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**REVIEW**

- 465 Current strategies for malignant pedunculated colorectal polyps
Ciocalteu A, Gheonea DI, Saftoiu A, Streba L, Dragoescu NA, Tenea-Cojan TS

ORIGINAL ARTICLE**Basic Study**

- 476 Histological analysis of human pancreatic carcinoma following irreversible electroporation in a nude mouse model
Su JJ, Xu K, Wang PF, Zhang HY, Chen YL

Retrospective Study

- 487 Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms
Hayashi Y, Esaki M, Suzuki S, Ihara E, Yokoyama A, Sakisaka S, Hosokawa T, Tanaka Y, Mizutani T, Tsuruta S, Iwao A, Yamakawa S, Irie A, Minoda Y, Hata Y, Ogino H, Akiho H, Ogawa Y

- 496 Stents combined with iodine-125 implantation to treat main portal vein tumor thrombus
Wu YF, Wang T, Yue ZD, Zhao HW, Wang L, Fan ZH, He FL, Liu FQ

Clinical Trials Study

- 505 Multicenter phase II trial of modified FOLFIRINOX in gemcitabin-refractory pancreatic cancer
Chung MJ, Kang H, Kim HG, Hyun JJ, Lee JK, Lee KH, Noh MH, Kang DH, Lee SH, Bang S, Pancreatobiliary Cancer Study Group of Korean Society of Gastrointestinal Cancer

CASE REPORT

- 516 Small intestinal hemangioma: Endoscopic or surgical intervention? A case report and review of literature
Hu PF, Chen H, Wang XH, Wang WJ, Su N, Shi B
- 522 Experience in the diagnosis and treatment of mesenteric lymphangioma in adults: A case report and review of literature
Chen J, Du L, Wang DR

LETTER TO THE EDITOR

- 528 Considering FOLFOXIRI plus bevacizumab for metastatic colorectal cancer with left-sided tumors
Sunakawa Y, Satake H, Ichikawa W

Contents

World Journal of Gastrointestinal Oncology
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ABOUT COVER

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Current strategies for malignant pedunculated colorectal polyps

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Abstract

Despite significant advances in imaging techniques, the incidence of colorectal cancer has been increasing in recent years, with many cases still being diagnosed in advanced stages. Early detection and accurate staging remain the main factors that lead to a decrease in the cost and invasiveness of the curative techniques, significantly improving the outcome. However, the diagnosis of pedunculated early colorectal malignancy remains a current challenge. Data on the management of pedunculated cancer precursors, apart from data on nonpolypoid lesions, are still limited. An adequate technique for complete resection, which provides the best long-term outcome, is mandatory for curative intent. In this context, a discussion regarding the diagnosis of malignancy of pedunculated polyps, separate from non-pedunculated variants, is necessary. The purpose of this review is to provide a critical review of the most recent literature reporting the different features of malignant pedunculated colorectal polyps, including diagnosis and management strategies.

Key words: Pedunculated colorectal polyps; Malignant colorectal polyp; Early colorectal cancer; Polypoid early colon cancer; Advanced adenoma; Depth of invasion; Colorectal cancer; Polypectomy; Colorectal surgery; Early colorectal carcinoma

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Core tip: Colorectal cancer has the highest chance of curability as long as it is detected at an early stage, before lymph node metastasis, or as a premalignant lesion. However, few relevant studies address pedunculated polyps separately from nonpolypoid type lesions, often resulting in a source of bias. The objective of this paper is to offer an up-to-date overview, particularly on the management of malignant pedunculated polyps.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide. Of all gut malignancies, it has the highest chance of curability as long as it is detected at an early stage – either as a premalignant lesion or before lymph node metastasis. In European national screening programs, approximately 17% of cancers detected were pT1 CRCs, and the risk of developing advanced neoplasia following polypectomy was estimated at 0.6%^[1].

