recorded: Initial body weight, body weight at presentation, weight loss prior to the treatment, weight changes after 12-24 mo following surgery or treatment initiation (*i.e.*, when most notable body weight changes are generally observed). Body weight and weight gain were defined based on the data acquired at the visit or provided in an information letter.

The pain level and rate were assessed using the Izbicki score^[38]. Patients were contacted by telephone between the beginning and the end of July 2020 to evaluate the clinical, imaging and laboratory data.

Statistical analysis

All data distribution was evaluated by the Shapiro-Wilk test of normality in frequentist statistics. Demographic or clinical characteristics such as the average age, the proportion of subjects of each sex, the symptoms, *etc.*, have been reflected by non-parametric descriptive statistics. The mean in variables was expressed as the median (Me) and interquartile range (LQ-UQ). Subgroups were compared using the Mann-Whitney and Kruskal-Wallis tests, as appropriate. $P = 0.05$ was considered statistically significant, and confidence intervals were calculated at 95%. All statistical analyses were performed using the SPSS software program, version 20.0 (SPSS, Chicago, IL, United States).

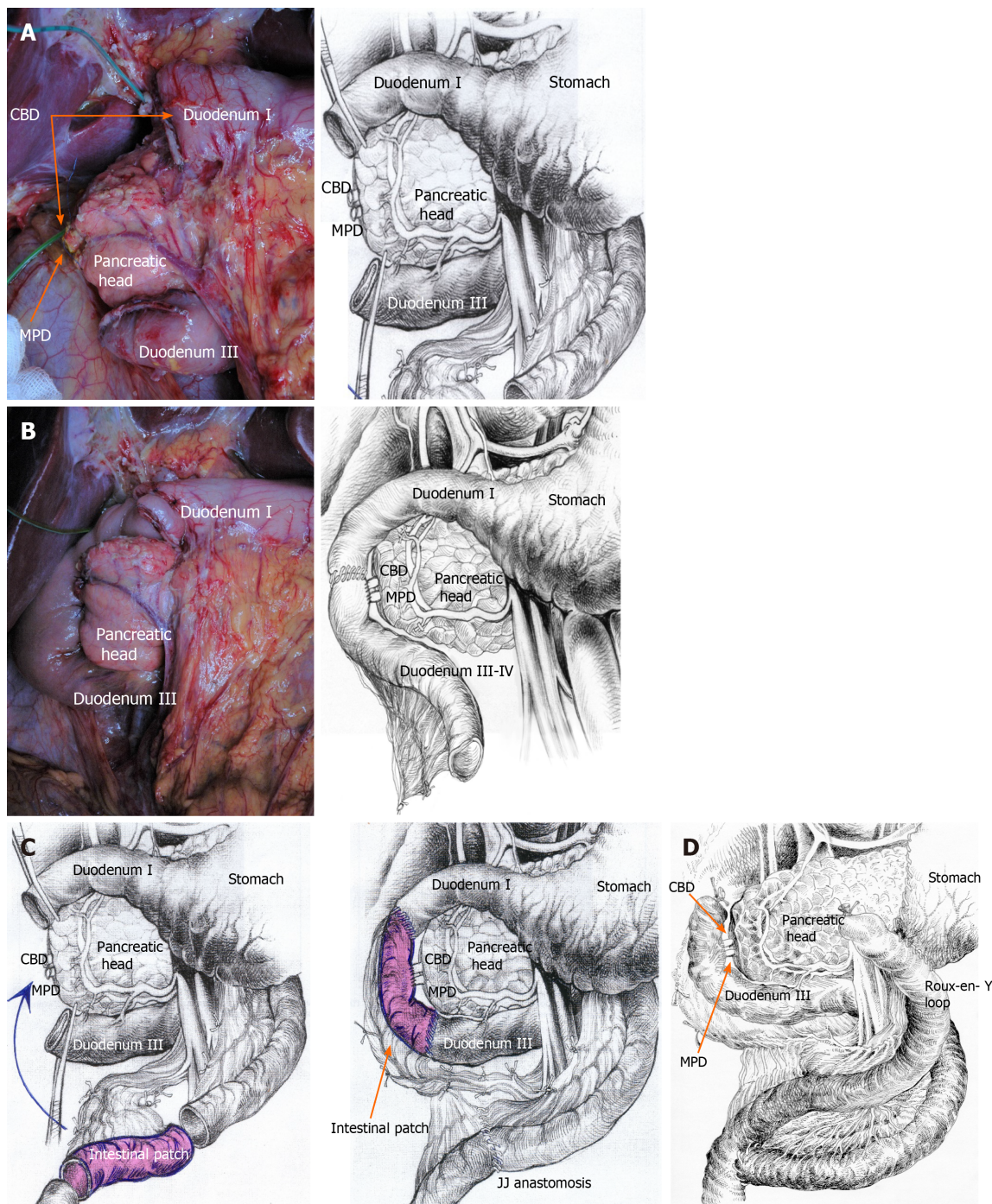


Figure 5 Isolated form of the cystic dystrophy of the duodenal wall. Scheme of the pancreas-preserving resection of the second portion of the duodenum (A) with reconstruction by direct duodeno-jejunostomy (B), intestinal interposition (C) or Roux-en-Y method (D). CBD: Common bile duct; MPD; Main pancreatic duct.

RESULTS

The patient flow chart is presented in [Figure 1](#). The treatment types and short- and long-term results are shown in [Table 1](#).

By April 2020, only 12 patients were left in the conservative therapy group due to rejection of surgery. One patient died of heart failure after two myocardial infarctions 7 years after the onset of the disease. Although the patients in this subgroup did not undergo surgery, 2 of them died during observation and 6 complications were observed: Migration of a stent that drained the duodenal wall cyst into the duodenal lumen ($n = 1$), gastrointestinal bleeding associated with NSAID administration ($n = 4$), and ectopic pancreas malignization with multiple liver metastases and death after 7 years of monitoring and 10 years of the disease. Pain completely resolved in 5 patients in this subgroup but at the expense of “burning out” of the pancreas, which

Table 1 Short- and long- term results of cystic dystrophy of the duodenal wall treatment (2004-2019)

Type of treatment	n	¹ Morbidity n (%)	Full pain control, n (%)	Steatorrhea, n (%)	New DM, n (%)
Conservative	12	5 (42%)	5 (42)	4 (33)	6 (50)
Draining OP	8	1/1 (12.5/12.5%)	2 (25)	2 (25)	2 (25)
DPPHR	6	1/2 (17/34%)	2 (33)		
PD	44	12/7 (27/16%)	37 (84)	6 (14)	12 (31)
PPDR	15	4/1 (27/7%)	14 (93)		

¹Postoperative complications are shown as minor/major (Dindo-Clavien I-II/III-IV).

DPPHR: Duodenum-preserving pancreatic head resection; PD: Pancreatoduodenectomy; PPDR: Pancreas-preserving duodenal resection; DM: Diabetes mellitus; Draining OP: Pancreatico- and/or cystoenterostomy.

manifested with exocrine and endocrine insufficiency. The median time of follow-up in this subgroup was 93 mo (LQ-UQ: 78-111).

With the exception of one patient from the conservative therapy subgroup (ASA class III), all other patients had ASA class II physical status.

Draining procedures were carried out between 2004 and 2008, when we treated CDDW by the methods traditionally used for CP. In this subgroup, only 2 of 8 patients became pain-free, but due to a “burned out” pancreas, both patients developed diabetes and exocrine insufficiency. Postoperatively, two patients developed gastrointestinal hemorrhage. In 2008, we stopped performing draining procedures because of their inefficiency. However, all patients in this subgroup refused reoperation. One patient died 10 years after surgery due to heart failure. Median follow-up before surgery was 48 mo (LQ-UQ: 42-66) and after surgery was 142 mo (LQ-UQ: 123-144).

Six patients with CDDW associated with diffuse CP underwent DPPHR due to substantial enlargement of the pancreatic head. One patient was subjected to ppPD with pain relapse one year after the DPPHR. Three patients developed post-operative complications (gastrointestinal bleeding, grade B pancreatic fistula and acute pancreatitis). Only two patients achieved complete pain relief. None suffered from or developed exocrine insufficiency or diabetes. Median follow-up before surgery was 36 mo (LQ-UQ: 29-48) and after surgery was 120 mo (LQ-UQ: 105-133).

The three aforementioned subgroups did not include patients with the isolated form of CDDW.

The PD group included 29 ppPD, 11 classic PDs, and 4 Nakao procedures (Tables 2 and 3). Three patients underwent surgery for an isolated form of CDDW and the rest for CDDW associated with CP. Complete pain control was achieved in 84% of these patients. Seven patients (17%) developed major postoperative complications: Grade B pancreatic fistula ($n = 3$), gastrointestinal bleeding ($n = 1$), grade B delayed gastric emptying ($n = 6$) and intraoperative ureter electric trauma in the presence of pronounced retroperitoneal fibrosis ($n = 1$). Pancreatic fistulas developed only in patients with isolated CDDW. In one patient (No. 43), early ductal adenocarcinoma was found in an ectopic pancreas. Four patients had steatorrhea, and 5 had either diabetes or glucose intolerance prior to surgery. Twelve patients developed new diabetes and 6 developed steatorrhea after surgery. One patient in this group had ankylosing spondylitis. One patient died from myocardial infarction 14 years after PD, and four patients died 5.5, 5.5, 11 and 14.5 years after surgery of unknown cause. Four patients were lost to follow-up 185, 167, 164 and 159 mo after surgery. Median follow-up was 42 mo (LQ-UQ: 36-60) pre-operatively and 98 mo (LQ-UQ: 67-138) post-operatively. Thirty-seven patients (84%) were alcohol drinkers, and 33 (75%) were tobacco users before surgery. After surgery, seven patients still smoke, and five still drink. After surgery, six patients had episodes of pancreatitis and 4 of them were hospitalized at least once due to this reason.

PPDR group. Tables 4 and 5 present demographic data, operative details, complications, and monitoring notes for patients undergoing PPDR. All patients were males with a mean age of 44.7 years (28-62 years). The mean body weight loss was 15.9 kg (5-44 kg). All patients suffered from pain of varying severity. Constant or frequent debilitating pain was recorded in 7 patients (46.6%). In 4 patients (26.6%), vomiting was associated with duodenal obstruction, whereas 3 patients (20%) had obstructive jaundice. Seven patients (46.6%) were addicted to alcohol, and 9 (60%) were active

Table 2 Demographic data and symptoms before and after pancreatoduodenectomy for cystic dystrophy of the duodenal wall, July 2020

No.	Age	Pain	Vomiting	Jaundice	Weight loss, kg	Weight gain after surgery, kg	Weight gain after surgery, %	PERT after surgery	Pain after surgery, status, events	Treatment before surgery, mo	Follow-up after surgery, mo, status, events
1	44	37.8	-	+	6	9	150	Yes	No, DM	72	188, NA
2	49	63	-		12	5	41	Yes	No, drinking, NDM	84	151, death of unknown cause
3	56	73.8	-		9	9	100	Yes	No, steatorrhea, Smoking, DM	54	166, death of MI
4	49	37.8	+	+	10	8	80	Yes	No, NDM	96	170, NA
5	55	81.3	+	+	12	6	50	Yes	31.5, drinking, NDM, steatorrhea	79	167, NA
6	52	73.8	-		12	9	75	Yes	No	50	162, NA
7	39	73.8	-		15	11	73	Yes	31.5, smoking, DM	60	167
8	43	63	+++		21	10	48	Yes	No	48	164
9	55	73.8	+++		18	13	72	Yes	No, smoking	38	162
10	39	63	++		17	12	71	No	No	60	156
11	57	73.8	-		6	6	100	Yes	No, NDM	8	69, death of unknown cause
12	40	73.8	-		11	8	78	Yes	No	36	155
13	51	77.5	-		10	6	60	Yes	37.8	36	152
14	61	81.3	++		8	6	75	Yes	No, steatorrhea, NDM	48	132, death of unknown cause
15	49	73.8	+++		14	8	57	Yes	37.8, NDM	72	147
16	48	77.5	++	+	12	7	58	Yes	31.5, drinking, smoking	31	147
17	40	63	+		13	7	54	No	no	60	141
18	53	77.5	-		7	7	100	Yes	no	48	129
19	59	31.5	+	+	13	9	69	Yes	No, steatorrhea	36	126
20	46	77.5	-		12	7	58	Yes	No	36	120
21	45	73.8	++		8	5	62.5	Yes	No, drinking	41	117
22	59	73.8	++		5	5	100	Yes	No	62	111
23	50	31.5	-		5	7	140	Yes	No, smoking	48	107
24	53	81.3	+++		16	9	56	Yes	No	66	105
25	47	37.8	++	+	10	8	80	Yes	No	54	103
26	44	63	-		10	7	70	Yes	No	48	101
27	46	63	+++		19	10	52	Yes	No, steatorrhea, NDM	36	97
28	51	63	+++		14	11	78.6	Yes	No	36	93
29	37	77.5	+++		15	9	60	No	No	40	93
30	54	73.8	++		10	8	80	Yes	No, DM	48	69, death of unknown cause
31	52	31.5	-	+	12	8	67	Yes	No, drinking, NDM	66	85
32	53	67.5	-		12	10	83	Yes	31.5	24	85
33	49	77.5	++		15	6	40	Yes	No, steatorrhea	12	79

34	46	81.3	+		13	9	69	Yes	No	9	69
35	48	37.8	++	+	15	10	67	Yes	No	16	69
36	50	63	++		14	9	64	Yes	No	32	69
37	51	81.3	-		7	6	86	Yes	No, smoking	39	60
38	58	31.5	-		11	8	73	Yes	No, NDM, smoking	42	57
39	54	37.8	-		12	8	67	Yes	No	30	52
40	49	73.8	++		8	6	75	Yes	No	36	45
41	47	77.5	++		7	6	86	Yes	No, DM	120	20
42	58	37.8	-		12	8	67	Yes	No, NDM	72	18
43	47	73.8	+		11	1	9	Yes	No, NDM	66	13
44	45	77.5	+++		21	5	23	Yes	No	63	6

Median preoperative follow-up was 42 mo (IQR: 36-60). All the patients, except two are males. Pain was assessed by the Izbicki score^[38]. DM: Diabetes mellitus; NDM: New diabetes mellitus; PERT: Pancreatic enzyme replacement therapy; NA: Not by April 2020.

tobacco users before surgery. After surgery, three patients still smoke and one still drinks. There were no patients with exocrine or endocrine insufficiency either before or after surgery.

The main diagnostic imaging modalities included MRI ($n = 13$), CT ($n = 14$), and endoscopic ultrasound (EUS, $n = 11$). In all patients, CDDW was diagnosed prior to surgery. In the isolated form of CDDW, no or minimal abnormalities of the pancreas were observed and only the duodenum was involved. Main pancreatic duct dilation (> 4 mm) was observed in 6 patients (40%) and common bile duct dilation (> 10 mm) in 8 patients (53%). Minor duodenal papilla was not detected. Accessory pancreatic duct (Santorini's duct) dilation or impairment was not observed. This subgroup included one patient with essential hypertension (No. 14) and two patients (No. 4 and No. 12) with ankylosing spondylitis. PPDR were standard (Chung *et al*^[36]) in 7 patients (46.6%) who were reconstructed with duodeno-duodenal anastomosis in 2 (13.3%), intestinal interposition in 2 (13.3%) and Roux-en-Y reconstruction in 4 (26.6%) (Table 2). No postoperative mortality occurred in any of the groups.

In all patients with isolated CDDW, macroscopic and microscopic examinations demonstrated intramural duodenal cysts completely separated from the pancreatic head and Brunner's gland hyperplasia of varying severity. The cysts were located in the medial ($n = 14$) and anterolateral duodenal walls ($n = 1$), abutted ($n = 7$) and surrounded the main pancreatic duct (MPD) ($n = 5$) and, in three cases, extended from the second portion of the duodenum towards the stomach. In 8 patients (53%) ectopic pancreatic tissue was identified at pathology, one of them with PanIN II. In 7 patients, the cysts matched the characteristics of postnecrotic cysts or were characterized as a dilated pancreatic duct with preserved or desquamated epithelium (Figure 2).

Four patients in this group developed minor complications (Clavien-Dindo grade I), and one patient (No. 4) suffered major postoperative complications (33.3%). All minor complications were grade A pancreatic fistulas (No. 3, No. 6, No. 10, and No. 14). Average length of hospital stay (with the exception of patient No. 4) was 15 (11-21) d (Table 3).

Patient No. 4 was reoperated on 19 d after PPDR with intestinal interposition due to leakage and bleeding from the proximal duodeno-enteroanastomosis. This complication was successfully treated with antrectomy and Roux-en-Y reconstruction. The rest of the patients were discharged without complications, and there were no readmissions within the next 90 d.

Patient No. 12 developed recurrent gastric bleeding due to rupture of a splenic artery aneurysm 46 mo after PPDR, having been asymptomatic all this period. Splenic artery aneurysm rupture led to retroperitoneal hematoma, splenic vein thrombosis, sinistral portal hypertension, acute gastric varices formation and hemorrhage. This delayed complication was successfully treated with distal pancreatectomy and splenectomy. Currently, the patient remains asymptomatic. In this case, the decision regarding the primary operation was based on non-contrast MRI and EUS findings due to the patient's allergy to intravenous contrast. Therefore, it is unclear whether the aneurysm developed after surgery or existed before.

Table 3 Operative data and complications of pancreatoduodenectomy for cystic dystrophy of the duodenal wall (July, 2020)

No.	Procedure	Blood loss, mL	Time, min	Postop stay	Morbidity (Clavien-Dindo)
1	pPD	130	290	16	Grade I, DGE A
2	pPD	150	310	11	No
3	pPD	50	230	14	No
4	PD	460	370	31	Grade IV, GI bleeding
5	pPD	500	350	18	Grade I, pneumonia
6	PD	120	305	10	No
7	pPD	150	290	10	No
8	pPD	100	280	10	Grade I, DGE A
9	PD	230	300	12	No
10	pPD	50	185	25	Grade III, POPF B
11	PD	100	340	12	No
12	pPD	100	270	14	No
13	pPD	130	220	15	Grade I, DGE A
14	pPD	140	280	16	Grade I, Lymphorrhea
15	pPD	50	270	11	No
16	PD	50	280	12	No
17	pPD	120	210	36	Grade III, POPF B, DGE B
18	pPD	70	225	10	No
19	PD	750	480	41	Grade III, ureter intraoperative trauma, DGE B
20	pPD	100	200	9	No
21	pPD	100	200	7	No
22	pPD	150	240	14	No
23	Nakao	100	330	27	Grade III, DGE B
24	pPD	50	230	16	Grade I, short-term bile leakage
25	pPD	50	280	11	No
26	Nakao	100	350	12	Grade I, DGE A
27	pPD	120	250	10	No
28	pPD	140	260	9	No
29	pPD	50	170	28	Grade III, POPF B, DGE B
30	Nakao	100	310	14	Grade I, short-term bile leakage
31	PD	120	290	12	No
32	Nakao	100	320	13	No
33	pPD	100	190	27	Grade III, DGE B
34	pPD	100	300	10	Grade I, lymphocele
35	PD	100	320	11	No
36	pPD	350	310	11	Grade I, wound infection
37	pPD	50	300	13	No
38	pPD	50	270	12	No
39	pPD	50	240	14	Grade I, DGE A
40	pPD	50	230	11	Grade I, POPF A
41	PD	100	230	10	No

42	pPD	150	410	12	No
43	PD	270	390	11	No
44	PD	250	440	10	No

PD: Pancreatoduodenectomy; pPD: Pylorus-preserving pancreatoduodenectomy; DGE A: Delayed gastric emptying A; GI: Gastrointestinal; POPF B: Postoperative pancreatic fistula grade B.

Table 4 Demographic data and symptoms before and after pancreas-preserving duodenal resections for isolated form of cystic dystrophy of the duodenal wall (pure form of groove pancreatitis), July 2020

No.	Age	Pain	Vomit	Jaundice	Weight loss, kg	Weight gain after surgery, kg	Weight gain after surgery, %	PERT after surgery	Pain after surgery, status, events	Treatment before surgery, mo	Follow-up after surgery, mo
1	53	31.5	+++	+	44	46	105	No	No	9.5	127
2	43	37.8	+++	+	21	18	86	No	No	10	124
3	47	62.5	-		18	16	89	No	No	13	118
4	45	81.3	+++		23	16	70	Yes	Pain 26.3, still drinking	7	116
5	41	62.5	+		11	8	73	No	No	11	110
6	46	62.5	+		9	8	89	No	No	8	108
7	28	67.5	-		5	3	60	No	No	8.5	104
8	30	73.8	-		6	8	75	No	No	9	103
9	56	77.5	-		14	10	71	No	No, smoking	10.5	101
10	40	68.8	+		12	8	67	No	No, smoking	12	98
11	44	81.3	-		7	8	114	No	No	13.5	97
12	52	37.8	+++		31	24	77	No	GI bleeding -DP 46 mo after surgery, no symptoms	11.5	89
13	29	77.5	+		6	8	86	No	No, smoking	11	68
14	62	68.8	+	+	11	11	100	No	No	5	65
15	55	77.5	++		21	12	57	No	No	7	31

All the patients were males. Pain assessed by the Izbicki score^[38]. PERT: Pancreatic enzyme replacement therapy; GI: Gastrointestinal; DP: Distal pancreatectomy.