Most reports focus on sessile or flat lesions of the colorectum, while few studies discuss the management of pedunculated cancer precursor lesions. Studies often combine data for both sessile and pedunculated polyps. Moreover, submucosal invasion is presented in the literature as absolute depth, disregarding the presence of the stalk^[2], resulting in further bias. In particular, describing the macroscopic appearance of pedunculated lesions and the final histopathological diagnosis often remain challenging. At first sight, pedunculated lesions can easily be treated endoscopically; however, no large-scale reports exist to establish the real risk of lymph node metastasis stratified by depth of invasion. Additionally, an adequate technique for complete resection is mandatory for curative intent, providing the best long-term outcome. In this respect, a discussion regarding the diagnosis of malignancy inside pedunculated, separate from nonpedunculated, polyps is necessary. A clear distinction between head and stalk invasion of malignant cells is also required.

LITERATURE SEARCH

The aim of this article was to address strategies for diagnosis, staging, and risk stratification of patients with malignant pedunculated colorectal polyps (MPCP), as well as to provide a critical review of the literature regarding their management, to summarize their current state and to consider future perspectives. The literature search was conducted with PubMed and included full-text articles, up-to-date guidelines and recent abstracts with obvious conclusions as well as additional relevant publications by using the reference lists of the identified articles as a starting point. The following keywords were used: “pedunculated colorectal polyps”, “malignant colorectal polyp”, “early CRC”, “polypoid early colon cancer”, “early diagnosis”, “staging”, and “depth of invasion”, alone or in various combinations.

DEFINITIONS, CLASSIFICATIONS AND HISTOPATHOLOGICAL CHARACTERISTICS

By definition, a malignant polyp – either sessile or pedunculated, consists of cancer cells that invade the submucosa through the muscularis mucosae without crossing the submucosa, regardless of lymph node status and without distant metastasis (T1NxMo)^[3]. The term “early colorectal carcinoma” can also be used^[4].

An advanced adenoma is defined as a lesion of at least 10 mm with villous components or high-grade dysplasia^[5,6]. Currently, “high-grade dysplasia” is a term used for adenomas in which there is mucosal invasion without extension below the muscularis mucosae^[7]. According to the recommendations of the World Health Organization (WHO), this term is preferable to “intramucosal carcinoma”^[7,8]. The reason is that focal cancer that has not yet invaded through the muscularis mucosae is considered to have no risk of spreading to the lymph nodes because no lymphatic channels are located superficially to the muscularis mucosae^[7]. The patients in this situation are considered to be safe candidates for endoscopic resection.

Pedunculated polyps are recognized by their stalk of variable lengths that is attached to the colonic mucosa^[9]. They are described endoscopically in the Paris international classification as 0-Ip lesions. Although it has been reported to anticipate high-grade dysplasia and even invasive carcinoma, interobserver variability associated with the Paris classification has not been studied^[10]. Class 5 of Kudo’s pit pattern classification, characterized by an unstructured or excavated surface, demarcated depressed areas, loss of lobulation and stalk swelling, has been shown to correlate with the diagnosis of malignancy^[11,12]. A large multicenter cohort study emphasized the difficult diagnosis, as there has been a lack of agreement on the diagnosis of MPCP in a high percentage of cases^[13].

The level of invasion of the stalk further dictates management, from a minimally invasive endoscopy to an invasive surgical resection. MPCP should be discussed separately from nonpedunculated polyps to obtain accurate conclusions. If in the case of a sessile polyp, the cancer cells travel a short distance to become invasive and metastatic, should the stalk length be considered a favorable prognostic factor as a first barrier through the advanced cancer pathway?

Haggitt *et al.*^[14] classified the level of invasion in a pedunculated malignant polyp as follows: Level 1: invasive adenocarcinoma limited to the polyp head (invading through the muscularis mucosae); Level 2: neck involvement; Level 3: carcinoma cells in the stalk; and Level 4: carcinoma cells infiltrating the submucosa at the level of the adjacent bowel wall. The Haggitt line is the imaginary border drawn as the baseline to distinguish between head invasion and stalk invasion. A low risk of local recurrence or metastasis was deduced when the level of invasion was under 4. Although many studies^[15-17] reported a correlation between Haggitt level, lymph node invasion risk and outcome, there are currently no consensus guidelines to be included in the pathology report of a malignant polyp.

FACTORS PREDICTING LYMPH NODE STATUS IN MALIGNANT PEDUNCULATED COLORECTAL POLYPS

Even if pedunculated polyps are generally considered to have fewer lymph node metastases, variable morphology and length of the stalk can lead to problematic measurement of the depth of the submucosal invasion and to further controversies (Table 1).

In a recent systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early CRC^[2], a separate analysis of pedunculated polyps from sessile tumors was not possible because of insufficient data. They concluded that in early CRC, a depth of invasion of more than 1 mm in the submucosa by the primary tumor, poorly differentiated cancers, the presence of tumor budding and lymphovascular invasion were significantly associated with lymph node involvement.

Moreover, Kitajima *et al.*^[15] previously found a rate of lymph node metastasis of zero in head invasion cases (the deepest portion of invasion limited to above the baseline) and in stalk invasion cases with a depth of submucosal invasion < 3000 μ m (MPCP with the level 2 line according to Haggitt's classification used as the baseline and depth of submucosal invasion measured to the deepest portion in the submucosa).

In a large retrospective cohort study^[16], the authors concluded that MPCP diagnosed as head invasion by the pathologist can be safely treated by endoscopic polypectomy alone. They included 383 patients with

pathologically proven adenocarcinoma spread through the muscularis mucosae into the submucosa but without extension to the muscularis propria. The invasion depth was classified into two groups by using the upper limit of level 2 according to Haggitt's classification as the baseline for all lesions. When an endoscopy was suggestive of submucosal invasion into the polyp stalk, those patients were managed directly by surgery with lymph node dissection. Thus, they found a lymph node involvement rate and recurrence rate of 3.5% (8/230; 95%CI: 1.5%–6.7%) and 0.3% (1/340; 95%CI: 0.01%–1.6%), respectively. The incidence of metastasis to the lymph nodes and recurrence rate were 0% (0/101; 95%CI: 0.0%–3.6%) and 0%, respectively, (0/219; 95%CI: 0.0%–1.7%) for the lesions with head invasion, compared with 6.2% (8/129; 95%CI: 2.7%–11.9%) and 0.8% (1/121; 95%CI: 0.02%–4.50%), respectively, for stalk invasion. A total of 29% of lesions with head invasion were lymphovascular invasion positive, while 38% of stalk invasion lesions were lymphovascular invasion positive. Finally, the authors noted no significant difference in any other factors (such as tumor size, tumor differentiation grades, or even lymphovascular invasion) except for the depth of invasion (stalk invasion) between lymph node metastasis positive and negative groups.

In a previous study on 151 patients with colorectal polyps that included invasive carcinoma treated by resection, Nivatvongs *et al.*^[17] concluded that, unlike tumor size and grading, only the depth of invasion to the base of the stalk (Level 4) was associated with a high risk of lymph node metastasis (27%).

On the other hand, in another approach with patients who underwent systematic lymph node dissection, metastasis was observed in 14.6% of cases, and multivariate analysis showed that tumor budding was the only independent factor associated with lymph node metastasis^[18].

Interestingly, Kimura *et al.*^[19] recently suggested that head invasion is not a lymph node metastasis-free condition in a study on 76 pedunculated polyps with no significant differences in the lymph node metastasis rate between "head invasion" (4/30, 13.3%) and "stalk invasion" (5/46, 10.9%). They stated that even for MPCP with "head invasion", additional surgical resection with lymph node dissection should be taken into consideration if there are other risk factors.

Indeed, the detection of tumor buds has been reported as an indication for colorectal surgery because of the high risk for lymph node metastasis. Pathologically, tumor budding is defined as single tumor cells or small clusters of four or fewer tumor cells in the tumor stroma, at the invasive front and in malignant polyps^[20,21]. Widespread reporting of tumor budding has been limited in daily diagnostic practice due to a lack of consensus regarding guidelines on scoring methods^[20,21]. Although some authors^[8,22] consider it important that at least

Table 1 Histopathological factors predicting risk of lymph node metastases in malignant pedunculated colorectal polyps