Median follow-up prior to surgery was 10 mo (LQ-UQ: 8-12), and after surgery was 81 mo (LQ-UQ: 70-93). Currently, 14 of 15 patients have no complaints or symptoms (93.3%, Table 1). One patient (No. 4) with ankylosing spondylitis experienced a significant decrease in the frequency and intensity of pain episodes, despite regular alcohol consumption. All remaining patients had no episodes of pancreatitis or hospitalizations due to pancreatitis.

Short- and long-term results after PD and PPDR are shown in Tables 6-8. Follow-up before PPDR (Figure 6) was considerably shorter compared to other procedures.

DISCUSSION

Today, most pancreatologists recognize CDDW as a distinct form of CP^[10,11]. Various terms have been used to define this condition, but all refer to the same set of clinical and histologic manifestations with typical imaging diagnostic criteria^[3,28,29]. Despite the increasing number of publications on CDDW, it is difficult to define its true incidence and prevalence. Based on the data of large series from specialized centers, CDDW is identified in 13%-24% of patients who undergo surgery for CP; whereas the isolated form of CDDW (pure form of GP) was present in 22%-37% of all CDDW cases

Table 5 Operative data and complications of pancreas-preserving duodenal resection, performed for isolated form of cystic dystrophy of the duodenal wall (July, 2020)

No.	PPDR	Blood loss, mL	Time, min	Postop stay, d	Morbidity (Clavien-Dindo)
1	Intest pouch	150	280	14	No
2	Standard	200	310	15	No
3	DDA	50	250	21	Grade I, POPF A
4	Intest pouch	50	270	39	Grade IV, upper DJA leakage, converted in Roux-en-Y
5	Standard	100	270	12	No
6	DDA	50	260	18	Grade I, POPF A
7	Standard	50	220	12	No
8	Standard	150	245	12	No
9	Standard	100	235	11	No
10	Standard	100	200	17	Grade I, POPFA
11	Roux-en-Y	50	215	14	No
12	Standard	100	215	16	No
13	Roux-en-Y	50	195	15	No
14	Roux-en-Y	50	230	14	Grade I, POPF A
15	Roux-en-Y	50	225	16	No
	Mean value	87			

PPDR: Pancreas-preserving duodenal resection; DDA: PPDR with duodeno-duodeno anastomosis reconstruction; DJA: Duodenojejunoanastomosis; Intest pouch: Pancreas-preserving duodenal resection with intestinal interposition reconstruction; Standard: Classical pancreas-preserving duodenal resection with one duodeno-jejuno anastomosis; Roux-en-Y: Pancreas-preserving duodenal resection with Roux-en-Y reconstruction; POPF: Postoperative pancreatic fistula.

Table 6 Pancreatoduodenectomy and pancreas-preserving duodenal resection for cystic dystrophy of the duodenal wall, comparison of demographic data and symptoms

Variables	PPDR	PD	P M-W value
<i>n</i>	15	44	
Age, yr	45 (40-52)	49 (46-54)	0.09
Pain score	69 (62.5-77.5)	73.8 (63-73.8)	0.08
Weight loss, kg	12 (7.5-21)	12 (10.5-13)	0.52
Vomiting, <i>n</i> (%)	5 (33)	18 (41)	0.53
Jaundice, <i>n</i> (%)	3 (25)	8 (18)	1
Treatment before surgery, mo	10 (8-12)	45 (36-57)	0 ¹

¹Difference is significant.

All data are presented as Me (95%CI). PD: Pancreatoduodenectomy; PPDR: Pancreas-preserving duodenal resection.

(Table 9).

At the time when we were not aware of the cause of CDDW and thought that the cystic lesion of the duodenal wall originated from the pancreatic head, we performed operations relevant to conventional CP, such as longitudinal pancreaticojejunostomy, pancreaticocystostomy and DPPHR. Due to high complications and low efficacy rates, we stopped practicing this procedure in any type of CDDW.

A comparison of short- and long-term results of the two most efficient methods of CDDW treatment, namely PD and PPDR (Tables 6-8 have shown that both groups were similar in most of the parameters. Preoperative follow-up in the PD group was

Table 7 Pancreas-preserving duodenal resections and pancreatoduodenectomy for cystic dystrophy of the duodenal wall, comparison of intraoperative data and complications

Variables	PPDR	PD	P M-W value
<i>n</i>	15	44	
Blood loss, mL	50 (50-100)	50 (100-125)	0.10
Time, min	235 (215-270)	275 (240-290)	0.05
Hospital stay, d	15 (13-17)	12 (11-14)	0.03
Morbidity (Clavien-Dindo > III), <i>n</i> (%)	1 (6)	6 (14)	0.67

PD: Pancreatoduodenectomy; PPDR: Pancreas-preserving duodenal resection.

Table 8 Pancreas-preserving duodenal resection vs pancreatoduodenectomy for cystic dystrophy of the duodenal wall, long term results

Variables	PPDR	PD	P M-W value
<i>n</i>	15	44	
Weight gain, kg	10 (8-16)	8 (7-9)	0.01
Weight gain, %	77 (70-89)	69 (63-75)	0.03
Pain after surgery, <i>n</i> (%)	1 (6)	5 (11.4)	0.66
New DM, <i>n</i> (%)		12 (31)	0.00 ¹
PERT, <i>n</i> (%)	1 (6)	43 (98)	0.00 ¹
Follow-up, mo	89 (78-100)	105 (80-134)	0.15

¹Difference is significant.

All data are presented as Me (95%CI). PERT: Pancreatic enzyme replacement therapy; DM: Diabetes mellitus.

Table 9 Literature review of the largest series of cystic dystrophy of the duodenal wall treatment

Ref.	Year	CDDW patients (<i>n</i>)	Pure form of CDDW	Surgery ¹	PD ²	PPDR ²
Stolte <i>et al</i> ^[6]	1982	30	11 (37%)	30 (100% ¹)	30 (100%)	-
Jouannaud <i>et al</i> ^[4]	2006	23	0	14 (61% ¹)	10 (71%)	-
Rebours <i>et al</i> ^[5]	2007	105	30 (29%)	29 (28%)	17 (59%)	-
Tison <i>et al</i> ^[35]	2007	9	5 (56%)	9 (100% ¹)	9 (100%)	-
de Pretis <i>et al</i> ^[17]	2017	82	22 (27%)	57 (69.5% ¹)	51(89%)	-
Our data		82	18 (22%)	70 (85%)	42 (60%)	15 (21%)
Overall		331	86	209	159	15

¹% of all patients.

²% of all surgical procedures.

CDDW: Cystic dystrophy of the duodenal wall; PD: Pancreatoduodenectomy; PPDR: Pancreas-preserving duodenal resection.

significantly longer because of long-lasting efficient conservative treatment, including endoscopic options. Patients in the PPDR subgroup were operated on much earlier due to intensive and/or frequent pain, with such CDDW complications as duodenal obstruction and jaundice. There were no significant differences in intraoperative details and short-term results. In spite of the advantages of PPDR in this data sample, transfer to the general population did not reveal significant differences in morbidity, which was probably due to the small number of cases. Hospital stay was not significantly longer in the PPDR group, depending mainly on the peculiarities of the

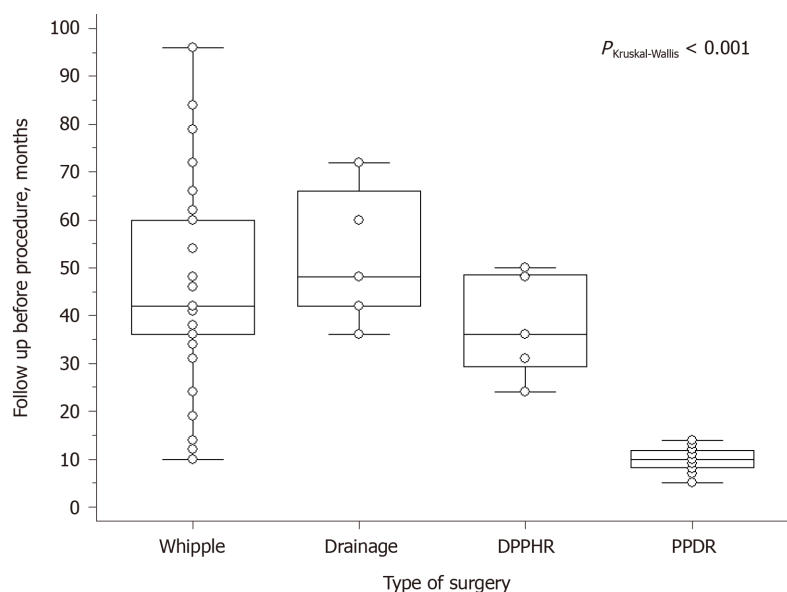


Figure 6 Duration of preoperative treatment of patients with cystic dystrophy of the duodenal wall. Preoperative treatment before pancreas-preserving duodenal resection was significantly shorter when compared with the other subgroups (explanations in the text). PPDR: Pancreas-preserving duodenal resection; DPPHR: Duodenum-preserving pancreatic head resection.

Russian Federation health care system relating to new treatment methods (Table 6).

Postoperative absolute and relative weight gain were higher in the PPDR group compared to the PD group, but not significantly so. New onset diabetes mellitus never occurred in the PPDR group, which was significantly better compared to 31% after PD. No patient required PERT after PPDR, which was significantly different compared to the PD group, where only two patients were PERT-free (Table 7). Six of our 44 patients (14%) suffered pain recurrence after PD, which is comparable to the results of the Italian studies (18.75%)^[17].

Only one major complication was recorded after PPDR: Leakage of the proximal duodenojejunostomy, and it was caused by marked fibrosis of the duodenal bulb, due to a long history of peptic ulcer disease. This observation changed our practice so that patients with a history of peptic ulcer disease were subsequently subjected to Roux-en-Y reconstruction with no serious complications since then. It is important to note that a significant history of peptic ulcer is common in patients with CDDW due to stenosis of the second portion of the duodenum. One other remote complication was splenic artery aneurysm rupture, which occurred in one case four years after PPDR. The aneurysm was not detected before surgery, since no contrast CT had been carried out. The patient underwent distal pancreatectomy and subsequently returned to normal life. All minor complications were confined to short-term grade A pancreatic fistulas, which might have occurred due to suturing normal pancreatic parenchyma. After PPDR, all patients except one, achieved long-term improvement. No patients developed endocrine or exocrine pancreatic insufficiency due to preservation of the whole gland, which was only mildly affected.

As for derivative procedures, they were quite effective in the French experience^[5], but in the Italian study^[17], they failed in more than 60% of patients, which is very similar to our results.

Based on our data (Table 1) and the works of Italian and French colleagues^[4,17], conservative treatment (including endoscopic) and draining procedures are ineffective when damaged pancreatic tissue is present in the context of CDDW, although there have been some reports of short-term positive results^[7,17,23,39,40].

In our series, neither minor duodenal papilla, nor Santorini's duct alterations were detected in the PPDR subgroup during pathologic examination. This corresponds to the radiological data by Wagner *et al.*^[41] and to Stolte *et al.*^[8] and Becker *et al.*'s^[9] histologic evidence. The latter also demonstrated that, in cases of CDDW, the minor duodenal papilla detection rate is 31%, which corresponds to the minor duodenal papilla distribution in the general population. All these findings are important to the surgeon making the decision to save or not to save the pancreas, and they do not argue for the importance of minor duodenal papilla and Santorini's duct pathology in the development of CDDW.

The efficacy of pancreas-preserving duodenectomy for the isolated form of CDDW (

i.e., pure form of GP) is important evidence indicating that, in the early stages of the disease the lesion is located in the duodenum, rather than in the pancreas or paraduodenal area.

It is worth mentioning that the imaging characteristics of CDDW are quite specific, so that preoperative diagnosis has become increasingly reliable^[3,28,29,42,43]. Eighty three of 84 patients were diagnosed as having CDDW prior to the operation and only one was operated on due to “impossibility to rule out duodenal or pancreatic head tumor.” The same “learning curve” for radiologists is mentioned by our Italian colleagues^[16].

The possibility of malignant transformation in ectopic pancreatic tissue should never be ruled out, although there have been only 15 such cases reported^[30,31,32]. In our pool of 84 patients, one in the conservative therapy subgroup died of metastatic cancer of the ectopic pancreas, early cancer was found in the ectopic pancreas after PD in a second, and PanIN II epithelial dysplasia of the ectopic pancreas was diagnosed after PPDR in a third patient^[27].

The limitations of the work are its retrospective design and the impossibility to compare PD and PPDR for the isolated form of CDDW only because of conventional practice and relative rarity of the disease. We tried to be strict in selecting only patients who abstained from smoking and alcohol consumption, but due to legislation in Russia, it is impossible to use opioids for CP treatment. As a result, we had to operate on patients with intractable pain. The same is true for such complications of CDDW as jaundice and duodenal obstruction, even if patients are still smoking and drinking.

The point of interest is the association of CDDW and ankylosing spondylitis in three patients in our series, which could be a topic of subsequent research.

In summary, CDDW is a distinctive form of CP. Its peculiarity lies in the fact that no or minimal damage to the orthotopic (main) pancreas occurs in its isolated form, while further development of the disease leads to involvement of the pancreas. The success of PPDR and the decreased probability of disease progression from its isolated form to segmental and, then, diffuse pancreatitis after PPDR, indicate that in the cases of CDDW: (1) PPDR may be the treatment of choice for the isolated form of CDDW; (2) Isolated CDDW, or the pure form of GP, is a disease of the duodenum; (3) Early detection of CDDW makes preservation of the pancreas possible; (4) PD appears to be overtreatment for the isolated form of CDDW, since it involves resection of undamaged pancreatic head parenchyma; (5) Prolonged conservative treatment in cases of the isolated form of CDDW may lead to the development of segmental and diffuse pancreatitis, which may deprive patients of the pancreas-preserving option; and (6) The abovementioned points make PPDR an alternative treatment for CDDW (GP).

Comments

Potet *et al*^[1] and Stolte *et al*^[8] and Becker *et al*^[9] demonstrated that clinical and pathologic manifestations of GP might occur with no pancreas involvement. In these cases, the pathologic process is localized in the duodenum as intramural duodenal cysts, chronic inflammation of ectopic pancreatic tissue in the duodenal wall, and perifocal fibrosis. These observations are also supported by other studies^[2-9,34]. This led to the conclusion that the pure form was an initial stage of GP, which is supported by our data regarding a much shorter time between the onset of the disease and the operation in the PPDR subgroup (Figure 6). Therefore, the disease is referred to by different authors as the isolated cystic form of CDDW^[1,2-7], pure form of GP^[8,9], or pure form of PP^[17]. The groove between the duodenum and pancreas has no organs to be inflamed, and this leads to fibrotic changes of the groove; therefore, its cicatrization may only be caused by the involvement of adjacent organ(s). If we do not detect considerable alterations of the pancreatic head, but do detect changes in the duodenal wall, it would be reasonable to assume that inflammation of the duodenal wall caused cicatrization of the groove and the development of other symptoms. This means that the involvement of the duodenum is the primary factor, while damage to the pancreas comes second. The idea that CDDW, GP or PP is a duodenal disease is not new. All main investigators of the subject^[5,8,15-17] unambiguously spoke about this. Some misunderstandings appeared when the pathologic examination was carried out in a series that only included cases of advanced disease (for example, 21 specimens in^[15], or 20 specimens from 10 hospitals^[4]). In all other large series, we can find specimens with isolated forms of CDDW (pure forms of GP) (Table 9). The organ of disease origin is impossible to establish in advanced stages with associated severe CP of the main gland^[4,15,42,43].

These observations lead to two conclusions. The first is the adoption of a legitimate term to refer to the condition. If this stage of the disease is called groove or PP, we describe pancreatitis with no pancreatitis, since all alterations are concentrated in the

duodenum. It does not seem reasonable to refer to a disease located in the duodenum as inflammation of the pancreas^[44]. Along with that, CDDW sounds like a diagnosis referring to a specific organ and incorporation of this term appears as a more logical alternative. The second conclusion is that the removal of the damaged area (*i.e.*, partial or total duodenectomy) may be the best possible method of treatment of the pure form of GP or PP^[27].

It is important to differentiate between the pure and segmental forms of GP (isolated form of CDDW) in order not to confuse “typical signs or symptoms of the disease”^[45,46]. These two forms of the disease may demonstrate the same clinical manifestations, but different typical signs, and based on the aforementioned data, may be treated differently.

CONCLUSION

The following conclusions were drawn: (1) PPDR may be the treatment of choice for the isolated form of CDDW; (2) Isolated CDDW, or the pure form of GP, is a disease of the duodenum; (3) Early detection of CDDW makes preservation of the pancreas possible; (4) PD appears to be overtreatment for the isolated form of CDDW, since it involves resection of undamaged pancreatic head parenchyma; (5) Prolonged conservative treatment in the isolated form of CDDW may lead to the development of segmental and diffuse pancreatitis, which may deprive patients of the pancreas-preserving option; and (6) the abovementioned points make PPDR a procedure that is changing the treatment of CDDW (GP).

ARTICLE HIGHLIGHTS

Research background

Today most pancreatologists recognize groove pancreatitis as a distinct form of chronic pancreatitis, but the natural history of the disease and the optimal time for surgery are unknown.

Research motivation

To understand the best technique and timing of pancreas-preserving procedures for groove pancreatitis (GP).

Research objectives

To compare the results of conventional (Whipple procedure) and organ-preserving surgery for the treatment of GP.

Research methods

A retrospective comparison of the different conservative and surgical modalities for the treatment of GP in 84 patients.

Research results

Timely pancreas-preserving procedures for GP are safe and provide better long-term results compared to conventional surgery, which is usually used at the late stages of the disease.

Research conclusions

Pancreas-preserving duodenal resection (PPDR) may be the treatment of choice for the isolated form of GP; the pure form of GP is a disease of the duodenum, early detection of which makes preservation of the pancreas possible; prolonged conservative treatment in the isolated form of GP may lead to the development of segmental and diffuse pancreatitis, which may deprive patients of the pancreas-preserving option; timely performed PPDR is a treatment-changing procedure for GP.

Research perspectives

If the author’s approach is widely accepted, more patients with GP will have the chance to save their pancreas, and prospective comparative trials will be possible on the above mentioned subject.

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Retrospective Study

Evaluation of prognostic factors and clinicopathological patterns of recurrence after curative surgery for colorectal cancer

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Abstract

BACKGROUND

Colorectal cancer is a common tumor with a quite high-related mortality. Despite the used curative treatments, patients will develop cancer recurrence in up to 50% of the cases and/or other primary neoplasms. Although most of the recurrences are discovered within 3 years from the first treatment, a small percentage is found after 5 years. The early detection of recurrence is crucial to allow further therapies improving patients' survival. Several follow-up programs have been developed but the optimal one is far from being established.

AIM

To evaluation of potential prognostic factors for timing and patterns of recurrence in order to plan tailored follow-up programs.

METHODS

Perioperative and long-term data of all consecutive patients surgically treated with curative intent, from January 2006 to June 2009, for colorectal adenocarcinoma, were retrospectively reviewed to find potential prognostic factors associated with: (1) Recurrence incidence; (2) Incidence of an early (within 3 years from surgery) or late recurrence; and (3) Different sites of recurrence. In addition, the incidence of other primary neoplasms has been evaluated in a cohort of patients with a minimum potential follow-up of 10 years.

RESULTS

Our study included 234 patients. The median follow-up period has been 119 ± 46.2 mo. The recurrence rate has been 25.6%. Patients with a higher chance to develop recurrence had also the following characteristics: Higher levels of preoperative glycemia and carcinoembryonic antigen, highest anaesthesiologists

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Score score, occlusion, received a complex operation performed with an open technique, after a longer hospital stay, and showed advanced tumors. The independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1 (multivariate analysis). Younger ages were significantly associated with an early recurrence onset. Patients that received intermediate colectomies or segmental resections, having an N stage 2 or American Joint Committee on Cancer stage 3 tumors were also associated with a higher risk of liver recurrence, while metastatic diseases at diagnosis were linked with local recurrence. Neoadjuvant treatments showed lung recurrence. Finally, bigger tumors and higher lymph node ratio were associated with peritoneal recurrence (marginally significant). Thirty patients developed a second malignancy during the follow-up time.

CONCLUSION

Several prognostic factors should be considered for tailored follow-up programs, eventually, beyond 5 years from the first treatment.

Key Words: Prognostic factors; Recurrence; Recurrence patterns; Colorectal cancer; Long-term follow-up; Follow-up programs

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Core Tip: In this retrospective study, several potential prognostic factors for recurrence, timing, and recurrence sites have been evaluated in patients who received curative colorectal surgery for adenocarcinoma with a potential minimum follow-up of 10 years. The independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1. Of note, younger ages were significantly associated with an early onset of recurrence. Some prognostic factors have been found for each site of recurrence: Liver, local, lung, and peritoneum. Thirty patients developed a second malignancy during the follow-up period. These findings may help in providing a tailored follow-up program.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms in the world with an age-standardized worldwide incidence of 19.7 and mortality of 8.9 per 100000 person-year, respectively^[1].