Histopathological factors	Risk of LNM	Management
Depth of invasion in submucosa by the primary tumor of more than 1mm (Beaton <i>et al</i> ^[21])	High	Surgery with lymph node dissection
Poorly differentiated cancers (Beaton <i>et al</i> ^[21])		
Tumor budding (Beaton <i>et al</i> ^[21] , Sohn <i>et al</i> ^[18] , Geramizadeh <i>et al</i> ^[7] , Graham <i>et al</i> ^[22])		
Lymphovascular invasion (Beaton <i>et al</i> ^[21])		
Depth of invasion to the base of the stalk-Level 4 Haggitt (Nivatvongs <i>et al</i> ^[17] , Kimura <i>et al</i> ^[19])		
Submucosal invasion into the polyp stalk (Matsuda <i>et al</i> ^[16])		
Micropapillary component (Sonoo <i>et al</i> ^[26] , by Verdú <i>et al</i> ^[27] , Mukai <i>et al</i> ^[28])		
Head invasion (Kimura <i>et al</i> ^[19])		Surgical resection with lymph node dissection in case of additional pathological risk factors
Head invasion (Kitajima <i>et al</i> ^[15] , Matsuda <i>et al</i> ^[16])	Low	Endoscopic polypectomy
Depth of submucosal invasion/stalk invasion < 3000 µm (Kitajima <i>et al</i> ^[15])		
Tumor size (Nivatvongs <i>et al</i> ^[17])		
Grading (Nivatvongs <i>et al</i> ^[17])		
Pseudoinvasion (Backes <i>et al</i> ^[13])		Confirmation of t1 colorectal cancer by a second expert pathologist

LNM: Lymph node metastases.

high-grade tumor budding (more than 10 tumor buds in any microscopic field viewed at 25X) should be recorded in the pathology report as a prognostic factor.

Invasive micropapillary carcinoma is composed of small clusters of tumor cells lying within clear stromal spaces simulating vascular channels^[23,24] and is considered to be related to a high incidence of lymph node metastasis. However, its actual prevalence among early CRCs has not been reported^[25,26], as a limited number of cases are reported in the literature. Similar cases of pedunculated early sigmoid colon cancer with a micropapillary component and multiple lymph node metastases were reported by Sonoo *et al*^[26], Verdú *et al*^[27] and by Mukai *et al*^[28]. In another case of a sigmoid pedunculated polyp with a depressed surface without evidence of lymph node involvement or distant metastases on initial computed tomographic scans, the patient had local recurrence with lymph node metastases but also lung, liver, and spleen metastases at 6 months follow-up after the polypectomy^[29].

Therefore, even if the initial diagnosis is an MPCP, extensive surgical resection may still be taken into consideration for tumors with a micropapillary component due to the high risk for lymph node metastasis and poor outcome.

Beyond the conclusions of these studies, immunohistochemistry for the confirmation of the difficult-to-assess lymphovascular invasion is usually reserved for equivocal cases (*e.g.*, tumors with positive margins after resection)^[30].

Chicken-skin-like mucosa is an endoscopic finding described as pale yellow-speckled mucosa frequently surrounding pedunculated adenomas of the distal colon. Its clinical and pathophysiological significance have yet to be determined. Histopathologically, it represents fat accumulation in macrophages within the muscularis propria and, rarely, intestine-like microvilli. In two studies^[31,32], the prevalence of chicken-skin-like mucosa

was higher in carcinoma patients than in adenoma patients, and its role as a potential predictive marker of carcinogenetic progression was taken into consideration. However, it is a colonoscopic sign to search for a polyp in challenging locations. Additionally, it may serve as a potential marker of advanced pathology of colorectal adenoma in future research and might offer a better perspective on postpolypectomy management^[33].