Surgical resection is the cornerstone of CRC management. However, according to the clinical and pathological stage, this treatment should be integrated with neoadjuvant and/or adjuvant therapies, where appropriate^[2].

Despite the curative-intent of the first treatment, the patients have a considerable risk of developing cancer recurrence and/or other primary tumors^[3,4]. Liver is the most frequent site of recurrence and liver metastases are diagnosed in up to 50% of the patients. Lungs are the second site for frequency of recurrence but, unfortunately, only a small percentage of them will develop lungs-only recurrence susceptible to resection^[5]. Locoregional and peritoneal recurrences are reported in 4% to 11.5% and 3% to 6%, respectively^[5,6]. Finally, the increasing cumulative risk to develop a second colorectal cancer is reported to be 3% every 6 years^[7].

Analysis of prognostic factors for recurrence and of the specific recurrence patterns is seldom reported since the great majority of the registries rarely detailed the sites of the development of metastases^[8].

About 80% of the recurrences occurs within the first 3 years of primary surgery and about 95% within 5 years with a small percentage of the patients (0.9%-9%) who will

suffer from recurrence 5 years after the treatment^[9]. The clinical and pathologic characteristics of early or late recurrence after curative surgery have been rarely described. Therefore, it is unclear whether there is a significant difference between these two groups in terms of prognosis^[10,11]. However, the early recurrence detection or the diagnosis of other neoplasms is an important factor to allow radical resection, when technically feasible and oncologically appropriate. Although the relation between early detection of recurrence and prognosis is still under debate^[12], many follow-up programs have been developed over the years and in different countries. There are significant variations in the length and strength of follow-up strategies in the different centers, in the type and timing of the examination, in the staff conducting and reviewing the tests, and the optimum follow-up schedule is far from being defined^[12,13]. The great majority of the surveillance programs ends in 5 years after the primary colorectal resection^[3,9,12] while colonoscopy follow-up programs are recommended to be continued beyond 5 years with the timing established on endoscopic findings^[7].

Our study aims to evaluate - in a cohort of patients who received curative surgery and who had a potential minimum of 10-years of follow-up - the clinical, operative, and pathological potential prognostic factors that may influence the recurrence development, the timing and site of disease presentation. This evaluation will allow us to fine-tune a tailored follow-up program.

MATERIALS AND METHODS

Study design

All patients submitted to an elective oncological colorectal surgery at the actually renamed Hepatobiliary Surgery Unit of Careggi Teaching Hospital, Florence, Italy from January 2006 to June 2009 and identified for follow-up of at least 10 years were evaluated for inclusion in this retrospective study.

Exclusion criteria were: Final histopathological diagnosis of benign pathology; other concomitant malignancies; histological report different from adenocarcinoma; previous oncological colorectal surgery; palliative-intent surgery, unavailability of data about recurrence status.

Data concerning demographic aspects, primary lesion, operative and postoperative outcomes, histopathological response, and long-term outcomes were prospectively recorded in a specific database. Standard preoperative work-up included triple-phase contrast-enhanced computed tomography (CT) scan and pancolonoscopy. Other radiological tests, including magnetic resonance imaging and positron emission tomography scan, were performed when required. Every decision about patients' treatments was taken after the weekly Multidisciplinary Team evaluation.

Some definitions: "Right colon" has been defined as the tract between the caecum and middle transverse colon while "left colon" has been defined as the tract between the splenic flexure and sigmoid colon.

The surgical technique was chosen according stage disease, patient conditions, and surgeon's preference and it was reported according to an "intention-to-treat" evaluation. Associated procedures were defined as "minor" including appendectomy, oophorectomy, or cholecystectomy, and "major" including hepatic resections. Histopathological evaluation was performed following the tumor node metastasis (TNM) classification, 6th edition^[14]. The lymph node ratio was defined as the number of positive lymph nodes on the total lymph nodes retrieved. Chemotherapy was considered if administered to the patient despite the interruption of the initially scheduled program due to intolerance or any other reasons. Recurrence was considered in case of high radiological suspicion and/or after the biopsy and it was divided into liver, lung, peritoneal, and "locoregional" metastasis (including tumor recurrence on the previous anastomotic line or in the lymph nodes or soft tissue near the previous surgical site). Recurrence was defined as "early" or "late" if it occurred within or beyond 3 years from surgery, respectively. In case of patient presentation with CRC and synchronous liver metastasis treated with two a 2-step surgery, disease-free survival (DFS) was considered as the time between the second intervention and the time of the first available diagnosis of recurrence or death. Recurrences were treated with surgery, chemotherapy, radiation, palliation of the symptoms including jaundice or best supportive care, as appropriated.

Within the subgroup of patients experiencing recurrence, an analysis of the potential prognostic factors for each site of recurrence was performed to try to find clinicopathological patterns of recurrence.

Follow-up program

Follow-up was conducted according to a standardized program. The complete follow-up program is reported in Table 1. Follow-up included a physical examination, carcinoembryonic antigen (CEA) determination, and a routine blood examination, endoscopy, chest radiography, abdominal sonography, and/or a CT scan. If recurrence was suspected or patients developed abdominal symptoms, further examinations were performed (*i.e.* whole-body positron emission tomography or hepatic magnetic resonance imaging). Scheduled tests could have been modified according to the oncologist's indications.

Retrieval of follow-up data was completed with a revision *via* available medical records and phone call interviews.

Analysis

Patients' data were prospectively collected into a database that was retrospectively reviewed. Continuous variables were reported as mean \pm SD while categorical variables were reported as frequency and percentage.

To evaluate the association between possible prognostic factors and DFS and overall survival (OS) a Cox model, Kaplan-Meier method, and log-rank test were used.

To estimate possible independent prognostic factors for recurrence a multiple Cox model with a backward selection method was used. To assess the association between each possible prognostic factor and timing to recurrence (< 3 years or ≥ 3 years) a simple logistic regression model was used.

Statistical significance was defined as P value ≤ 0.05 .

Data were analyzed using the statistical software SPSS, version 24 (IBM Corp.). The statistical review of the study was performed by the biostatistic Lorenzo Tofani.

RESULTS

During the study period, 360 patients underwent colorectal surgery for neoplasms. According to the exclusion criteria, 234 patients were included in our analysis. Further details are shown in Figure 1.

Analysis of survival and recurrence

The median follow-up time was 119 ± 46.2 mo. Tumor recurrences occurred in 60 patients (25.6%). The OS rate was 86.7%, 78.1%, and 59.9% at 3, 5, and 10 years, respectively. The DFS rate was 75.7%, 71.2%, and 58.3% at 3, 5, and 10 years, respectively, with a median DFS of 150 mo.

Table 2 includes the significant potential prognostic factors for DFS and OS. The American Joint Committee on Cancer (AJCC) stage and the pathological M stage resulted as strong prognostic factors for both DFS and OS. The recurrence timing resulted in a significant prognostic factor for OS but there were no significant differences in post recurrence OS ($P = 0.011$ and $P = 0.991$, respectively, Figure 2).

Recurrence characteristics and related treatments are reported in Table 3.

Fifty-one patients (85% of those experiencing recurrence) recurred within 3 years from the first intervention while 9 (15%) of them recurred beyond 3 years. The recurrence rate after 5 years was 1.7% within the entire cohort and 6.7% within the recurrence group. Consequently, 15.3 patients had to be observed between 5 and 10 years from the first treatment in order to detect 1 recurrence beyond 5 years.

Twenty-two out of the 24 patients who received a second surgical curative intervention, with or without subsequent chemotherapy protocols, achieved a status of disease-free. Four of them resulted in disease-free and alive 10 years after surgery while twelve of them developed further recurrence within a mean time from the first intervention of 44.4 mo (11-85 mo). Additional analysis involving recurrence treatments will be no object of the present study.

Fifty patients (83.3% of those experiencing recurrence) presented with the persistence of tumoral disease at death or at the time of the last follow-up.

Actual 10-years survivors were 111 (47.4%), 6 of them had developed a recurrence during the follow-up time and had received a second treatment.

Moreover, during the follow-up period, 30 patients developed a second malignancy: Colorectal ($n = 6$), breast ($n = 4$), prostate ($n = 2$), other urologic cancer ($n = 3$), intracranial cancer ($n = 4$), pancreas ($n = 4$) and other ($n = 7$). The mean time of second malignancies development was 80 mo (range 8-153). Amongst these patients, 18 developed a second neoplasm beyond 5 years and 6 died because of second neoplasms.

Table 1 Complete follow-up program

Time from surgery	Tests				
	Full blood count, liver function tests, CEA	Abdominal US	Chest X-Ray	Abdominal CT scan	Colonoscopy
3 mo	√				
6 mo	√	√	√		
9 mo	√				
12 mo	√		√	√	√
18 mo	√				
2 yr	√		√	√	√
3 yr	√		√	√	√
4 yr	√	√	√		
5 yr	√		√	√	√

CEA: Carcinoembryonic antigen; US: Ultrasonography; CT: Computed tomography.

Analysis of the prognostic factors for recurrence and comparison between early and late recurrence

Demographic and patient-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence are shown in [Table 4](#).

Preoperative glycemia and abnormal CEA values were significantly higher in the recurrence group.

Anaesthesiologists Score (ASA) score grade 4 has a more than 3-fold higher recurrence risk compared to the American Society of ASA grade 1 ($P = 0.045$). Patients presenting with bowel obstruction were 32. Four of them received a transverse loop colostomy before curative surgery. The tumor appearance with occlusive symptoms was higher in the recurrence group ($P = 0.021$).

Younger ages resulted significantly associated with early recurrence ($P = 0.050$).

[Table 5](#) reports the treatment-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence.

Ten percent of the patients with a rectal cancer location received neoadjuvant chemoradiation and administration of neoadjuvant therapy did not result in a significant prognostic factor although the high rate of missing data has to be taken into account. Patients treated with an associated major procedure have a 3.5-fold higher risk of recurrence when compared to the patients receiving only the colorectal resection ($P = 0.007$). Patients treated with open surgery have a high risk of recurrence ($P < 0.001$) and the open technique showed a marginally significant association ($P = 0.061$) with “early recurrence”.

During the hospital stay, 10 patients required reoperations due to complications: Anastomotic leak ($n = 5$), hemoperitoneum ($n = 2$), wound dehiscence ($n = 1$), rectal bleeding not amenable to endoscopic treatments ($n = 1$), acute pancreatitis ($n = 1$). However, reoperation did not result associated with higher recurrence risk. A longer hospital stay resulted significantly associated with recurrence ($P = 0.001$).

Chemotherapy mainly consisted of 5-fluorouracil and folinic acid. Some patients were also treated with capecitabine, irinotecan, and oxaliplatin-based chemotherapy. Administration of adjuvant chemotherapy showed a marginally significant association with recurrence rate and with the early onset of the disease ($P = 0.064$ and $P = 0.057$, respectively).

Pathological-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence are presented in [Table 6](#).

Each parameter of the TNM classification and the AJCC stage resulted strongly associated with recurrence and the group patients of the AJCC stage 3 showed a marginally significant higher chance to develop an early recurrence when compared to the AJCC stage 1 ($P = 0.053$).

The mean number of lymph nodes retrieved was 19.4 (range 3-133). An incorrect disease stadiation following the retrieval of fewer than 12 nodes did not significantly influence the recurrence ($P = 0.535$). The lymph node ratio was significantly higher in the recurrence group ($P < 0.001$).

Table 2 Potential prognostic factor for disease-free survival and overall survival

	Disease free survival (DFS)			P value	Overall survival (OS)			P value
	3 yr (%)	5 yr (%)	10 y (%)		3 yr (%)	5 yr (%)	10 yr (%)	
CEA				0.095				0.045
< 5 ng/mL	84.4	80.8	73.1		88.3	79.8	69.6	
≥ 5 ng/mL	72.2	61.1	50.0		81.0	66.7	42.9	
AJCC stage				< 0.0001				< 0.0001
1	86.9	82.9	70.6		91.1	83.5	70.4	
2	87.7	76.2	57.9		92.9	82.1	54.3	
3	59.3	57.9	50.6		72.0	61.0	48.5	
4	20.0	-	-		63.6	45.5	18.2	
Pathologic M stage ¹				< 0.0001				0.002
0	77.0	71.2	58.4		85.1	74.4	57.0	
1	20.0	-	-		63.6	45.5	18.2	
Retrieved LN				0.819				0.688
< 12	81.5	75.4	58.1		87.5	76.4	54.7	
≥ 12	73.3	69.3	58.8		83.2	73.8	56.4	
LN ratio				0.068				0.043
< 15	66.8	64.0	55.6		78.0	70.7	56.0	
≥ 15	41.5	41.5	36.2		61.7	44.7	33.8	
Timing of recurrence								0.028
Early (< 3 yr ²)					54.9	33.3	11.8	
Late (≥ 3 yr ²)					100	77.8	22.2	

¹According to the tumor node metastasis staging system.

²Recurrence from the first treatment.

CEA: Carcinoembryonic antigen; AJCC: American Joint Committee on Cancer; LN: Lymph node.

At the multivariate analysis, the only independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1 (Table 7). None of the prognostic factors analyzed remained significant at the multivariate analysis of the comparison between early or late recurrence.

Pattern of recurrence

Two patients were excluded from this analysis because there were no available data about the recurrence site. The most frequent site of recurrence was the liver (41.7%), followed by the locoregional recurrence (28.3%), the lung (26.7%), and the peritoneum (11.7%).

Tables 8-10 reported the results of the univariate analysis of the previously reported potential prognostic factors for liver and lung recurrence.

Patients receiving intermediate colectomies or segmental resections, having an N stage 2 or AJCC stage 3 tumor showed a higher risk of developing a liver recurrence. Patients receiving postoperative blood transfusions and adjuvant chemotherapy had a marginally significant higher chance of suffering from liver recurrence ($P = 0.067$ and $P = 0.055$).

Patients receiving neoadjuvant treatments had a higher rate of lung recurrence ($P = 0.010$).

In Tables 11-13, we have summarized the results of the analysis of the previously reported potential prognostic factors for locoregional and peritoneal recurrence.

Patients with bigger tumors and higher lymph node ratio had a marginally significant probability to develop a peritoneal recurrence ($P = 0.062$ and $P = 0.066$, respectively).

Patients having metastatic disease at diagnosis had a significantly higher probability

Table 3 Recurrence characteristics and related treatment

	Total, <i>n</i> = 234	%
Recurrence		
No	174	67.7
Yes	60	23.3
Timing of recurrence ¹		
< 3 yr	51	19.8
≥ 3 yr	9	3.5
Liver recurrence		
No	207	80.5
Yes	25	9.7
Missing	2	9.7
Lung recurrence		
No	216	84.0
Yes	16	6.2
Missing	2	9.7
Local recurrence		
No	215	83.7
Yes	17	6.6
Missing	2	9.7
Peritoneal seeding		
No	225	87.5
Yes	7	2.7
Missing	2	9.7
Treatment of the first recurrence		
Surgery	25	41.7
Chemotherapy	20	33.3
Best supportive care	8	13.3
Palliation	2	3.3
Missing	5	8.3

¹Recurrence from the first treatment.

to experience a local recurrence while patients receiving a low anterior resection of the rectum or a Miles intervention had a marginally significant higher chance to develop a local recurrence ($P = 0.059$).

Due to the paucity of significant prognostic factors found for each subgroup, multivariate analysis was not performed.

DISCUSSION

Many known and unknown factors, including patient and tumor characteristics together with surgical technical aspects, take part in the recurrence after curative treatments for colorectal cancer. Therefore, it is rather difficult to investigate every single variable, especially in a cohort with a very long follow-up period.

In agreement with previous reports^[3,4,9], we documented that the recurrence rate was 25.6% with 85% during the 3 years from surgery.

In this study, a higher value of preoperative glycemia and abnormal (> 5 ng/mL)

Table 4 Demographic and patient-related preoperative potential prognostic factors for recurrence and evaluation of early vs late recurrence (univariate analysis)

	Recurrence, <i>n</i> = 234			Timing of recurrence, <i>n</i> = 60					
	All	No	Yes	HR (95%CI)	<i>P</i> value	Early recurrence (<i><</i> 3 yr)	Late recurrence (<i>≥</i> 3 yr)	OR (95%CI)	<i>P</i> value
	<i>n</i> (%)	<i>n</i> = 174 (67.7%)	<i>n</i> = 60 (23.3%)			<i>n</i> = 51 (85.0%)	<i>n</i> = 9 (15.0%)		
Age, yr; mean \pm SD	68 \pm 12	68 \pm 11	69 \pm 12	1.00 (0.98-1.02)	0.868	67 \pm 12	77 \pm 8	1.10 (1.00-1.21)	0.050
Gender, <i>n</i> (%)					0.179				0.421
Male	128 (54.7)	99 (77.3)	29 (22.6)	Reference		25 (86.2)	4 (13.8)	Reference	
Female	106 (45.3)	75 (70.7)	31 (29.2)	1.42 (0.85-2.37)		26 (83.9)	5 (16.1)	1.85 (0.41-8.21)	
Preop Hb, g/dL, mean \pm SD	12.3 \pm 2.1	12.6 \pm 2.1	11.6 \pm 2.3	0.84 (0.71-1.01)	0.058	11.9 \pm 2.2	9.67 \pm 2.3	0.60 (0.31-1.17)	0.136
Preop glycemia, g/dL, mean \pm SD	0.99 \pm 0.26	0.96 \pm 0.24	1.08 \pm 0.31	3.44 (1.05-11.24)	0.040	1.10 \pm 0.34	0.99 \pm 0.19	0.25 (0.00-16.06)	0.518
Preop total proteins, g/dL, mean \pm SD	6.8 \pm 0.7	6.8 \pm 0.6	6.8 \pm 1	1.07 (0.54-2.11)	0.839	6.7 \pm 1.0	7.3 \pm 0.2	2.43 (0.47-12.54)	0.288
Preop CEA, <i>n</i> (%)					0.029				0.440
< 5 ng/mL	85 (82.5)	71 (83.5)	14 (16.5)	0.36 (0.15-0.90)		12 (85.7)	2 (14.3)	Reference	
\geq 5 ng/mL	18 (17.5)	11 (61.1)	7 (38.9)	Reference		5 (71.4)	2 (28.6)	2.40 (0.26-22.10)	
Missing	131	131				39			
BMI, mean \pm SD	26 \pm 4	25 \pm 4	27 \pm 5	1.06 (0.99-1.14)	0.085	27 \pm 5	27 \pm 5	0.98 (0.81-1.19)	0.866
ASA, <i>n</i> (%)									
1	31 (14.5)	26 (83.9)	5 (16.1)	Reference		5 (100)	0 (0)	Reference	
2	80 (37.4)	61 (76.2)	19 (23.8)	1.50 (0.56-4.02)	0.421	16 (84.2)	3 (15.8)	-	0.951
3	94 (43.9)	72 (76.6)	22 (23.4)	1.51 (0.57-3.40)	0.404	16 (72.7)	6 (27.3)	-	0.948
4	9 (4.2)	5 (55.6)	4 (44.4)	3.85 (1.03-14.41)	0.045	4 (100)	0 (0)	-	1.000
Missing	20	20				10			
Presentation with occlusion, <i>n</i> (%)					0.021				0.366
No	42 (59.2)	33 (78.6)	9 (21.4)	Reference		7 (77.8)	2 (22.2)	Reference	
Yes	29 (40.8)	15 (51.7)	14 (48.3)	2.60 (1.15-5.87)		13 (92.9)	1 (7.1)	0.31 (0.02-3.97)	
Missing	163	163				37			
Tumor site, <i>n</i> (%)									
Right colon	70 (29.9)	53 (75.7)	17 (24.3)	Reference		13 (76.5)	4 (23.5)	Reference	
Left colon	103 (44)	76 (73.8)	27 (26.2)	0.93 (0.50-1.70)	0.807	24 (88.9)	3 (11.1)	0.41 (0.08-2.10)	0.282
Rectum	61 (26.1)	45 (73.8)	16 (26.2)	0.94 (0.47-1.85)	0.851	14 (87.5)	2 (12.5)	0.46 (0.07-2.98)	0.418

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Preop: Preoperative value; Hb: Haemoglobin; CEA: Carcinoembryonic antigen; BMI: Body mass index; ASA: American Society of Anaesthesiologists Score.

preoperative CEA levels resulted in prognostic recurrence factors. Although there are conflicting results^[15,16], a relationship between metabolic syndrome and a higher risk of recurrence has been reported in a large cohort study including more than 1000 patients^[17]. The discrepancies between these studies may be explained with the use of non-uniform definitions, however, the insulin role in stimulating cell proliferation *via* mitogen-activated protein kinase pathway is well documented^[18]. The role of preoperative CEA as an independent risk factor for both DFS and OS has been already reported, especially in AJCC stage I-III, with the optimal cut off value ranging from 3 ng/mL^[19] to 5 ng/mL if associated with positive lymph nodes or 10 ng/mL if in presence of negative lymph nodes^[20].

Patients with ASA score grade 4 had a more than 3-fold higher risk of recurrence compared to ASA score grade 1 in our study. Association between ASA score and recurrence has been seldom reported^[21,22]. It is reasonable to think that patients with more comorbidity may show a less efficient anti-tumoral response. Similarly, few data are available regarding the relationship between clinical presentation modalities and prognosis after elective surgery. A presentation with perforation, but not with obstruction, was found to be associated with very late (more than 5 years) onset of recurrence^[23]. A possible explanation may be related to the presence of an undetectable micro-perforation and/or bacterial translocation with an impairment of the immune response, but it was not demonstrated yet.

Administration of neoadjuvant therapies, especially the combination of radio and chemotherapy for rectal cancer, has been progressively increased during the last decade but in the study period, only a few patients underwent these treatments. Therefore, it was impossible to evaluate this parameter in the present study.

The finding of higher recurrence risk in patients receiving additional major procedures, treated with the open technique, and receiving adjuvant chemotherapy (marginally significant) is easily explainable with more advanced tumor stages diagnosed in each subgroup. Similarly, the interpretation of the length of hospital stay as an independent prognostic factor should take into account that this parameter is actually the result of many other variables including patient's conditions, kind of received operation, and postoperative course.

Our data confirmed the prognostic value of the TNM staging system. Furthermore, the N stage 2 and M stage 1 resulted to be independent prognostic factors for recurrence. Patients with a higher lymph node ratio had significantly higher to develop recurrence. Interestingly, a potential incorrect disease stadiation following the retrieval of fewer than 12 nodes did not significantly influence the recurrence.

Lymph nodes ratio is considered as an effective parameter for stratification, especially because it seems to be independent of the resection length^[24], and as a strong predictor for tumor recurrence^[25,26]. However, the more recent paper of Jakob *et al*^[27] reported the bigger impact of pN than lymph node ratio on recurrence suggesting that the latter parameter could be more helpful in presence of a relatively low number of harvested lymph nodes^[27].

Tumor size did not confer a higher risk of recurrence in this analysis. However, previous studies reported a direct correlation between diameter and TNM parameter or, on the contrary, a poorer prognosis of small tumors when associated with advanced T stage^[28,29]. These findings could suggest that tumor biology may have a bigger impact on prognosis than tumor size.

Administration of adjuvant chemotherapy and an earlier start of it (within 6 wk from surgery) did not affect the recurrence risk while previously published papers reported opposite results^[13]. Administration of chemotherapy in more advanced cancer stages, together with the possible impact of missing data of the present analysis may explain these different findings.

Several factors affecting the timing of recurrence have been proposed and they may differ in subgroups' analysis of different CRC stages^[13].

We found that younger ages resulted significantly associated with early recurrence while AJCC stage 3 and administration of adjuvant chemotherapy showed a trend toward higher probability to develop an early recurrence without reaching statistical significance. These findings may be related to more aggressive tumor biology. Advanced T and N stages have been reported to be related to the early onset of recurrence^[9,10,13]. It has been reported that adjuvant chemotherapy may or not influence the rate of recurrence^[9,13]. These conflicting results may be explained with the use of

Table 5 Treatment-related potential prognostic factors for recurrence and evaluation of early versus late recurrence (univariate analysis)

	Recurrence, <i>n</i> = 234			Timing of recurrence, <i>n</i> = 60					
	All	No	Yes	HR (95%CI)	<i>P</i> value	Early recurrence (<i><</i> 3 yr)	Late recurrence (<i>≥</i> 3 yr)	OR (95%CI)	<i>P</i> value
	<i>n</i> , %	<i>n</i> = 174 (67.7%)	<i>n</i> = 60 (23.3%)			<i>n</i> = 51 (85.0%)	<i>n</i> = 9 (15.0%)		
Neoadjuvant therapy, <i>n</i> (%)					0.921				0.949
No	97 (93.3)	68 (70)	29 (30)	Reference		25 (86.2)	4 (13.8)	Reference	
Yes	7 (6.7)	5 (71)	2 (29)	1.07 (0.26-4.51)		2 (100)	0 (0)	1.13 (0.02-53.57)	
Missing	130	130				29			
Surgery, <i>n</i> (%)									
Right emicolectomy	55 (23.5)	42 (76.4)	13 (23.6)	Reference		10 (76.9)	3 (23.1)	Reference	
Extended right emicolectomy	15 (6.4)	12 (80)	3 (20)	1.16 (0.37-3.59)	0.801	2 (66.7)	1 (33.3)	4.20 (0.37-47.64)	0.247
Intermediate colectomy	10 (4.3)	6 (60)	4 (40)	2.16 (0.70-6.71)	0.182	3 (75)	1 (25)	1.80 (0.14-23.6)	0.655
AR/Hartmann	106 (45.3)	80 (75.5)	26 (24.5)	1.09 (0.55-2.17)	0.798	24 (92.3)	2 (7.7)	0.43 (0.06-3.02)	0.395
LAR/Miles	38 (16.2)	28 (73.7)	10 (26.3)	1.16 (0.50-2.68)	0.731	8 (80)	2 (20)	1.23 (0.16-9.69)	0.841
Total/Sub-total Colectomy	6 (2.6)	3 (50)	3 (50)	2.69 (0.76-9.53)	0.126	3 (100)	0 (0.0)	0.60 (0.01-24.50)	0.787
Segmental resection	4 (1.7)	3 (75)	1 (25)	1.12 (0.14-8.68)	0.916	1 (100)	0 (0.0)	1.7 (0.02-162.35)	0.819
Associated procedure, <i>n</i> (%)									
No	52 (50.5)	39 (75)	13 (25)	Reference		11 (84.6)	2 (15.4)	Reference	
Minor	40 (38.8)	27 (67.5)	13 (32.5)	1.30 (0.60-2.80)	0.505	11 (84.6)	2 (15.4)	1.00 (0.13-7.44)	1.00
Major	11 (10.7)	4 (36.4)	7 (63.6)	3.56 (1.41-8.96)	0.007	7 (100)	0 (0)	0.31 (0.01-8.95)	0.492
Missing	131	131				27			
Operative technique, <i>n</i> (%)					<i><</i> 0.001				0.061
Open	99 (42.7)	61 (61.6)	38 (38.4)	Reference		35 (92.1)	3 (7.9)	Reference	
Laparoscopy	133 (57.3)	111 (83.5)	22 (16.5)	0.37 (0.22-0.62)		16 (72.7)	6 (27.3)	4.00 (0.94-17.01)	
Missing	2	2				-			
Duration of surgery, min – mean \pm SD	232 \pm 67	230 \pm 61	239 \pm 83	1.00 (0.99-1.01)	0.496	238 \pm 78	242 \pm 112	1.00 (0.99-1.01)	0.808
Postop blood transfusion, <i>n</i> (%)					0.123				0.119
No	174 (75.7)	134 (77)	40 (23)	Reference		36 (90)	4 (10)	Reference	
Yes	56 (24.3)	37 (66.1)	19 (33.9)	1.54 (0.89-2.66)		14 (73.7)	5 (26.3)	3.08 (0.75-12.64)	

Missing	4	4				1			
Reoperation, <i>n</i> (%)						0.262			0.559
No	82 (91.1)	60 (73.2)	22 (26.8)	Reference		17 (77.3)	5 (22.7)	Reference	
Yes	8 (8.9)	5 (62.5)	3 (37.5)	1.99 (0.60-6.61)		2 (66.7)	1 (33.3)	2.13 (0.17-26.68)	
Missing	144	144				35			
Hospital stay, d, mean ± SD	9.2 ± 6	8.7 ± 3.7	10.9 ± 9.1	1.05 (1.02-1.07)	0.001	10.9 ± 9.8	10.6 ± 4.0	1.01 (0.95-1.08)	0.737
Adjuvant therapy, <i>n</i> (%)						0.064			0.057
No	127 (56.4)	103 (81.1)	24 (18.9)	Reference		18 (75)	6 (25)	Reference	
Yes	98 (43.5)	67 (68.4)	31 (31.6)	1.65 (0.97-2.81)		28 (90.3)	3 (9.7)	0.22 (0.04-1.04)	
Missing	9	9				5			
Start of adj CHT, <i>n</i> (%)						0.268			0.401
< 6 wk	26 (48.1)	13 (50)	13 (50)	Reference		12 (92.3)	1 (7.7)	Reference	
≥ 6 wk	28 (51.9)	19 (67.9)	9 (32.1)	1.63 (0.69-3.95)		8 (88.9)	1 (11.1)	4.4 (0.14-141.01)	
Missing	180	180				38			

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; AR: Anterior resection of the rectum; LAR: Low anterior resection of the rectum; Adj CHT: Adjuvant chemotherapy.

different chemotherapy protocols and, again, by different aggressiveness of the disease. Although the early or late recurrence is a debate prognostic factor for the OS^[13], we observed that the early recurrence onset resulted significantly associated with a shorter OS rate but not with post recurrence overall survival. Similarly, Lan *et al*^[13] reported that there was no difference in terms of post-recurrence survival between early or late recurrence^[13].

Regarding the recurrence site, we documented that liver was the most frequent site (41.7%) followed by locoregional recurrence, lung, and peritoneal recurrence. In detail, patients receiving intermediate colectomies or segmental resections, having an N stage 2 or AJCC stage 3 tumor had a higher risk of developing a liver recurrence. Patients receiving postoperative blood transfusions and adjuvant chemotherapy had a marginally significant higher chance of suffering from recurrence.

Patients receiving neoadjuvant treatments had a higher rate of lung recurrence suggesting the probable association with the presence of advanced primary tumors located in the lower rectum as a prognostic factor.

Finally, in the present study, patients with bigger tumors and higher lymph node ratio had a marginally significant probability to develop a peritoneal recurrence. Previously reported risk factors for peritoneal carcinomatosis included also mucinous and signet ring adenocarcinomas^[8].

Patients having metastatic disease at diagnosis had a significantly higher probability to experience a local recurrence while patients receiving a low anterior resection of the rectum or a Miles intervention had a marginally significant higher chance to develop a local recurrence. These findings may be related to complex technical surgical aspects and to pathological aspects including the circumferential radial margin, which was recently introduced in routine practice as a parameter of correct dissection. While in this analysis anastomotic leak did not result in a higher risk of local recurrence, this association has been previously reported^[30,31]. Notably, as we previously reported, the research of a relationship between gut microbiota, anastomotic leak, and local recurrence is a promising field under evaluation^[32].

Kind of tests, frequency, and duration of the follow-up is still debated^[33,34].

Data from a review of several moderate-high quality randomized controlled trials showed better OS and a higher resectability rate of the recurrence but no differences in cancer-specific mortality rate with a more intensive follow-up program^[12].

Most of the follow-up programs end in five years after primary surgery. Only

Table 6 Pathological-related potential prognostic factors for recurrence and evaluation of early versus late recurrence (univariate analysis)

	Recurrence, <i>n</i> = 234			Timing of recurrence, <i>n</i> = 60					
	All	No	Yes	HR (95%CI)	<i>P</i> value	Early recurrence (< 3 yr)	Late recurrence (≥ 3 yr)	OR (95%CI)	<i>P</i> value
	<i>n</i> (%)	<i>n</i> = 174 (67.7%)	<i>n</i> = 60 (23.3%)			<i>n</i> = 51 (85.0%)	<i>n</i> = 9 (15.0%)		
Major tumor diameter, mm, mean ± SD	43 ± 23	41.6 ± 23	46.8 ± 24.5	1.01 (0.99-1.02)	0.130	47.6 ± 23.5	42.8 ± 29.8	0.99 (0.96-1.02)	0.694
Pathological T stage ¹ , <i>n</i> (%)									
1	46 (19.7)	44 (95.7)	2 (4.3)	Reference		2 (100)	0 (0)	Reference	
2	40 (17.2)	32 (80)	8 (20)	3.44 (0.91-12.99)	0.068	6 (75)	2 (25)	0.64 (0.04-10.57)	0.756
3	141 (60.5)	94 (66.7)	47 (33.3)	6.14 (1.91-19.77)	0.002	40 (85.1)	7 (14.9)	0.27 (0.02-3.20)	0.298
4	6 (2.6)	4 (66.7)	2 (33.3)	6.19 (1.03-37.96)	0.046	2 (100)	0 (0)	0.33 (0.00-24.94)	0.624
Missing	1	1				1			
Pathological N stage ¹ , <i>n</i> (%)									
0	155 (66.5)	129 (83.2)	26 (16.8)	Reference		18 (69.2)	8 (30.8)	Reference	
1	51 (21.9)	36 (70.6)	15 (29.4)	1.95 (1.03-3.69)	0.039	15 (100)	0 (0)	0.07 (0.00-1.44)	0.085
2	27 (11.6)	9 (33.3)	18 (66.7)	6.35 (3.50-11.64)	< 0.001	17 (94.4)	1 (5.6)	0.19 (0.03-1.25)	0.084
Missing	1	1				1			
Pathological M stage ¹ , <i>n</i> (%)					< 0.001				0.408
0	223 (95.6)	171 (76.7)	52 (23.3)	Reference		43 (82.7)	9 (17.3)	Reference	
1	10 (4.3)	2 (20)	8 (80)	5.31 (2.50-11.30)		8 (100)	0 (0)	0.27 (0.01-6.02)	
Missing	1	1				-			
AJCC stage, <i>n</i> (%)									
1	77 (32.9)	68 (88.3)	9 (11.7)	Reference		7 (77.8)	2 (22.2)	Reference	
2	75 (32)	59 (78.7)	16 (21.3)	1.65 (0.74-3.67)	0.220	10 (62.5)	6 (37.5)	1.12 (0.20-6.17)	0.894
3	72 (30.8)	45 (62.5)	27 (37.5)	3.59 (1.73-7.42)	< 0.001	26 (96.3)	1 (3.7)	0.12 (0.01-1.03)	0.053
4	10 (4.3)	2 (20)	8 (80)	11.1 (4.35-28.52)	< 0.001	8 (100)	0 (0)	0.13 (0.00-3.43)	0.220
Retrieved LN, <i>n</i> (%)					0.535				0.741
< 12	65 (29.3)	53 (81.5)	12 (18.5)	Reference		10 (83.3)	2 (16.7)	Reference	
≥ 12	157 (70.7)	112 (71.3)	45 (28.7)	0.84 (0.47-1.47)		38 (84.4)	7 (15.6)	0.78 (0.18-3.40)	
Missing	12	12				3			
LN ratio, mean ± SD	20 ± 16	16 ± 13	25 ± 19	25.8 (8.22-80.93)	< 0.001	25 ± 19	22	0.00 (0.00-2.20)	0.073

Colloid component, <i>n</i> (%)				0.168				0.607
No	63 (60)	49 (77.8)	14 (22.2)	Reference	12 (85.7)	2 (14.3)	Reference	
Yes	42 (40)	27 (64.3)	15 (35.7)	1.68 (0.80-3.53)	13 (86.7)	2 (13.3)	0.55 (0.06-5.22)	
Missing	129	129			31			

¹According to the tumor node metastasis staging system.

AJCC: American Joint Committee on Cancer; LN: Lymph nodes; HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals.

Table 7 Multivariate analysis of potential prognostic factors for recurrence

	HR	95%CI	P value
Hospital stay, d	1.053	1.023-1.084	< 0.001
Pathological N stage ¹			
0	Reference		
1	1.608	0.773-3.343	0.204
2	6.129	3.070-12.236	< 0.001
Pathological M stage ¹			
0	Reference		
1	5.521	2.113-14.425	< 0.001

¹According to the tumor node metastasis staging system.

HR: Hazard ratio; CI: Confidential intervals.

routine surveillance is recommended beyond this period but recurrence continues to occur after 5 years. Our data showed a rate of very late first recurrence (> 5 years) of 1.7%, similar to other previously published studies^[3,9]. Moreover, a mean time of more than 60 mo for the development of the second recurrence in the patients with lung metastases was observed and the presentation of the second liver recurrence ranged between 24 and 76 mo. Finally, as a collateral finding, 15 patients developed a second neoplasm beyond 5 years from primary colorectal surgery. Perhaps, in these patients, a longer surveillance program could have allowed an earlier diagnosis. Similarly, Chauvenet *et al*^[35] estimated the achievement of cure at 9.3 years^[35] while Bouvier *et al*^[23] reported a recurrence rate of 6.7% between 5 and 10 years after the first treatments, independently from cancer stage^[23]. These data could suggest the necessity to extend the actual follow up programs up to 10 years, especially for selected patients. On the other hand, patients may suffer from test-related anxiety and the tests may rarely provoke adverse reactions^[12]. No relevant reports about the economic aspect have been found^[12]. Consequently, a tailored approach for each patient seems advisable.

Our study has several drawbacks. This has been a retrospective study with an inherent selection bias. Missing data, mostly due to the chosen long follow-up period, may also cause bias throughout the analysis. Patients lost during follow-up and patients who did not undergo radiological imaging after the 5th years of follow-up could have a silent recurrence causing a recurrences' underestimation. On the contrary, not all the patients with a radiological suspicion of metastasis underwent a histological assessment causing a potential overestimation of the recurrence rate. Data concerning chemotherapy are quite simplified and those about molecular biology were almost completely missing, therefore further statistical analysis could not be performed. Similarly, data regarding mesorectal excision were still not available in the histological reports making impossible the analysis of its adequacy. Finally, an accurate cost/benefit evaluation should be considered. Therefore, further analyses, possibly in a larger sample, are needed and could offer stronger evidence.

Table 8 Demographic and patient-related preoperative potential prognostic factors for liver and lung recurrence

	Recurrence, <i>n</i> = 58							
	Liver				Lung			
	No, <i>n</i> = 33 (55.0%)	Yes, <i>n</i> = 25 (41.7%)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 42 (70.0%)	Yes, <i>n</i> = 16 (26.7%)	HR (95%CI)	<i>P</i> value
Age, yr, mean ± SD	67.4 ± 12.3	68.0 ± 12.3	1.00 (0.97-1.03)	0.945	67.3 ± 12.7	68.7 ± 11.0	1.00 (0.96-1.04)	0.837
Gender, <i>n</i> (%)				0.702				0.185
Male	16 (55.2)	13 (44.8)	Reference		19 (65.5)	10 (34.5)	Reference	
Female	17 (58.6)	12 (41.4)	0.86 (0.39-1.88)		23 (79.3)	6 (20.7)	0.50 (0.18-1.39)	
Preop Hb, g/dL, mean ± SD	11.28	11.93	1.16 (0.88-1.53)	0.296	11.4 ± 2.3	12.0 ± 2.5	1.14 (0.81-1.61)	0.446
Preop glycemia, g/dL, mean ± SD	1.08 ± 0.36	1.08 ± 0.31	1.72 (0.14-10.00)	0.884	1.06 ± 0.33	1.14 ± 0.35	1.47 (0.12-18.20)	0.764
Preop total proteins, g/dL, mean ± SD	6.7 ± 0.7	7.1 ± 0.8	1.33 (0.56-3.17)	0.514	6.9 ± 0.9	6.9 ± 0.5	0.87 (0.19-3.93)	0.861
Preop CEA, <i>n</i> (%)				0.868				0.891
< 5 ng/mL	6 (46.2)	7 (53.8)	Reference		10 (76.9)	3 (23.1)	Reference	
≥ 5 ng/mL	4 (57.1)	3 (42.9)	0.89 (0.23-3.46)		5 (71.4)	2 (28.6)	1.14 (0.18-7.14)	
Missing	23	15			27	11		
BMI, mean ± SD	26.3 ± 4.9	27.8 ± 4.7	1.04 (0.94-1.15)	0.465	27.6 ± 4.8	25.7 ± 4.6	0.96 (0.83-1.13)	0.646
ASA, <i>n</i> (%)								
1	3 (60)	2 (40)	Reference		4 (80)	1 (20)	Reference	
2	8 (42.1)	11 (57.9)	0.64 (0.15-2.75)	0.544	14 (73.7)	5 (26.3)	0.46 (0.06-3.38)	0.447
3	13 (61.9)	8 (38.1)	0.34 (0.07-1.55)	0.163	15 (71.4)	6 (28.6)	0.31 (0.04-2.35)	0.258
4	3 (100)	0 (0.0)	0.30 (0.01-7.69)	0.471	2 (66.7)	1 (33.3)	2.09 (0.16-27.56)	0.573
Missing	6	4			7	3		
Presentation with occlusion, <i>n</i> (%)				0.465				0.470
No	5 (62.5)	3 (37.5)	Reference		6 (75)	2 (25)	Reference	
Yes	6 (46.2)	7 (53.8)	1.58 (0.46-5.44)		9 (69.2)	4 (30.8)	1.89 (0.34-10.61)	
Missing	23	15			27	11		
Tumour site, <i>n</i> (%)								
Right colon	11 (68.7)	5 (31.3)	Reference		13 (81.3)	3 (18.7)	Reference	
Left colon	11 (42.3)	15 (57.7)	2.48 (0.89-6.88)	0.081	20 (76.9)	6 (23.1)	1.73 (0.42-7.04)	0.445
Rectum	11 (68.7)	5 (31.3)	0.98 (0.28-3.41)	0.972	9 (56.3)	7 (43.7)	2.34 (0.59-9.32)	0.226

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Preop: Preoperative value; Hb: Haemoglobin; CEA: Carcinoembryonic antigen; BMI: Body mass index; ASA: American Society of Anaesthesiologists Score.