Both endoscopists and histopathologists should also pay attention to possible pseudoinvasion. A histopathological pseudoinvasion (prolapse of the adenomatous epithelium into the polyp stalk), associated with ischemic changes when the polyp stalk is twisted, can be observed more often in large pedunculated polyps, which are typically located in the sigmoid colon and rarely in the rectum^[7]. Despite the lack of a gold standard diagnosis, invasive carcinoma could be distinguished from pseudoinvasion by the presence of stromal desmoplasia and high-grade dysplasia^[34]. However, the exact incidence of discordant diagnosis cannot be estimated; moreover, misplaced epithelium in pedunculated polyps has a lobular contour with a rim of lamina propria, along with hemorrhage, and/or hemosiderin^[35]. Biopsy-related misplacement can be even more difficult to recognize than typical pseudoinvasion in polyps with stalks^[36].

Thus, because misplaced epithelium can simulate early CRC in pedunculated polyps, British guidelines currently recommend diagnostic confirmation of T1 CRC by a second expert pathologist^[13].

CHALLENGES IN ENDOSCOPIC RESECTION TECHNIQUES

When we suspect a malignant pedunculated polyp, the snare should be placed as close as possible to the bowel wall to increase the chance of obtaining a cancer-free resection margin. Snare polypectomy is considered

curative when the histopathology report is favorable, but there is no consensus on the accurate assessment of negative margins. Most authors^[37,38] consider polypectomy technically satisfactory, with the lowest rate of local recurrence and metastases, if the margin from the invasive component to the diathermy burn is at least 2 mm. A new study^[39] reported a similar 5-year cumulative recurrence rate between surgical and endoscopic resection (8.2% and 2.4%, respectively) for patients with MPCP and a pathological margin ≥ 1 mm.

The site of resection should be inked with a tattoo to facilitate easy recognition if surgery is necessary; however, there is no guideline on the optimal placement of tattoos or metallic clips^[40].

Unlike sessile or flat polyps, in the case of pedunculated lesions, it is easier for the pathologist to avoid a diathermy artifact of the resected specimen and to better identify eventual invasive cancer cells at the polypectomy margin due to the distance of resection from the invasive component. Many studies^[16,41] have stated that pedunculated early polyp CRCs limited to the polyp head, without unfavorable histological features, could be managed by endoscopic resection alone with minimal risk of locoregional recurrence. However, in cases of unfavorable histological criteria (resection margins less than 1 mm, poor differentiation, lymphovascular invasion, invading the submucosa of the bowel wall below the stalk), endoscopy is not considered curative; therefore, surgery is recommended^[40].

Generally, giant pedunculated polyps (over 30 mm) have been managed surgically; further prospective studies are needed to establish if endoscopic resection of giant MPCP represents a feasible safe procedure^[42]. Recently, a prospective pilot study explored the safety and feasibility of insulated-tip knife endoscopic polypectomy for difficult giant polyps^[43]. Endoscopic submucosal dissection^[44] and the use of a dual knife procedure^[45] were reported to be options as well, but the patient number was too small to make definitive conclusions.

Pedunculated polyps have a higher risk of bleeding compared to sessile polyps^[46]. Postpolypectomy bleeding is the most common complication reported in the literature, and the rate varies between 24%^[47] and the more usual frequency of 3%–4%^[48]. When considering referral bias, the general frequency is thought to be lower, while other complications such as postcoagulation syndrome or perforation can rarely occur^[49]. The only polyp-related factor that has been constantly proven to increase the risk of delayed bleeding is the large size of the lesion^[50,51]. Therefore, pretreatment of stalks in large polyps may be necessary, and a variety of techniques are available. For polyps with a head ≥ 20 mm or a stalk ≥ 10 mm in diameter, recent European guidelines (ESGE) have recommend pretreatment of the stalk with injection of diluted adrenaline and/or mechanical hemostasis (moderate quality evidence,

strong recommendation)^[52].

Endoclips

Prophylactic clipping before or after polypectomy remains controversial, with conflicting results reported in different studies^[46].

Quintanilla *et al.*^[53] reported in a prospective randomized study of large pedunculated polyps that prophylactic clips (prior to polyp resection) did not decrease the risk of delayed bleeding after polypectomy. Technically, they suggested the use of hemoclips in the case of polyps with long and thin pedicles. However, this study was suspended early because of the high risk of morbidity in the clipping group, with higher rates of mucosal burns and perforation rather than bleeding.