CONCLUSION

In conclusion, several prognostic factors for recurrence and some specific factors for each site of recurrence have been found and should be taken into account in scheduling a tailored follow-up program for each patient. Since recurrence or other primary tumors may occur even 5 years from the first treatment, an extension of the recommended 5-years follow-up program should be evaluated according to the presence of potential prognostic factors.

Table 9 Treatment-related potential prognostic factors for liver and lung recurrence

	Recurrence, <i>n</i> = 58							
	Liver				Lung			
	No, <i>n</i> = 33 (55.0%)	Yes, <i>n</i> = 25 (41.7%)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 42 (70.0%)	Yes, <i>n</i> = 16 (26.7%)	HR (95%CI)	<i>P</i> value
Neoadjuvant therapy, <i>n</i> (%)				0.952				0.010
No	13 (46.4)	15 (53.6)	Reference		21 (75)	7 (25)	Reference	
Yes	2 (100)	0 (0)	0.91 (0.04-18.42)		0 (0)	2 (100)	13.21 (1.86-93.92)	
Missing	18	10			21	7		
Surgery, <i>n</i> (%)								
Right emicolectomy	10 (83.3)	2 (16.7)	Reference		10 (83.3)	2 (16.7)	Reference	
Extended right emicolectomy	1 (33.3)	2 (66.7)	2.02 (0.31-13.21)	0.461	2 (66.7)	1 (33.3)	0.81 (0.09-7.66)	0.857
Intermediate colectomy	0 (0)	4 (100)	7.05 (1.34-36.94)	0.021	4 (100)	0 (0)	0.75 (0.03-21.49)	0.864
AR/Hartmann's procedure	11 (44)	14 (56)	2.44 (0.59-10.18)	0.220	19 (76)	6 (24)	1.07 (0.21-5.39)	0.936
Low anterior resection/Miles	9 (90)	1 (10)	0.54 (0.06-4.67)	0.579	3 (30)	7 (70)	2.20 (0.45-10.78)	0.332
Total/Sub-total colectomy	2 (66.7)	1 (33.3)	2.37 (0.27-20.60)	0.433	3 (100)	0 (0)	0.84 (0.03-24.19)	0.920
Segmental resection	0 (0)	1 (100)	110 (5.3-2304.7)	0.002	1 (100)	0 (0)	-	-
Associated procedure, <i>n</i> (%)								
No	4 (33.3)	8 (66.7)	Reference		10 (83.3)	2 (16.7)	Reference	
Minor	9 (69.2)	4 (30.8)	0.37 (0.11-1.23)	0.106	10 (76.9)	3 (23.1)	0.92 (0.16-5.43)	0.928
Major	2 (28.6)	5 (71.4)	1.65 (0.53-5.47)	0.377	4 (57.1)	3 (42.9)	3.37 (0.55-20.65)	0.188
Missing	18	8			18	8		
Operative technique, <i>n</i> (%)				0.253				0.658
Open	19 (51.4)	18 (48.6)	Reference		27 (73)	10 (27)	Reference	
Laparoscopy	14 (66.7)	7 (33.3)	0.60 (0.25-1.44)		15 (71.4)	6 (28.6)	0.79 (0.28-2.24)	
Duration of surgery, min, mean \pm SD	250 \pm 90	227 \pm 75	1.00 (0.99-1.00)	0.579	231 \pm 83	264 \pm 86	1.00 (1.00-1.01)	0.221
Hospital stay, d, mean \pm SD	10.0 \pm 3.9	9.5 \pm 2.1	0.97 (0.84-1.11)	0.637	9.8 \pm 2.8	9.9 \pm 4.3	1.00 (0.86-1.17)	0.980
Postoperative blood transfusion, <i>n</i> (%)				0.067				0.992
No	20 (50)	20 (50)	Reference		30 (75)	10 (25)	Reference	
Yes	13 (76.5)	4 (23.5)	0.37 (0.12-1.07)		11 (64.7)	6 (35.3)	0.99 (0.36-2.75)	
Missing	-	1			1	-		
Reoperation due to complications, <i>n</i> (%)				0.723				0.705
No	12 (57.1)	9 (42.9)	Reference		18 (85.7)	3 (14.3)	Reference	
Yes	2 (100)	0 (0)	0.58 (0.03-12.07)		1 (50)	1 (50)	1.53 (0.17-13.57)	

Missing	19	16		23	12		
Adjuvant therapy, <i>n</i> (%)				0.055			0.703
No	16 (72.7)	6 (27.2)	Reference	15 (68.2)	7 (31.8)	Reference	
Yes	14 (45.2)	17 (54.8)	2.52 (0.98-6.48)	23 (74.2)	8 (25.8)	1.23 (0.42-3.62)	
Missing	3	2		4	1		
Start of adj CHT, <i>n</i> (%)				0.913			0.344
< 6 wk from surgery	6 (46.2)	7 (53.8)	Reference	8 (61.5)	5 (38.6)	Reference	
≥ 6 wk from surgery	4 (44.4)	5 (55.6)	1.07 (0.33-3.43)	8 (88.9)	1 (11.1)	0.35 (0.04-1.04)	
Missing	23	13		26	10		

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Adj CHT: Adjuvant chemotherapy.

Table 10 Pathological-related potential prognostic factors for liver and lung recurrence

	Recurrence, <i>n</i> = 58							
	Liver				Lung			
	No, <i>n</i> = 33 (55.0%)	Yes, <i>n</i> = 25 (41.7%)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 42 (70.0%)	Yes, <i>n</i> = 16 (26.7%)	HR (95%CI)	<i>P</i> value
Major tumor diameter, mm, mean ± SD	55.71	42.74	0.99 (0.98-1.01)	0.368	29.09	30.01	0.99 (0.97-1.01)	0.326
Pathological T stage ¹ , <i>n</i> (%)								
1	1 (50)	1 (50)	Reference		1 (50)	1 (50)	Reference	
2	6 (75)	2 (25)	0.68 (0.06-7.50)	0.752	6 (75)	2 (25)	0.77 (0.07-8.58)	0.835
3	25 (55.6)	20 (44.4)	1.66 (0.22-12.44)	0.623	33 (73.3)	12 (26.7)	1.52 (0.19-12.45)	0.695
4	1 (50)	1 (50)	2.18 (0.13-35.75)	0.585	1 (50)	1 (50)	4.28 (0.24-76.14)	0.981
Missing	-	-			1	-		
Pathological N stage ¹ , <i>n</i> (%)								
0	17 (65.4)	9 (34.6)	Reference		18 (69.2)	8 (30.8)	Reference	
1	9 (64.3)	5 (35.7)	1.75 (0.55-5.53)	0.341	10 (71.4)	4 (28.6)	2.31 (0.60-8.88)	0.222
2	7 (41.2)	10 (58.8)	3.48 (1.31-9.27)	0.013	13 (76.5)	4 (23.5)	2.17 (0.57-8.51)	0.264
Missing	-	1			1	-		
Pathological M stage ¹ , <i>n</i> (%)				0.321				0.092
0	29 (58)	21 (42)	Reference		37 (74)	13 (26)	Reference	
1	4 (50)	4 (50)	1.74 (0.58-5.22)		5 (62.5)	3 (37.5)	3.13 (0.83-11.79)	
AJCC stage, <i>n</i> (%)								
1	7 (77.8)	2 (22.2)	Reference		6 (66.7)	3 (33.3)	Reference	
2	10 (62.5)	6 (37.5)	2.12 (0.43-10.51)	0.359	11 (68.7)	5 (31.3)	1.45 (0.33-6.33)	0.623
3	12 (48)	13 (52)	5.09 (1.10-23.52)	0.037	20 (80)	5 (20)	2.11 (0.42-10.47)	0.361
4	4 (50)	4 (50)	5.57 (0.96-32.24)	0.055	5 (62.5)	3 (37.5)	3.06 (0.85-30.09)	0.075

Retrieved LN, <i>n</i> (%)				0.803			0.961
< 12	6 (54.5)	5 (45.5)	Reference		8 (72.7)	3 (27.3)	Reference
≥ 12	26 (59.1)	18 (40.9)	0.90 (0.38-2.12)		31 (70.5)	13 (29.5)	0.97 (0.34-2.82)
Missing	1	2			3	-	
LN ratio, mean ± SD	22 ± 18	28 ± 20	4.21 (0.79-22.42)	0.092	27 ± 21	18 ± 8	1.07 (0.96-18.11)
Colloid component, <i>n</i> (%)				0.367			0.200
No	6 (46.2)	7 (53.8)	Reference		8 (61.5)	5 (38.5)	Reference
Yes	11 (73.3)	4 (26.7)	0.56 (0.16-1.98)		14 (93.3)	1 (6.7)	0.24 (0.03-2.12)
Missing	16	14			20	10	

¹According to the tumor node metastasis staging system. HR: Hazard ratio; CI: Confidential intervals; AJCC: American Joint Committee on Cancer; LN: Lymph nodes.

Table 11 Demographic and patient-related preoperative potential prognostic factors for local and peritoneal recurrence

	Recurrence, <i>n</i> = 58							
	Peritoneal				Local			
	No, <i>n</i> = 51 (87.9%)	Yes, <i>n</i> = 7 (12.1%)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 41 (70.7%)	Yes, <i>n</i> = 17 (29.3%)	HR (95%CI)	<i>P</i> value
Age, yr, mean ± SD	67.6 ± 11.9	66.3 ± 14.9	0.98 (0.92-1.04)	0.489	68.6 ± 11.3	67.5 ± 14.2	0.98 (0.95-1.02)	0.345
Gender, <i>n</i> (%)				0.434				0.862
Male	27 (93.1)	2 (6.9)	Reference		21 (72.4)	8 (27.6)	Reference	
Female	24 (82.8)	5 (17.2)	1.97 (0.36-10.77)		20 (69)	9 (31)	0.91 (0.32-2.61)	
Preop Hb, g/dL, mean ± SD	11.7 ± 2.3	11.1 ± 2.7	0.91 (0.55-1.50)	0.712	11.9 ± 2.2	9.9 ± 1.9	0.71 (0.38-1.31)	0.273
Preop glycemia, g/dL, mean ± SD	1.08 ± 0.32	1.08 ± 0.41	2.42 (0.05-123.6)	0.659	1.12 ± 0.33	0.82 ± 0.16	-	0.210
Preop total proteins, g/dL, mean ± SD	7.0 ± 0.7	6.5 ± 1.1	0.17 (0.02-1.23)	0.079	6.9 ± 0.9	7.0 ± 0.4	0.60 (0.02-14.06)	0.750
Preop CEA, <i>n</i> (%)				0.727				0.860
< 5 ng/mL	11 (84.6)	2 (15.4)	Reference		12 (92.3)	1 (7.7)	Reference	
≥ 5 ng/mL	6 (85.7)	1 (14.3)	0.52 (0.01-21.28)		5 (71.4)	2 (28.6)	1.32 (0.06-29.55)	
Missing	34	4			24	14		
BMI, mean ± SD	26.7 ± 4.5	30.7 ± 7.2	1.15 (0.91-1.44)	0.238	27.4 ± 5.1	26.0 ± 3.6	0.95 (0.81-1.11)	0.510
ASA, <i>n</i> (%)								
1	4 (80)	1 (20)	Reference		4 (80)	1 (20)	Reference	
2	17 (89.5)	2 (10.5)	0.25 (0.02-2.83)	0.264	15 (78.9)	4 (21.1)	0.42 (0.06-3.18)	0.401
3	18 (85.7)	3 (14.3)	0.19 (0.02-2.14)	0.178	14 (66.7)	7 (33.3)	0.35 (0.05-2.61)	0.307
4	3 (100)	0 (0)	0.47 (0.01-23.31)	0.707	1 (33.3)	2 (66.7)	2.32 (0.24-21.92)	0.464
Missing	9	1			7	3		

Presentation with occlusion, <i>n</i> (%)				0.674				0.962
No	7 (87.5)	1 (12.5)	Reference		6 (75)	2 (25)	Reference	
Yes	11 (84.6)	2 (15.4)	1.67 (0.15-18.56)		12 (92.3)	1 (7.7)	0.93 (0.06-15.21)	
Missing	33	4			23	14		
Tumour site, <i>n</i> (%)								
Right colon	14 (87.5)	2 (12.5)	Reference		9 (56.3)	7 (43.7)	Reference	
Left colon	24 (92.3)	2 (7.7)	0.80 (0.11-5.70)	0.825	19 (73.1)	7 (26.9)	0.79 (0.27-2.30)	0.671
Rectum	13 (81.2)	3 (18.8)	1.36 (0.23-8.17)	0.735	13 (81.3)	3 (18.7)	0.44 (0.11-1.69)	0.232

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Preop: Preoperative value; Hb: Haemoglobin; CEA: Carcinoembryonic antigen; BMI: Body mass index; ASA: American Society of Anaesthesiologists Score.

Table 12 Treatment-related potential prognostic factors for local and peritoneal recurrence

	Recurrence, <i>n</i> = 58							
	Peritoneal				Local			
	No, <i>n</i> = 51 (87.9%)	Yes, <i>n</i> = 7 (12.1%)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 41 (70.7)	Yes, <i>n</i> = 17 (29.3)	HR (95%CI)	<i>P</i> value
Neoadjuvant therapy, <i>n</i> (%)				0.569				0.475
No	23 (82.1)	5 (17.9)	Reference		23 (81.1)	5 (17.9)	Reference	
Yes	2 (100)	0 (0)	2.71 (0.09-84.27)		2 (100)	0 (0)	3.88 (0.09-160.22)	
Missing	26	2			16	12		
Surgery, <i>n</i> (%)								
Right emicolectomy	10 (83.3)	2 (16.7)	Reference		6 (50)	6 (50)	Reference	
Extended right emicolectomy	3 (100)	0 (0)	0.23 (0.01-11.90)	0.468	2 (66.7)	1 (33.3)	0.20 (0.02-1.68)	0.140
Intermediate colectomy	4 (100)	0 (0)	1.20 (0.03-47.50)	0.923	4 (100)	0 (0)	0.35 (0.01-8.18)	0.511
AR/Hartmann's procedure	23 (92)	2 (8)	0.36 (0.04-3.04)	0.350	17 (68)	8 (32)	0.41 (0.13-1.29)	0.127
Low Anterior resection/Miles	8 (80)	2 (20)	0.68 (0.07-6.27)	0.731	9 (90)	1 (10)	0.15 (0.02-1.07)	0.059
Total/Sub-total colectomy	2 (66.7)	1 (33.3)	2.99 (0.25-35.10)	0.383	2 (66.7)	1 (33.3)	0.98 (0.14-6.95)	0.981
Segmental resection	1 (100)	0 (0)	-	-	1 (100)	0 (0)	-	-
Associated procedure, <i>n</i> (%)								
No	11 (91.7)	1 (8.3)	Reference		11 (91.7)	1 (8.3)	Reference	
Minor	11 (84.6)	2 (15.4)	1.16 (0.10-14.11)	0.905	7 (53.8)	6 (46.2)	2.41 (0.33-17.37)	0.384
Major	7 (100)	0 (0)	0.61 (0.01-31.26)	0.808	5 (71.4)	2 (28.6)	3.26 (0.36-29.71)	0.295
Missing	22	4			18	8		
Operative technique, <i>n</i> (%)				0.128				0.368
Open	35 (94.6)	2 (5.4)	Reference		25 (67.6)	12 (32.4)	Reference	
Laparoscopy	16 (76.2)	5 (23.8)	3.64 (0.69-		16 (76.2)	5 (23.8)	0.61 (0.21-1.77)	

			19.14)					
Duration of surgery, min, mean \pm SD	239 \pm 85	249 \pm 87	1.00 (0.99-1.01)	0.869	244 \pm 81	232 \pm 93	1.00 (0.99-1.01)	0.934
Hospital stay, d, mean \pm SD	9.8 \pm 3.2	10.0 \pm 4.1	0.98 (0.76-1.27)	0.907	9.4 \pm 3.3	10.7 \pm 3.1	1.09 (0.96-1.23)	0.181
Postoperative blood transfusion, <i>n</i> (%)				0.272				0.518
No	37 (92.5)	3 (7.5)	Reference		30 (75)	10 (25)	Reference	
Yes	13 (76.5)	4 (23.5)	2.32 (0.52-10.38)		10 (58.8)	7 (41.2)	1.39 (0.51-3.74)	
Missing	1	-			1	-		
Reoperation due to complications, <i>n</i> (%)				0.344				0.182
No	17 (81)	4 (19)	Reference		18 (75)	6 (25)	Reference	
Yes	1 (50)	1 (50)	3.00 (0.31-29.24)		1 (50)	1 (50)	4.35 (0.50-37.59)	
Missing	33	2			22	10		
Adjuvant therapy, <i>n</i> (%)				0.481				0.852
No	20 (90.9)	2 (9.1)	Reference		14 (63.6)	8 (36.4)	Reference	
Yes	28 (90.3)	3 (9.7)	2.26 (0.23-21.77)		23 (74.2)	8 (25.8)	1.11 (0.38-3.21)	
Missing	3	2			4	1		
Start of adj chemotherapy, <i>n</i> (%)				0.648				0.953
< 6 wk from surgery	12 (92.3)	1 (7.7)	Reference		9 (69.2)	4 (30.8)	Reference	
\geq 6 wk from surgery	8 (88.8)	1 (11.1)	1.91 (0.12-30.85)		7 (77.8)	2 (22.2)	0.95 (0.18-5.13)	
Missing	31	5			25	1		

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Adj: Adjuvant.

Table 13 Pathological-related potential prognostic factors for local and peritoneal recurrence

	Recurrence, <i>n</i> = 58							
	Peritoneal				Local			
	No, <i>n</i> = 51 (87.9)	Yes, <i>n</i> = 7 (12.1)	HR (95%CI)	<i>P</i> value	No, <i>n</i> = 41 (70.7)	Yes, <i>n</i> = 17 (29.3)	HR (95%CI)	<i>P</i> value
Major tumor diameter, mm, mean \pm SD	46.2 \pm 22.4	64.0 \pm 35.1	1.02 (0.99-1.05)	0.062	44.2 \pm 19	55.8 \pm 31.9	1.01 (0.99-1.03)	0.107
Pathological T stage ¹ , <i>n</i> (%)								
1	2 (100)	0 (0)	Reference		2 (100)	0 (0)	Reference	
2	7 (87.5)	1 (12.5)	1.41 (0.03-62.92)	0.858	4 (50)	4 (50)	4.91 (0.19-124)	0.335
3	39 (86.7)	6 (13.3)	3.8 (0.05-270.74)	0.538	33 (73.3)	12 (23.7)	6.29 (0.22-177)	0.281
4	2 (100)	0 (0)	7.03 (0.04-1358)	0.468	1 (50)	1 (50)	21.47 (0.51-897)	0.107
Missing	1	-			1	-		
Pathological N stage ¹ , <i>n</i> (%)				0.196				
0	25 (96.2)	1 (3.8)	Reference		17 (65.4)	9 (34.6)	Reference	
1	11 (78.6)	3 (21.4)	14.5 (0.52-	0.115	8 (57.1)	6 (42.9)	2.41 (0.76-	0.135

			405.2)				7.65)	
2	14 (82.4)	3 (17.6)	15.4 (0.55-428)	0.107	15 (88.2)	2 (11.8)	0.88 (0.19-4.11)	0.874
Missing	1	-			1	-		
Pathological M stage ¹ , n (%)				0.546				0.032
0	44 (88)	6 (12)	Reference		37 (74)	13 (26)	Reference	
1	7 (87.5)	1 (12.5)	1.84 (0.25-13.22)		4 (50)	4 (50)	3.57 (1.12-11.40)	
AJCC Stage, n (%)								
1	8 (88.9)	1 (11.1)	Reference		5 (55.6)	4 (44.4)	Reference	
2	16 (100)	0 (0)	0.78 (0.01-73.61)	0.916	12 (75)	4 (25)	1.45 (0.28-7.51)	0.659
3	20 (80)	5 (20)	6.16 (0.21-178)	0.290	20 (80)	5 (20)	1.62 (0.31-8.37)	0.567
4	7 (87.5)	1 (12.5)	5.16 (0.12-215)	0.389	4 (50)	4 (50)	4.64 (0.84-25.69)	0.079
Retrieved LN, n (%)				1.000				0.477
< 12	10 (90.9)	1 (11.1)	Reference		8 (72.7)	3 (27.3)	Reference	
≥ 12	38 (86.4)	6 (13.6)			31 (70.5)	13 (29.5)	1.56 (0.46-5.32)	
Missing	3	-						
LN Ratio, mean ± SD)	24 ± 17	27 ± 29	12.13 (0.84-174)	0.066	29 ± 20	15 ± 16	0.64 (0.04-11.17)	0.757
Colloid component, n (%)				0.106				0.396
No	13 (100)	0 (0)	Reference		9 (69.2)	4 (30.8)	Reference	
Yes	10 (66.7)	5 (33.3)	13.77 (0.57-330)		9 (60)	6 (40)	1.77 (0.47-6.62)	
Missing	28	2			23	7		

¹According to the tumor node metastasis staging system.

HR: Hazard ratio; CI: Confidential intervals; AJCC: American Joint Committee on Cancer; LN: Lymph node.

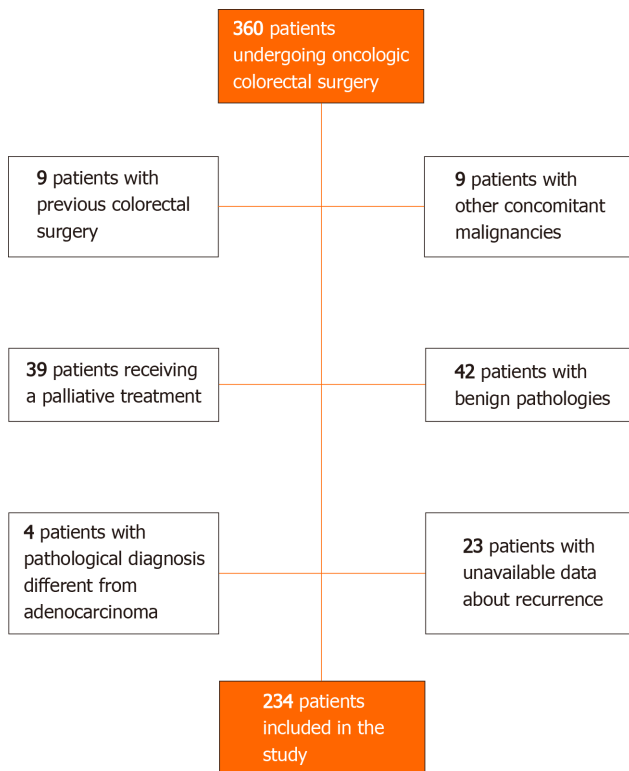


Figure 1 Inclusion flow-chart. Patients excluded from the study (white boxes) and included in the study.

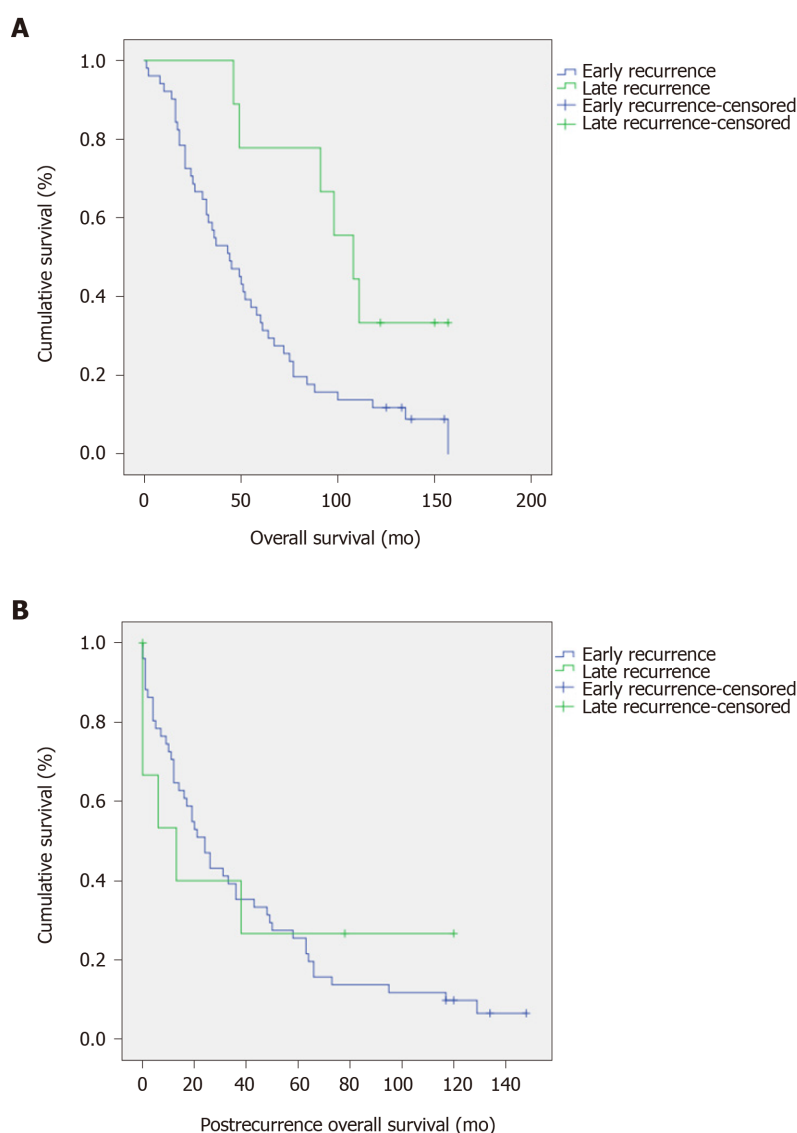


Figure 2 Kaplan-Meier curves for overall survival. A: Kaplan–Meier curve of overall survival (OS) stratified by Timing of Recurrence. Median OS for patients with recurrence < 3 years was 44 mo (95% Confidential interval 29-59 mo) vs 108 (95% Confidential interval 79-137 mo) for those with recurrence \geq 3 years ($P = 0.011$); B: Kaplan Meier curve of post recurrence OS stratified by Timing of Recurrence. Median post recurrence OS for patients with recurrence < 3 years was 24 mo (95% Confidential interval 16-32 mo) vs 13 (95% Confidential interval 0-30 mo) for those with recurrence \geq 3 years ($P = 0.991$).

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is a common malignancy with a quite high recurrence rate in spite of the curative treatments utilized. Although most of the recurrences occur within the first three years, a percentage of them appear beyond five years after surgery. Early detection of these recurrences is of paramount importance to allow further curative treatments and improve patient prognosis. However, several different follow-up programs have been proposed over the year, mostly ending in 5 years after surgery.

Research motivation

Prognostic factors for recurrence, patterns of recurrence, and different prognostic factors for early or late recurrence are rarely reported in the literature, especially in cohorts of patients with a long follow-up period. Identifications of these parameters may allow a correct allocation of the patients in specific and tailored follow-up programs to improve patient prognosis and to reduce the costs.

Research objectives

The objectives of this study are the research of prognostic factors for overall recurrence, for early or late recurrence, and the analysis of the potential patterns of

recurrence for the most frequent sites of recurrence evaluating patients with a potential minimum follow-up period of 10 years. Clinical, operative, and pathological potential prognostic factors were evaluated and significant results were found for each one of the prospected objectives. These results may help clinicians in predicting patient prognosis and in choosing more cost-effective patient surveillance strategies.

Research methods

All the consecutive patients curatively treated for colorectal adenocarcinoma from January 2006 to June 2009 were prospectively included in a database that was retrospectively reviewed. A standardized follow-up program was applied to all the patients. Several prognostic factors about the patient, the treatment used, and the pathological response were evaluated. To evaluate the association between possible prognostic factors and disease-free survival and overall survival a Cox model, Kaplan-Meier method, and log-rank test were used. To estimate possible independent prognostic factors for recurrence a multiple Cox model with a backward selection method was used. To assess the association between each possible prognostic factor and timing to recurrence (< 3 years or ≥ 3 years) a simple logistic regression model was used.

Research results

Patients with higher levels of preoperative glycemia and carcinoembryonic antigen, highest anaesthesiologists score, presenting with occlusion, receiving a complex operation performed with an open technique, after a longer hospital stay, and showing advanced tumors had a higher chance to develop recurrence. At the multivariate analysis, the independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1. Younger ages were significantly associated with an early recurrence onset. Receiving intermediate colectomies or segmental resections, having an N stage 2 or American Joint Committee on Cancer stage 3 tumors was associated with a higher risk of liver recurrence; metastatic disease at diagnosis with local recurrence; receiving neoadjuvant treatments with lung recurrence; bigger tumors and higher lymph node ratio with peritoneal recurrence (marginally significant). However, these results and, in particular, those about the early *vs* late recurrence and the pattern of recurrence should be verified in larger series.

Research conclusions

Several prognostic factors for recurrence and some specific factors for each site of recurrence have been found and should be taken into account to perform a correct allocation of the patient within tailored cost-effective follow-up programs, eventually extended beyond five years after surgery.

Research perspectives

Further studies are needed to confirm these results, possibly prospective studies. The use of the learning machine may offer interesting opportunities in this area. Finally, the analysis of the second malignancies developed during the follow-up, which is marginally mentioned in this study, may represent another potential field of research.

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Xanthogranulomatous appendicitis: A comprehensive literature review

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Abstract

BACKGROUND

Xanthogranulomatous inflammation is characterized histologically by a collection of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts.

AIM

To review the medical literature on xanthogranulomatous appendicitis (XGA).

METHODS

We present a patient with XGA and review published articles on XGA accessed via the PubMed, MEDLINE, Google Scholar, and Google databases. Keywords used were "appendix vermiformis," "appendectomy," "acute appendicitis," and "XGA." The search included articles published before May 2020, and the publication language was not restricted. The search included letters to the editor, case reports, review articles, original articles, and meeting presentations. Articles or abstracts containing adequate information about age, sex, clinical presentation, white blood cells, initial diagnosis, surgical approach, histopathological and immunohistochemical features of appendectomy specimens were included in the study.

RESULTS

A total of 29 articles involving 38 patients with XGA, were retrospectively analyzed. Twenty (52.6%) of the 38 patients, aged 3 to 78 years (median: 34; IQR:

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31) were female, and the remaining 18 (47.4%) were male. Twenty-five patients were diagnosed with acute appendicitis, ruptured appendicitis, or subacute appendicitis, and the remaining 13 patients underwent surgery for tumoral lesions of the ileocecal region. Twenty-two of the patients underwent urgent or semi-urgent surgery, and the remaining 16 patients underwent interval appendectomy.

CONCLUSION

Xanthogranulomatous inflammation rarely affects the appendix vermiformis. It is associated with significant diagnostic and therapeutic dilemmas due to its variable presentation. It is often associated with interval appendectomies, and a significant number of patients require bowel resection due to the common presentation of a tumoral lesion. XGA is usually identified retrospectively on surgical pathology and has no unique features in preoperative diagnostic studies.

Key Words: Appendix vermiformis; Acute appendicitis; Appendectomy; Interval appendectomy; Xanthogranulomatous inflammation; CD68 antibody staining

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Core Tip: Xanthogranulomatous inflammation is characterized histologically by a collection of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts. Xanthogranulomatous appendicitis (XGA) has rarely been reported to date. In this review article, we present a patient with XGA, and review data from all articles published on this rare situation. This review study shows that XGA is associated with significant diagnostic and therapeutic dilemmas due to its variable presentation. It is often associated with interval appendectomies, and a significant number of patients require bowel resection due to the common presentation of a tumoral lesion.

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INTRODUCTION

Xanthogranulomatous inflammation is a well-known form of inflammation, characterized histologically by a collection of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts^[1]. Xanthogranulomatous inflammation was first described in the urogenital system by Osterlind in 1944^[2]. Since then, it has been reported in other organs, such as the gallbladder, stomach, colon, anorectal area, endometrium, ovary, epididymis, vagina, testis, prostate, skin, urinary bladder, bone, thyroid, lung and adrenal glands, fallopian tubes, and the appendix vermiformis^[3-9].

Xanthogranulomatous appendicitis (XGA) is rarely reported in the appendix vermiformis. Some studies stated that the first XGA case was reported by Cozzuto and colleagues^[1,3]. Other studies stated that Birch and colleagues^[4,10-13] were the first to report this entity. However, according to our literature search, the first case of XGA was described by Dymock and colleagues in 1977^[14]. Its clinical significance includes the significant diagnostic challenge it causes because it can mimic clinically, radiologically, and even pathologically malignant tumors as well as other inflammatory processes of the appendix vermiformis. It is usually found retrospectively on surgical pathology and has no unique features on imaging studies, including abdominopelvic computed tomography. Little information has been written in the literature regarding this entity. Moreover, its clinical implications remain to be evaluated. In this review article, we present a case of XGA, and review data from all articles published on XGA.

MATERIALS AND METHODS

The primary aim of this study was to review the articles published in the medical literature on XGA. To achieve this objective, a literature search was conducted on PubMed, MEDLINE, Google Scholar, and Google databases using the following keywords: "Appendix vermiformis," "acute appendicitis," "XGA," "interval appendectomy," and "appendectomy." All documents published on XGA before May 2020 were reviewed. The corresponding authors of the articles with substantially large amounts of missing information were e-mailed to obtain information on their cases. As a result, articles without an accessible full-text version, those that did not provide adequate information in their abstracts, and those that did not include comprehensive information as that provided in other studies were excluded. As some enrolled articles were published in the form of a literature review, their tables were also used. The following information was collected: Reference list, publication year, paper type (full text, abstract, poster), age, sex, clinical presentation, white blood cell (WBC) count, radiological tools, surgical approach, histopathological features (giant cells, plasma cells, foamy histiocytes, CD68 stain), and follow-up. The secondary aim of this study was to present a 66-year-old woman with XGA.

RESULTS

Review of the literature

Although a total of 36 article titles^[3-38] matched as a result of the literature review conducted in accordance with the criteria specified in the methodology section, seven articles^[1,14,33-37] were excluded from the study due to the absence of demographic and clinical data of the patients. A total of 38 patients, 20 (52.6%) female and 18 (47.4%) male, aged from 3 to 78 years (median: 34; IQR: 31) were included in this study. Fifteen patients' WBC values were reported, and 13 (86.7%) of them had leukocytosis. Treatment was planned for 25 patients with a pre-diagnosis of acute appendicitis, ruptured appendicitis, or subacute appendicitis. On the other hand, treatment was planned for nine patients due to a mass in the ileocecal region. After appropriate medical treatment for a total of 16 patients, interval appendectomy was performed. Of the 29 articles, 27 were published in English, one in Japanese, and one in Spanish. The full text was obtained for 28 of the 29 articles, whereas only the abstract was available for one paper. The details of the demographic and clinical characteristics of the patients are given in Tables 1 and 2.

Case presentation

A 66-year-old female patient was admitted to our emergency unit because of right lower quadrant pain, which started 3 d prior to admission. She had a medical history of left hemiparesis secondary to cerebrovascular events, mitral valve stenosis, and atrial fibrillation. As the patient had a speech disorder, the history was taken from her husband and children who lived in the same house. Physical examination revealed significant rebound tenderness in the right lower quadrant. Biochemical analyses were as follows: WBC count 12.900/mL (4.300-10.300), platelets 337000/mL (156000-373000), neutrophils 80.7%, CRP 13.7 mg/dL (0-0.35), and international normalized ratio 1.7 (0.8-1.2). Ultrasonography revealed an edematous and aperistaltic tubular structure with a diameter of 2 cm in the right lower quadrant of the abdomen that was not compressible with external pressure. In addition, free fluid was detected around the defined structure, suggesting ruptured appendicitis. After evaluating the clinical, radiological, and biochemical blood parameters of the patient, she was diagnosed with ruptured appendicitis, and underwent surgery under emergency conditions. In view of the logistic problems with laparoscopic equipment at the time of surgery, laparotomy was performed using an infraumbilical midline incision. The exploration showed that the ileocecal region was completely surrounded by the omentum, and the sigmoid colon was attached to this defined area. After careful dissection of the omentum and sigmoid colon, a ruptured appendix with distal necrosis was observed, and the surrounding pus was then aspirated. As the stump of the appendix was very large and inflamed, appendectomy was performed after a clamp was placed at the junction with the cecum. The stump was closed with 3/0 polypropylene sutures using the transfixion suture technique. One drain was placed in the pelvis, and the operation was terminated. The pathology report was prepared as ruptured appendicitis secondary to xanthogranulomatous inflammation (Figures 1-3). Antibiotic treatment consisting of ceftriaxone and metronidazole was administered for 5 d postoperatively.

Table 1 Summary of 29 articles involving 38 patients with xanthogranulomatous appendicitis published in the medical literature between 1992 and 2019

No.	Ref.	Year	Country	Language	Article type	Article type	Age	Sex	Clinical presentation	WBC
1	Quadri <i>et al</i> ^[15]	2019	United States	English	Case series	Full text	64	M	RLQ pain + palpable mass	NA
2	Yang <i>et al</i> ^[16]	2018	South Korea	English	Congress present	Full text	69	M	NA	NA
3	Al-Zaidi <i>et al</i> ^[36]	2018	India	English	Case report	Full text	48	M	RLQ pain	16000
4	Adhikari <i>et al</i> ^[4]	2019	India	English	Case report	Full text	49	F	RLQ pain + fever	12200
5	Kaushik <i>et al</i> ^[17]	2017	India	English	Case report	Full text	47	F	Abdominal pain, vomiting, fever	14000
6	Hoabam <i>et al</i> ^[10]	2017	India	English	Case report	Full text	56	F	RLQ pain	14000
7	Mehrotra <i>et al</i> ^[18]	2017	India	English	Case report	Full text	30	F	RLQ pain	Normal
8	Laiphrakpam <i>et al</i> ^[19]	2017	India	English	Case report	Full text	36	M	RLQ Pain	Normal
9	Nam <i>et al</i> ^[20]	2016	South Korea	English	Case report	Full text	23	F	Low abdominal pain	NA
10	Cavusoglu <i>et al</i> ^[21]	2016	Turkey	English	Case report	Full text	12	M	NA	NA
							11	M	NA	NA
11	Jusoh <i>et al</i> ^[5]	2016	Malaysia	English	Case report	Full text	16	M	RLQ pain	NA
12	Thapa <i>et al</i> ^[6]	2016	Nepal	English	Case report	Full text	19	F	RLQ pain	NA
13	Singh <i>et al</i> ^[7]	2015	India	English	Case report	Full text	21	F	RLQ pain	NA
14	Altay <i>et al</i> ^[22]	2015	Turkey	English	Case report	Full text	73	F	RLQ pain	Leukocytosis
15	Chandanwale <i>et al</i> ^[11]	2015	India	English	Case report	Full text	40	F	RLQ pain	NA
16	Montazer <i>et al</i> ^[23]	2014	Iran	English	Case report	Full text	29	F	RLQ pain	13000
17	Kochhar <i>et al</i> ^[24]	2014	India	English	Case report	Full text	50	M	RLQ pain + fever	24000
18	Al-Rawabdeh <i>et al</i> ^[12]	2013	United States	English	Case report	Full text	11	M	RLQ pain	4900
19	Mado <i>et al</i> ^[25]	2013	Japan	English	Image in surgery	Full text	78	M	RLQ pain	NA
20	Martinez-Garza <i>et al</i> ^[26]	2011	Spain	Spanish	Case report	Full text	30	F	RLQ pain	13700
21	Omer <i>et al</i> ^[8]	2011	Sudan	English	Case report	Full text	49	M	RLQ pain	NA
22	Omori <i>et al</i> ^[27]	2011	Japan	Japanese	Case report	Full text	57	F	RLQ pain	NA
23	Young <i>et al</i> ^[28]	2009	United States	English	Case report	Full text	32	F	RLQ pain	22000
24	Chuang <i>et al</i> ^[29]	2005	Taiwan	English	Case report	Abstract	39	M	RLQ pain	NA
25	Guo <i>et al</i> ^[30]	2003	United States	English	Original article	Full text	4	F	NA	NA
							12	M	NA	NA
							13	M	NA	NA
							3	M	NA	NA
							9	M	NA	NA
							29	F	NA	NA
							29	F	NA	NA
							27	M	NA	NA
26	Munichor <i>et al</i> ^[3]	2000	Israel	English	Case report	Full text	37	F	RLQ pain	12000
27	McVey <i>et al</i> ^[32]	1994	United States	English	Letter	Full text	40	F	RLQ pain	12100

28	Birch <i>et al</i> ^[13]	1993	United Kingdom	English	Brief report	Full text	51	M	Perineal pain	NA
							66	F	Right flank pain	20000
29	Rogers <i>et al</i> ^[9]	1992	United Kingdom	English	Case report	Full text	56	F	RLQ pain	NA

WBC: White blood cell; RLQ: Right lower quadrant.

The patient was discharged without any postoperative complications.

DISCUSSION

Acute appendicitis is the most common acute surgical condition of the abdomen. Most of the resected appendectomy specimens have been reported to have marked cellular infiltration, predominantly by neutrophils. In contrast, the occurrence of xanthogranulomatous inflammation is extremely rare. In a 2-year study that was performed to determine the incidence of various non-neoplastic and neoplastic lesions of the appendix, only one case of this entity was identified (0.22%)^[34]. Similarly, Laishram and colleagues^[37] reported that the incidence of XGA was 0.25% in 4298 appendectomy specimens. On the other hand, Shaik and colleagues^[35] stated that the incidence of XGA among patients who underwent appendectomy was 0.64%.