Very thick and/or short stalks may be a challenge for clip placing, causing mucosal burns and risk of perforation due to the contact of the base of the polyp with the snare and the clip^[54].

Indeed, prophylactic clips applied before endoscopic removal for this type of polyps were actually associated with further risk of mucosal deep erosions and perforation^[55].

For MPCP resected by hot snaring, neither early nor delayed bleeding complications occurred for more than two decades during which clips were not used^[56].

On the other hand, Parikh *et al.*^[57] concluded that prophylactic placement of hemoclips after polypectomy was a cost-effective plan for patients on antiplatelet or anticoagulation therapy.

Endoloops

The use of the endoloop can also generate technical difficulties from looping large polyps and the endoloop removal^[53] to the transection by the loop of a thin stalk before the polypectomy or insufficient tightening of the loop^[58]. A prospective randomized multicenter study^[59] suggested that the application of a prophylactic hemoclip is as effective and safe as an endoloop in the prevention of postpolypectomy bleeding in large pedunculated colonic polyps.

Anchor clip technique

Mizukami *et al.*^[60] described the anchor clip device, which, placed before the resection of large polyps, constrains the base of the stalk after resection, avoiding immediate bleeding and mucosal burns.

Adrenaline injection

A prospective study on pedunculated polyps larger than 20 mm has shown that there are no differences between adrenaline injection and the use of endoloops or hemoclips in postpolypectomy bleeding prophylaxis^[48], although its addition to both techniques appeared to increase the efficiency in other studies^[61,62]. Recently, a prospective randomized study^[63] that compared the rates of bleeding after resection following single clipping alone

and a combined method (hemoclips plus epinephrine-saline injection) concluded that large pedunculated polyps can be successfully removed *via* hot snare by using the single prophylactic clipping method.

A recent meta-analysis of three randomized controlled studies^[64] that compared the efficacy of epinephrine injection and mechanical hemostasis in postpolypectomy bleeding in patients with pedunculated polyps over 20 mm demonstrated that prophylactic treatment with mechanical hemostasis is more effective than epinephrine injection for preventing overall postpolypectomy bleeding (2.2% vs 6.3%) and early postpolypectomy bleeding (1.1% vs 4.5%). The rate of delayed postpolypectomy bleeding was 1.9% in the epinephrine group and 1.1% in the mechanical group, and their implementation was not found to significantly affect the rate of delayed postpolypectomy bleeding (OR = 0.58, 95%CI: 0.13, 2.49; *P* = 0.46) without significant heterogeneity between the studies (*P* = 0.94, *I*² = 0%).

The impact of underlying comorbidities and other pedunculated polyp characteristics

The presence of comorbidity, beyond the size and location of the polyp, should also be taken into consideration when discussing further management.

Different risk factors for postpolypectomy complications, such as old age (older than 65 years of age), underlying diseases (cardiovascular or chronic renal disease), anticoagulant use, polyp size > 10 mm, a stalk size > 5 mm, polyps located on the right side of the colon, malignant polyps, use of cutting mode and low-volume endoscopists, have been described^[47,64-67].

A recently published review and meta-analysis^[68] identified cardiovascular disease, hypertension, polyp size over 10 mm, and polyp location as significant risk factors for delayed postpolypectomy bleeding, whereas pedunculated morphology, carcinoma histology, age, sex, alcohol use, smoking, diabetes and cerebrovascular disease were not.

Related to the polyp location, recent evidence^[50] suggests that right-sided polyps have a significantly higher risk of bleeding and perforation in comparison with left-sided polyps, for both sessile and pedunculated polyps.

In conclusion, the effectiveness of common preventive methods is variable, and no consensus has been reached to date on the strategy to avoid postpolypectomy bleeding. Large randomized controlled trials are necessary to confirm these observations, taking into consideration more potential risk factors such as pedunculated polyp characteristics (e.g., length of the pedicle) or other patient comorbidities (e.g., the bleeding risk from heparin - bridging therapy in patients with high thromboembolic risk^[69]). Interestingly, Shibuya *et al.*^[70] showed that the overall postpolypectomy bleeding rate under the new Japanese guidelines, which indicate that antithrombotic agents

are not to be discontinued in cases with a high-risk of thromboembolic incidents, was not significantly higher when compared with data from previous guidelines, without particularly addressing pedunculated polyps.