Grossly, the typical findings are bright yellow or golden yellow mass-like lesions associated with abscess cavities^[1,36]. Kaushik and colleagues^[17] studied the cytological evaluation of the touch imprint preparation for intraoperative diagnosis of XGA. The smears revealed benign glandular epithelial cell groups and sheets of xanthoma cells along with multinucleate histiocytic giant cells in the background of neutrophils and mononuclear inflammatory cells. Microscopic examination of XGA usually reveals a nodular or diffuse mucosal to transmural collection of macrophages, including foamy histiocytes (xanthoma-type cells), intermixed with varying amounts of other inflammatory cells^[7].

Although the histopathological features of the xanthogranulomatous process have been defined, the exact etiopathogenesis of XGA is still unknown. Proposed theories include defective lipid transport, immunologic disturbances of leukocyte and macrophage chemotaxis, infection by lowvirulence organisms, such as *Proteus* and *Escherichia* species, and lymphatic obstruction^[7,13,17,25,31,34].

Cozzutto and colleagues^[1] performed an extensive review of all cases from various organs. In that study, the authors noted that the xanthogranulomatous process is usually associated with inflammation, hemorrhage, and necrosis. They suggested that hemorrhage may play a major role in the development of foamy macrophages, postulating that the ingested erythrocytes and platelets at the bleeding site overwhelm the lysosomal system of the macrophages, causing deposition of phospholipids, which results in a foamy appearance of the macrophages. Other authors have suggested that there are several factors that may precipitate XGA, including lumen obstruction, suppurative inflammation, hemorrhage, and local tissue hypoxia, with no single pathophysiological factor that can possibly cause XGA^[5,30,37].

Other lesions with granulomatous inflammation and foam cells can be seen in the differential diagnoses, such as Crohn's disease and malakoplakia. The absence of transmural involvement by granulomas can exclude Crohn's disease, and the absence of Michaelis Gutmann bodies can rule out malakoplakia. Furthermore, it can be very challenging to differentiate XGA from an infiltrative cancer because XGA might present as a mass lesion with extension of fibrosis and inflammation to the surrounding tissues, mimicking an infiltrative cancer^[4,7,11,24,30,36].

Most XGA cases reported were in the adult age group, with the median age of presentation in this review being 34 years. The mean age (35.9 years) identified in this review was lower than the previously reported mean age of 47.9 years (83%, 21-78 years)^[36]. This appears to be caused by the recent, more XGA pediatric reports published. However, this disease remains more common in adults, with only 6 out of 38 patients in this review belonging to the pediatric age group (15.8%). The oldest patient diagnosed with XGA in this review was 78 years old, who presented with a mucocoele of the appendix^[25], and the youngest affected patient was 3 years old, diagnosed with interval appendectomy^[30]. No sex predilection was reported for XGA^[34,36], and in this review, there was no significant difference in the number of cases reported between females (52.6%) and males (47.4%).

Table 2 Introduction to 29 articles published in the medical literature from 1992 to 2019 involving 38 xanthogranulomatous appendicitis patients

No.	Preoperative Diagnosis	Surgical approach	Giant Cells	Plasma Cells	Eosinophils	CD68 Stain	Foamy Histiocytes
1	Mass	Right hemicolectomy	NA	NA	NA	NA	NA
2	Perforated App	Appendectomy (Interval)	NA	NA	NA	NA	NA
3	Perforated App	Right hemicolectomy	Yes	Yes	NA	Yes	Yes
4	AAp	Appendectomy	Yes	Yes	Yes	NA	Yes
5	Neoplastic mass	Limited colon resection	Yes	Yes	Yes	NA	Yes
6	AAp	Appendectomy	Yes	Yes	NA	NA	Yes
7	AAp	Appendectomy	Yes	NA	NA	NA	Yes
8	AAp	Appendectomy	Yes	Yes	NA	NA	Yes
9	Chronic Ap or mucocele	Appendectomy	NA	NA	NA	Yes	Yes
10	Mass	Appendectomy (Interval)	Yes	Yes	NA	Yes	NA
	AAp	Appendectomy (Interval)	Yes	Yes	NA	NA	NA
11	AAp	Appendectomy (Interval)	Yes	NA	NA	NA	Yes
12	AAp	Appendectomy (Interval)	Yes	Yes	Yes	NA	Yes
13	AAp	Appendectomy	Yes	Yes	Yes	Yes	Yes
14	Mass	Appendectomy	NA	NA	NA	Yes	NA
15	Mass	Right hemicolectomy	Yes	Yes	NA	NA	Yes
16	AAp	Appendectomy	Yes	NA	NA	Yes	Yes
17	AAp	Right hemicolectomy + ileostomy	Yes	Yes	NA	NA	Yes
18	AAp	Appendectomy	Yes	Yes	NA	NA	NA
19	Mucocele	Ileocecal resection	NA	NA	NA	NA	Yes
20	AAp	Appendectomy	NA	NA	NA	NA	Yes
21	Mass	Appendectomy (Interval)	Yes	Yes	NA	NA	NA
22	Mass	Right hemicolectomy + right nephrectomy + oophorectomy	NA	Yes	NA	NA	Yes
23	AAp	Appendectomy (Interval)	NA	NA	NA	NA	NA
24	Colitis of cecum	Right hemicolectomy	NA	NA	Yes	NA	NA
25	AAp	Appendectomy (Interval)	Yes	NA	NA	NA	NA
	AAp	Appendectomy (Interval)	No	NA	NA	NA	NA
	AAp	Appendectomy (Interval)	No	NA	NA	NA	NA
	AAp	Appendectomy (Interval)	No	NA	NA	NA	NA
	AAp	Appendectomy (Interval)	Yes	NA	NA	NA	NA
	AAp	Appendectomy (Interval)	No	NA	NA	NA	NA
	Subacute AAp.	Appendectomy (Interval)	No	NA	NA	NA	NA
	Subacute AAp.	Appendectomy (Interval)	Yes	NA	NA	NA	NA
26	AAp	Appendectomy	NA	Yes	Yes	Yes	Yes
27	Mass	Appendectomy (Interval)	NA	Yes	NA	NA	Yes
28	AAp	Appendectomy	NA	Yes	NA	NA	Yes
	Mass	Appendectomy	NA	Yes	NA	NA	Yes
29	Fistula	Appendectomy	NA	NA	NA	NA	NA

Patients with XGA usually present with right lower abdominal quadrant pain, fever, nausea, and vomiting. However, the clinical presentation of XGA is variable, which seems to vary with the spread of the disease. While some authors suggested an association of the xanthogranulomatous response with long-standing inflammation of the appendix and formation of the appendiceal mass^[34], others have reported cases of XGA with typical signs and symptoms of acute appendicitis^[31]. In this review, 22 of the 38 reported cases were diagnosed with acute appendicitis (57.9%), two of which were found to be ruptured.

XGA showed a higher incidence in interval appendectomies^[6,16,20]. Guo *et al*^[30] reviewed the histopathology of all interval appendectomy specimens within a four-year period, and compared them with a control group of patients who had acute appendicitis and underwent routine acute appendectomy. The study revealed that xanthogranulomatous inflammation is common in interval appendectomy specimens. They represented 36% of the interval appendectomy cases in their series, but they did not occur in the emergency appendectomy group.

Due to the destructive nature of the disease, XGA can occasionally present with a mass lesion that can mimic locally advanced cancer, but it has a benign course and can be cured surgically. Altay and colleagues reported uterine and right adrenal involvement, presenting as a complicated pelvic abscess on radiological imaging^[22]. In this review, 13 of the 38 patients had a mass (34%), and two patients had a mucocele. Eight patients required bowel resection ranging from limited ileocecal resection to formal right hemicolectomy. Of the 38 patients, 30 underwent appendectomy, 16 of which as an interval appendectomy.

The variable presentation of XGA requires the consideration of acute appendicitis, a mucinous epithelial neoplasm, a non-mucinous epithelial neoplasm, and a range of chronic infectious diseases. Atypical appendiceal pathologies ranging from neoplasms to inflammatory conditions can mimic and even cause a superimposed acute appendicitis, making them difficult to differentiate from typical inflammation. Contrast-enhanced multidetector computed tomography is the gold standard and the most cost-effective diagnostic test for appendicitis in non-pregnant adults with right lower quadrant pain^[15,38,39]. However, radiological findings are non-specific, and XGA is usually found retrospectively on surgical pathology and has no unique features on abdominopelvic contrast-enhanced computed tomography^[15].

CONCLUSION

In summary, xanthogranulomatous inflammation is an unusual, destructive, chronic inflammatory process that involves various organs. While it rarely affects the appendix vermiformis, it is associated with significant diagnostic and therapeutic dilemmas due to its variable presentation. It is more often associated with interval appendectomies, and a significant number of patients require bowel resection due to the common presentation of a mass lesion. XGA is usually identified retrospectively on pathological examination of the appendiceal specimen, and has no unique features on imaging studies including contrast-enhanced computed tomography.

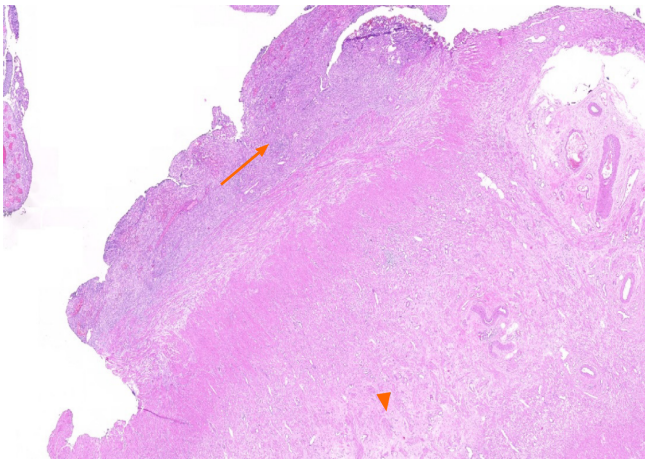


Figure 1 Fibrous obliteration of appendix vermiformis (arrow head), acute and chronic inflammatory cell infiltration (arrow) within the appendix wall and subserosal fatty tissue (HE \times 10).

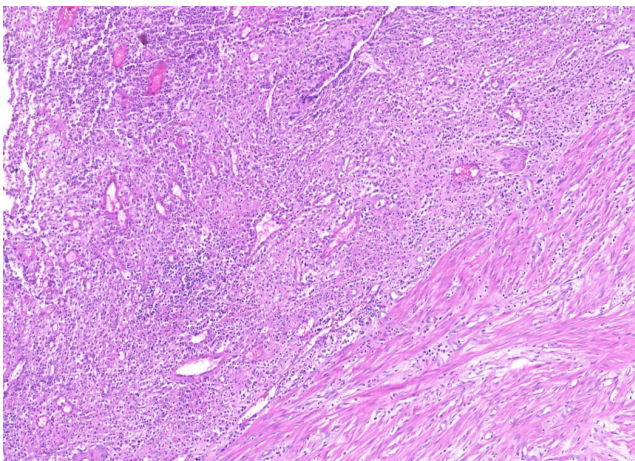


Figure 2 Xanthogranulomatous inflammation (a mixture of macrophages, lymphocytes, plasma cells, and neutrophils) (HE \times 50).

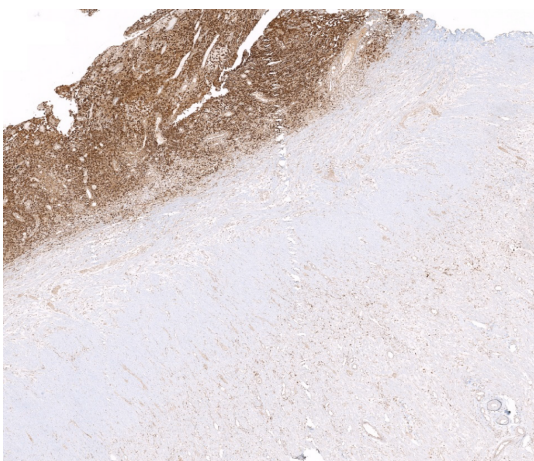


Figure 3 Macrophages showing positive staining for CD68 antibody.

ARTICLE HIGHLIGHTS

Research background

Xanthogranulomatous inflammation is characterized histologically by a collection of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and often multinucleated giant cells with or without cholesterol clefts

Research motivation

Although a limited number of case reports on xanthogranulomatous appendicitis (XGA) have been published to date, no systematic literature analysis has been conducted.

Research objectives

The main objective of this study was to review the articles published in the medical literature on XGA. A secondary objective of this study was to present the medical history of a female patient diagnosed with XGA.

Research methods

A systematic literature search was conducted on PubMed, Medline, Google Scholar, and Google databases using the following keywords: Appendix vermiformis, acute appendicitis, XGA, interval appendectomy, and appendectomy. The search included articles published before May 2020, and the publication language was not restricted.

Research results

A total of 29 articles involving 38 patients with XGA, were retrospectively analyzed. A total of 38 patients, 20 (52.6%) female and 18 (47.4%) male, aged from 3 to 78 years were included in this study. Fifteen patients' WBC values were reported, and 13 (86.7%) of them had leukocytosis. Twenty-five patients were diagnosed with acute appendicitis, ruptured appendicitis, or subacute appendicitis, and the remaining 13 patients underwent surgery for tumoral lesions of the ileocecal region. Twenty-two of the patients underwent urgent or semi-urgent surgery, and the remaining 16 patients underwent interval appendectomy.

Research conclusions

Xanthogranulomatous inflammation rarely affects the appendix vermiformis. It is associated with significant diagnostic and therapeutic dilemmas due to its variable presentation. It is often associated with interval appendectomies, and a significant number of patients require bowel resection due to the common presentation of a tumoral lesion.

Research perspectives

A review of the literature and our experience of appendiceal diseases suggest that XGA is usually identified after histopathological examination of the appendectomy specimen and XGA has no unique features in preoperative diagnostic studies. Therefore, the most important factors regarding the preliminary diagnosis of XGA are surgeon's experience, clinical suspicion and intraoperative findings.

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Multidetector computed tomography three-dimensional and multiplanar reconstruction diagnosis of a rare cause of gastrointestinal bleeding: A case report

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Abstract

BACKGROUND

Anastomosis of the testicular vein with the superior mesenteric vein rarely causes severe gastrointestinal bleeding. To date, there have been few studies describing its appearance on medical imaging. Here, we present multidetector computed tomography three-dimensional and multiplanar reconstruction (MPR) images of a typical digital subtraction angiography showing proven ectopic bleeding and provide the first review of the image performance.

CASE SUMMARY

A 68-year-old man who had been rushed to the hospital with a four-day history of melena and fainting underwent multiple esophagogastroduodenoscopy procedures that failed to identify the source of bleeding. We used MPR combined with three-dimensional reconstruction images, and found that the testicular vein had anastomosed with the superior mesenteric vein, and they clustered together in the jejunal vessel wall, which caused severe gastrointestinal bleeding. Digital subtraction angiography confirmed the location of bleeding. After transfusion and embolization therapy, the patient's condition improved.

CONCLUSION

Computed tomography-MPR combined with three-dimensional images offers significant value in the localization and qualitative assessment of rare gastrointestinal hemorrhage. The features of multiphase spiral scanning can improve the accuracy of the diagnosis.

Checklist (2016).

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Core Tip: We report a case of anastomosis of the testicular vein with the superior mesenteric vein that caused severe gastrointestinal bleeding. We used multidetector computed tomography three-dimensional and multiplanar reconstruction, and found that the testicular vein had anastomosed with the superior mesenteric vein, and gathered together in the jejunal vessel wall. Digital subtraction angiography confirmed the location of bleeding. After vascular intervention, the patient's symptoms significantly improved.

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INTRODUCTION

Varices can develop anywhere in the upper or lower gastrointestinal tract. They may develop at any site of portal hypertension, but they are most commonly located in the esophagus and gastric fundus^[1]. In patients with portal hypertension, the absence of hemorrhage from the esophageal and gastric fundal veins does not rule out the presence of varicose veins in other areas, which may lead to gastrointestinal bleeding. Statistically, ectopic varices account for approximately 5% of all variceal bleeding, of which 17% occurs in the duodenum^[2,3]. Colonic varices are extremely rare, and the diagnosis and treatment strategies have not been standardized^[2]. However, traditional endoscopy cannot reach the distal portion of the duodenum, and angiography sometimes fails to show duodenal varicose veins^[4]. Recently, there have been reports of multidetector computed tomography (CT) with multiplanar reconstruction (MPR) for the diagnosis and therapeutic management of duodenal varices^[5,6]. Our case suggests the usefulness of multidetector CT with MPR combined with three-dimensional (3D) images for the diagnosis and therapeutic management of duodenal varices.

CASE PRESENTATION

Chief complaints

A 68-year-old man with liver cancer due to liver cirrhosis was referred to our hospital on March 3, 2020, with persistent melena for 4 d.

History of present illness

The patient's symptoms started a month ago with abdominal pain and weakness.

History of past illness

His significant past history included liver cancer, colon cancer, diabetes, hypertension, and benign prostatic hyperplasia.

Personal and family history

The patient's family had no previous medical history.

Physical examination

The patient's temperature was 36.5°C, heart rate was 92 bpm, respiratory rate was 16 breaths/min, blood pressure was 120/70 mmHg and oxygen saturation in room air

was 98%. No other pathological signs were observed. Physical examination revealed abdominal tenderness. Our clinical consideration was gastrointestinal bleeding.

Laboratory examinations

His hemoglobin level was 56 g/L (normal range 120-160 g/L).

Imaging examinations

He underwent multiple esophagogastroduodenoscopy (EGD) procedures that failed to identify the source of bleeding. For the initial diagnosis, we believed that decompensated cirrhosis led to gastrointestinal bleeding caused by esophageal and gastric varices. However, EGD revealed no bleeding from the esophagus fundus ventricularis varication or duodenal ulcer (Figure 1). To determine the location of bleeding, an abdominal CT examination was conducted using a multidetector row CT. CT (scan and enhancement) revealed numerous enlarged branches of the blood vessels of the jejunum and tortuous irregular vessels relative to the prior physical examination on May 29, 2019 (Figure 2). Imaging of the stomach and the bottom of the pelvis showed varices but no bleeding. Postoperative changes indicated liver cancer and sigmoid colon cancer, liver cirrhosis, splenomegaly, and ascites. Follow-up CT and routine blood reexamination and routine stool examination showed no complications, such as bleeding, between May 2019 and March 2020. The MPR image clearly showed a varicocele on the left side and the venae testicularis as a tangled mass of vessels that formed varicose veins, which anastomosed with the superior mesenteric vein. It also showed local bleeding. On CT, it presented as a high-density hemorrhage and a hematoma (orange arrows in Figure 3). Axial, coronal, and sagittal volume rendering CT images, including maximum intensity projection (MIP), with contrast showed venous anastomosis, varicose veins, and a tortuous collection of irregular vessels (Figure 3). To further confirm the diagnosis, we conducted CT of the arterial-phase, portal-phase, equilibrium-phase, and delayed-phase scanning, and then performed dynamic observation of the changes in jejunal bleeding. The results showed vascular mass enlargement during the delayed phase (Figure 4). Portal angiography indicated that the portal, splenic, and superior mesenteric veins were twisted and dilated. We not only observed spermatic veins but also noted connections with the superior mesenteric vein, and they formed an anastomosis. Contrast media had also leaked into the intestine. An inferior vena digital subtraction angiography (DSA) also showed that the superior mesenteric vein and the spermatic vein had formed a varicose venous anastomosis (Figure 5A and C).

FINAL DIAGNOSIS

The final diagnosis in the present case was chronic portal hypertension leading to the development of collateral circulation, which was manifested as anastomosis of the testicular vein with the superior mesenteric vein that gathered together in the jejunal vessel wall, causing gastrointestinal bleeding.

TREATMENT

The patient was treated conservatively by stopping the bleeding and omeprazole administration during management. After transfusion and infusion with a hemostatic agent, the patient's condition did not improve, and his red blood cell count decreased and hemoglobin decreased to 51 g/L. Finally, we decided that the patient should undergo embolization. Seldinger's technique was used to puncture the femoral vein and percutaneous hepatic portal vein for DSA. A varicocele was observed on the left side and the venae testicularis was a tangled mass of vessels that formed varicose veins, which anastomosed with the superior mesenteric vein. A spring coil was inserted to embolize the communication branch, and imaging was performed again. DSA revealed that the communicating branches had disappeared, and there was no contrast agent extravasation after this treatment (Figure 5B and D).

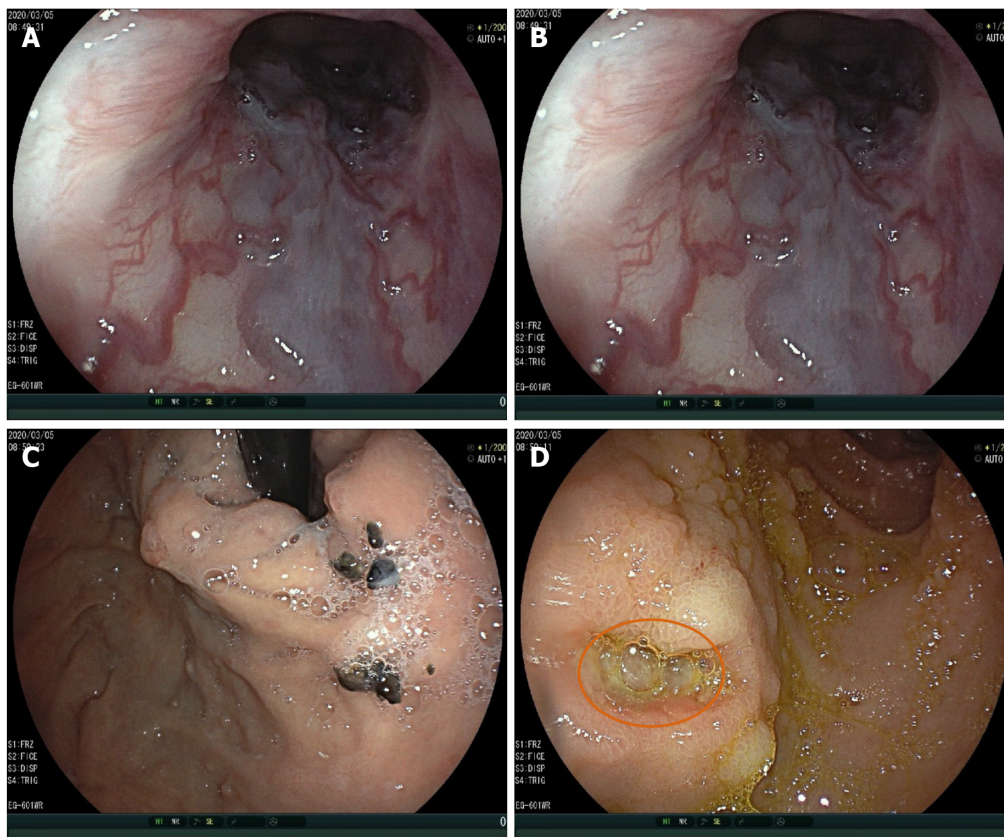


Figure 1 An esophagogastroduodenoscopy was performed to rule out esophageal and gastric variceal bleeding. A and B: Esophageal varices; C: Gastric varices; and D: No hemorrhage from the superficial ulcer (orange circle).

OUTCOME AND FOLLOW-UP

No gastrointestinal bleeding was observed after embolization. The patient agreed to undergo routine blood examination. After transfusion and embolization therapy, the patient's condition improved, and his hemoglobin level reached 78 g/L; he was then discharged (Figure 6). We performed follow-up CT imaging, blood and stool sample tests, liver function tests, and determination of hemoglobin level, and no bleeding was observed at the embolized site, as indicated by tests at 1, 2, and 3 mo after surgery (Table 1). We suggested the use of a transjugular intrahepatic portosystemic shunt, which not only reduces the recurrence rate of gastrointestinal bleeding due to the high-pressure portal vein but also improves liver function. The patient refused the operation and received conservative treatment only in the internal medicine department. Perhaps the principal reasons why the patient declined to undergo the operation were because the surgery involved a risk of damage to liver function, and involved other risks, his older age, and the considerable financial cost.

DISCUSSION

Gastrointestinal varices are abnormally dilated submucosal veins in the digestive tract. They can be caused by portal hypertension, and they can cause life-threatening bleeding^[7]. Ectopic varices, which are varices other than esophageal and gastric varices, are thought to be relatively rare. Approximately 5% of all varices associated with gastrointestinal bleeding are ectopic varices^[8]. However, the ectopic malformations associated with varices vary greatly in size and location. Rapid, abundant blood flow makes it difficult to diagnose them definitively. In this case, we used multidetector CT with MPR combined with 3D image delineation to localize the bleeding point and provide interventional embolization. Eventually, it was clear that chronic portal hypertension may have led to the development of collateral circulation, which was manifested as anastomosis of the testicular vein with the superior mesenteric vein, and they gathered together in the jejunal vessel wall, causing

Table 1 Hemoglobin changes during hospitalization

Date	Hemoglobin (g/L)	Red blood cells ($10^{12}/L$)	Hematocrit (%)
March 4, 2020	56.0	2.05	17.10
March 5, 2020	51.0	1.99	16.00
March 6, 2020	61.0	2.39	20.00
March 6, 2020	57.0	2.12	17.30
March 7, 2020	70.0	2.63	21.80
March 9, 2020	66.0	2.4	20.70
March 10, 2020	74.0	2.71	23.30

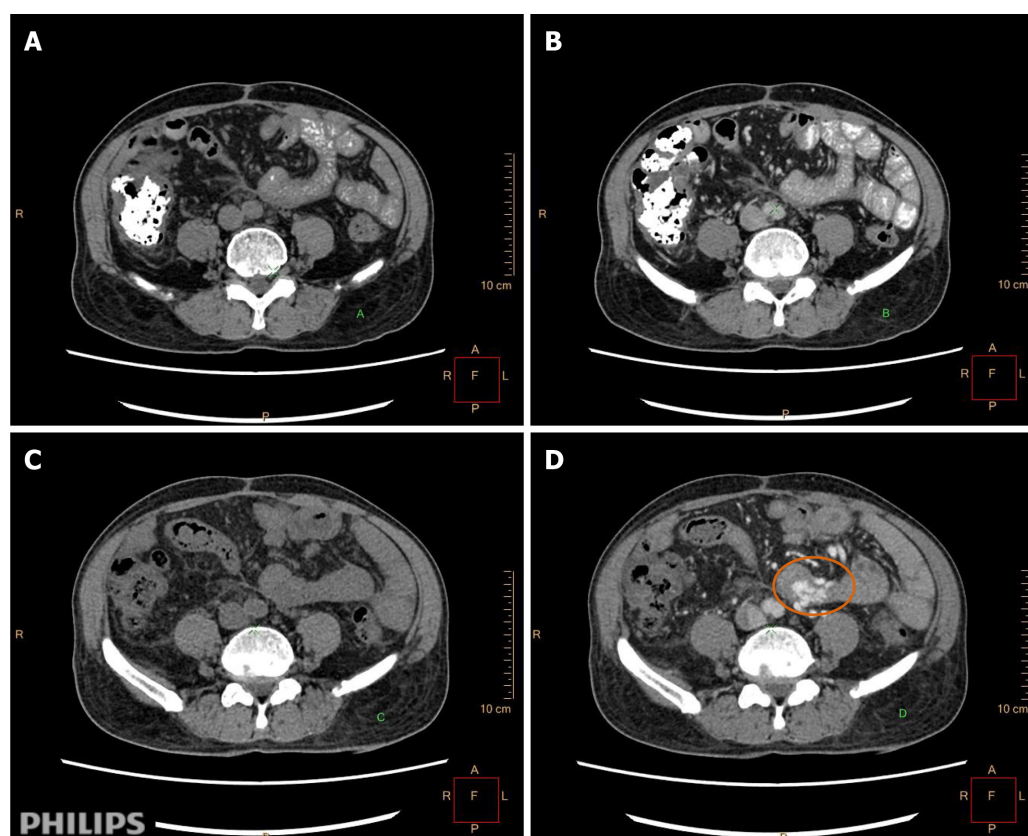


Figure 2 Abdominal computed tomography enhancement scan with intravenous iodixanol-320 administration. A and B: Scans, imaging and physical examination were normal on May 29, 2019; C and D: Enhancement, numerous enlarged branches of the blood vessels of the jejunum and tortuous irregular vessels (orange circle).

gastrointestinal bleeding. According to a recently published report, CT angiography has excellent sensitivity (90%) and specificity (92%) for lower gastrointestinal bleeding^[9].

Globally, the most common etiologies of portal hypertension are cirrhosis due to alcoholic liver disease, nonalcoholic steatohepatitis, and hepatitis C infection^[10]. There are data showing that the prevalence of varicose veins increases with the severity of liver function grade (Child-Pugh class). For classes A, B, and C, the incidence of varicose veins was 42.7%, 70.7%, and 75.5%, respectively^[7,11]. The pathophysiology of portal hypertension is a multifactorial process involving changes in both the portal and systemic circulation. First, hepatocellular injury and expression of pro-inflammatory genes alter the intrahepatic hemodynamics^[12]. Second, there is increased vascular resistance from increased production of vasoconstrictors and a reduction in nitric oxide synthesis^[13]. Extrahepatic hemodynamics are also important. Excessive nitric oxide can reduce splanchnic and systemic vascular resistance^[14]. Activation of the renin-angiotensin mechanism leads to increased cardiac output and hepatic blood

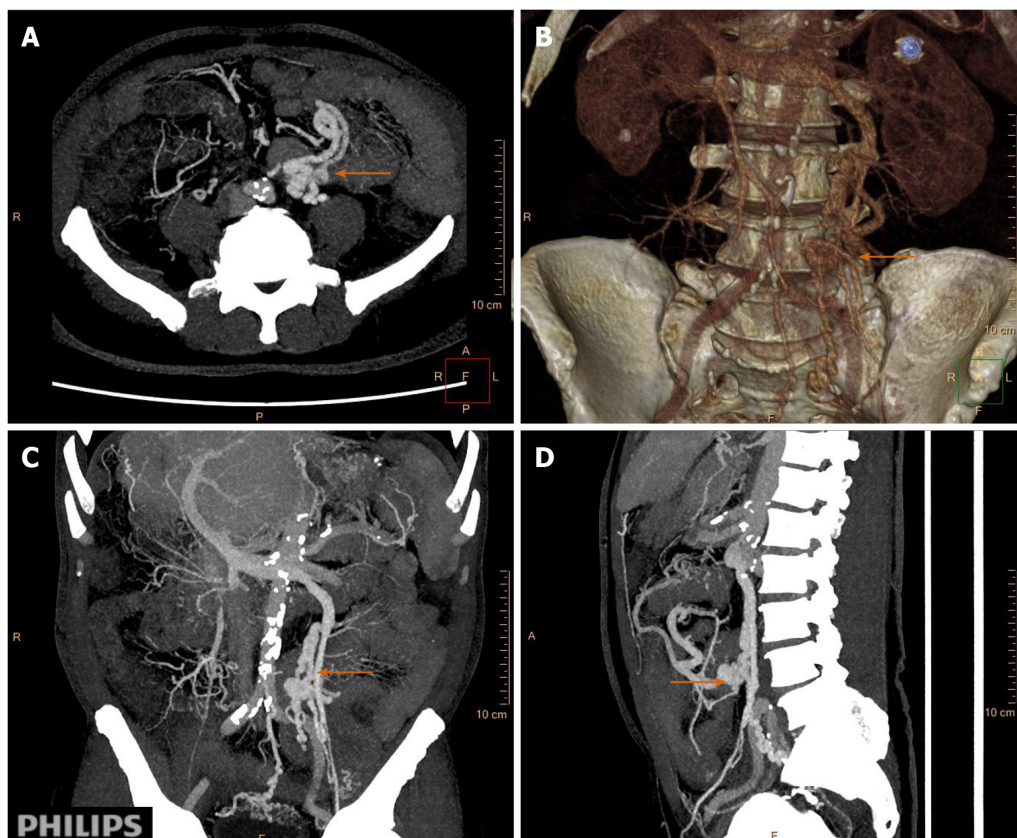


Figure 3 Multiplanar reconstruction showed a varicocele on the left side and venae testicularis as a tangled mass of vessels forming varicose veins, which anastomosed with the superior mesenteric vein (orange arrow). A: Axial plus coronal scanning; B: Sagittal scans; C: Images reconstructed with maximum intensity projection; and D: Images showing volume rendering three-dimensional reconstruction by spiral computed tomography.

flow^[15]. Clear establishment of the mechanism through which varicose veins lead to gastrointestinal bleeding would facilitate the diagnosis and treatment.

Our case shows the effectiveness of multidetector CT with MPR union 3D images for the diagnosis of duodenal varices. The MPR of CT more clearly displays the ectopic duodenal varices at sites that EGD cannot access. Few reports have suggested the importance of MPR in the diagnosis of ectopic varices^[16,17]. The usefulness of multidetector helical CT with multiplanar reconstruction for depicting duodenal varices with multiple collateral shunt vessels has been reported^[6]. CT-MIP is a clinically useful modality to distinguish gastric varices from ectopic varices^[18]. Few papers have also explored MPR union 3D images in the diagnosis of duodenal varices. With the development and application of imaging examination and endoscopic technology, most cases of gastrointestinal bleeding can be definitively diagnosed by gastroscopy. However, the ectopic malformations associated with varices vary greatly in size and location; thus, the results of gastroscopy can be difficult to determine, and it is not exactly clear what causes gastrointestinal bleeding. At this point, CT-MPR, CT-MIP, and CT-volume rendering play a key role in the diagnosis.

There are no management guidelines for this relatively rare condition (Accdon1), and the available literature includes only case reports, with few literature reviews. According to the severity of the disease, treatment can be divided into endoscopy, interventional radiology, and surgery. Although endoscopic ligation and injection sclerotherapy are the first line of treatment^[19,20], they are not always appropriate for gastrointestinal hemorrhage, partly because the site of bleeding cannot be visualized using an endoscope. Embolization must be performed in a specific way to decrease the risk of bowel ischemia^[21]. In our case, endovascular interventional embolization was an appropriate measure because the anastomosis, varicose veins, and tortuous collection of irregular vessels bled profusely during the CT examination, and although conservative medical treatment can better cope with hemorrhage, it did not solve the problem^[9].

We did not conduct multidisciplinary consultation on time as multiple EGD procedures failed to identify the source of bleeding, which was the primary take-away

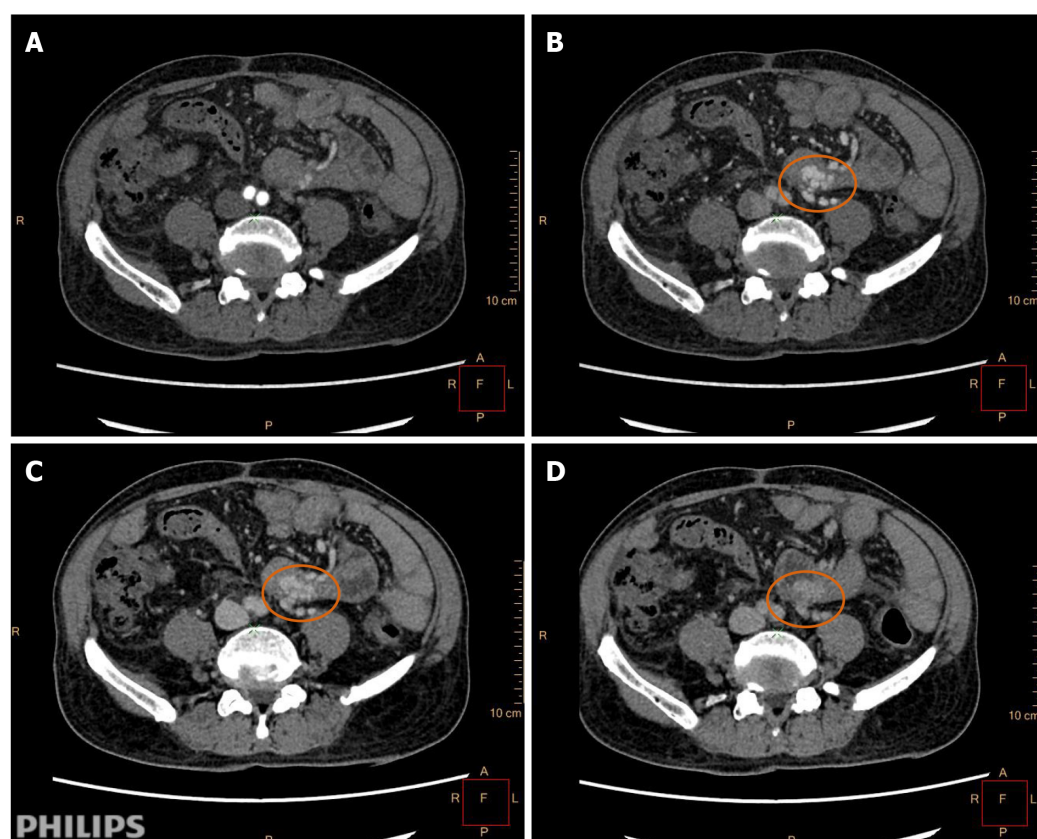


Figure 4 Four-phase dynamic computed tomography features and identifying the bleeding in arterial-phase, portal-phase, equilibrium-phase, and delayed-phase scanning. A: The arterial-phase showed no abnormal signs of the blood vessel on computed tomography images; B: During the portal-phase, the testicular vein and the superior mesenteric vein gathered together with vascular dilatation, tortuosity, and active bleeding (orange circle); C: The equilibrium-phase also showed bleeding; and D: Delayed-phase scanning showed vascular mass enlargement.

lesson of this case report. Blood transfusion was performed during this period, but the symptoms did not improve significantly.

CONCLUSION

In conclusion, we herein report that CT-MPR, CT-MIP, and CT-volume rendering are effective means of locating duodenal varices with complicated varicose veins and tortuous collections of irregular vessels, and all of these methods provide the necessary information for deciding upon the best treatment. CT-MPR was found to be a simple and rapid modality, and it clearly reflected the pathological morphology. CT-MPR is valuable for the early diagnosis of rare variceal bleeding; however, in the present case, the diagnosis was delayed. This method provides reliable diagnostic information for clinical treatment; thus, we expect that it will be widely used in the future.

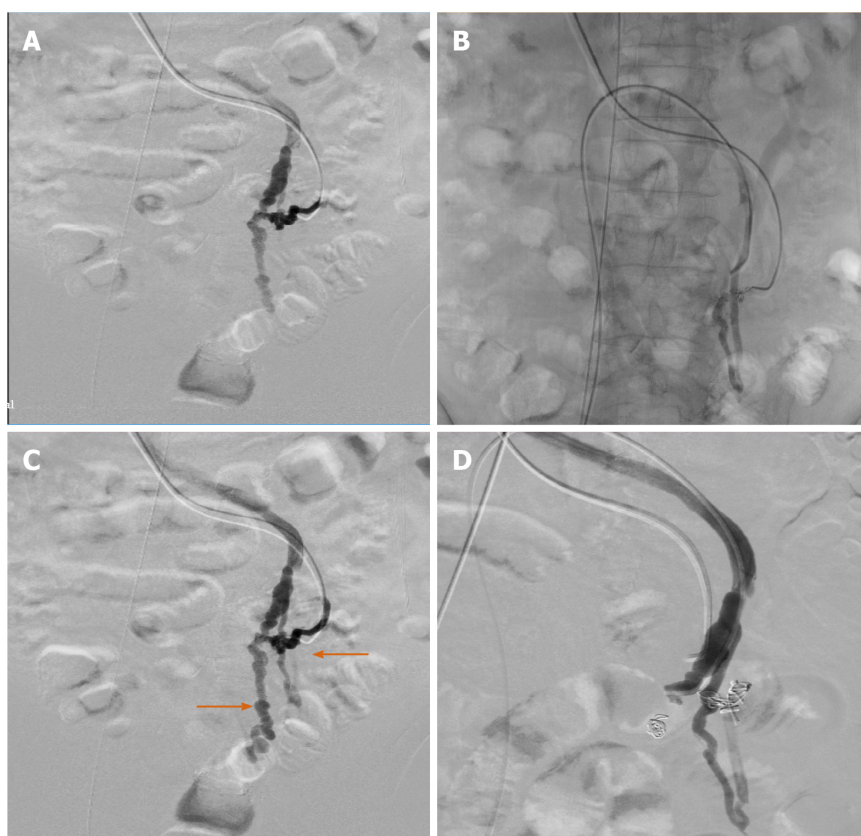


Figure 5 Digital subtraction angiography indicating the bleeding points, which were then embolized to the feeding branches. A and C: Portal angiography, with bleeding points and contrast media extravasating into the intestinal tract; B: Digital subtraction angiography of the inferior vena cava; and D: No contrast agent extravasation after embolization therapy.

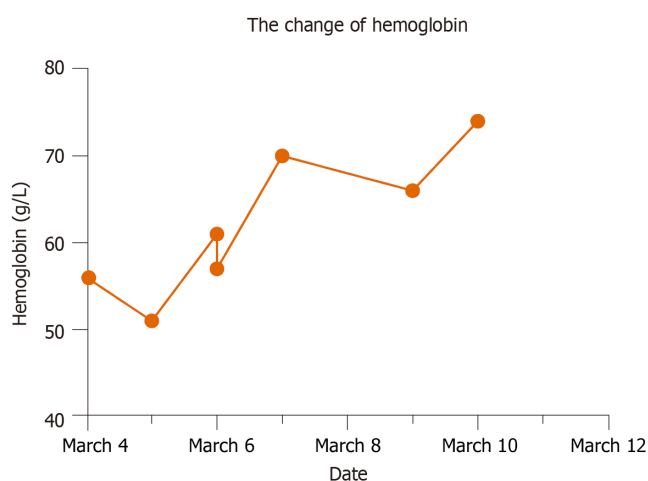


Figure 6 Hemoglobin level changes during hospitalization. After transfusion and embolization therapy, the patient's hemoglobin level reached 78 g/L.

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