STRATEGIES FOR PATIENTS ON ANTIPLATELET THERAPY OR ANTICOAGULANTS

The risk of bleeding, as the most common adverse effect of polypectomy and particularly the higher risk of bleeding of pedunculated polyps, was already described in the section "Challenges in endoscopic resection techniques". Therefore, endoscopic polypectomy is considered to be a high-risk procedure based on the risk of bleeding, which is increased by the addition of antiplatelet or anticoagulant therapy. In this group of patients, the risk of hemorrhage should be balanced against the risk of thrombosis when antiplatelet or anticoagulant therapy is discontinued.

Patients with MPCP and indication of polypectomy should be managed as summarized in Table 2, according to the most recent British Society of Gastroenterology and ESGE general recommendations^[71].

ADEQUATE FOLLOW-UP AFTER RESECTION

Discussing surveillance after polypectomy can be challenging because the risks and outcomes are difficult to calculate. Generally, when the risk of the lesion seems to be low, interval surveillance is performed. For patients with a higher risk, further surgical resection is necessary, but there is no consensus on follow-up procedures and subsequent intervals for early cancer in pedunculated lesions. The management of an MPCP following endoscopic resection can generate anxiety for both the physician and patient because of possible residual cancerous cells and/or positive lymph nodes that are variable from one case to another^[72]. However, further management remains balanced between the general approach of postpolypectomy surveillance of patients with high-risk adenomas^[6,73,74] and the follow-up of a resected CRC with curative intent^[75-77]. However, it is also based on the experience and clinical sense of the physician.

The recent recommendations of the United States Multi-Society Task Force on Colorectal Cancer endorsed by the American Society for Gastrointestinal Endoscopy^[75] address only the use of colonoscopy in the follow-up of patients with resected CRC with curative intent and insist on the fact that the colorectum should be carefully cleared of synchronous neoplasia in the perioperative period, without any particular information on early cancer in pedunculated polyps.

Fortunately, pedunculated polyps are unusual

Table 2 Endoscopic polypectomy in patients on antiplatelet therapy or anticoagulants (British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy Recommendations^[71])

Thrombosis risk factors		High thrombotic risk	Low thrombotic risk	Post-polypectomy
Discontinuation of warfarin concerning the requirement for heparin bridging	Discontinuation of clopidogrel, prasugrel or ticagrelor	Continuing aspirin and liaising with a cardiologist about the risk/benefit of discontinuing P2Y ₁₂ receptor antagonists (high quality evidence, strong recommendation)	Continuing aspirin in patients on dual antiplatelet therapy (low quality evidence, weak recommendation)	Antiplatelet or anticoagulant therapy should be suspended up to 48 h after the procedure depending on the perceived bleeding and thrombotic risks (moderate quality evidence, strong recommendation)
Prosthetic metal heart valve in mitral position	Drug-eluting coronary artery stents within 12 mo of placement	Warfarin should be temporarily stopped and substituted with LMWH (low quality evidence, strong recommendation)	Discontinuing P2Y ₁₂ receptor antagonists 5 d before the procedure (moderate quality evidence, strong recommendation)	
Prosthetic heart valve and atrial fibrillation	Bare metal coronary artery stents within 1 mo of placement	The last dose of DOAC should be taken at least 48 h before the procedure (very low quality evidence, strong recommendation)	Discontinuing warfarin 5 d before the procedure (high quality evidence, strong recommendation)	
Atrial fibrillation and mitral stenosis			Ensure the INR target < 1.5 prior to the procedure (low quality evidence, strong recommendation)	
< 3 mo after venous thromboembolism				

LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulants.

in the rectum. However, rectal cancer is generally associated with a higher risk of local recurrence than other segments of the colon, and additional considerations for surveillance^[77], such as endoscopic ultrasound for better detection of suspicious lymph nodes and recurrences^[75], are suggested. The utility of adjuvant chemoradiation or chemoradiation alone for high-risk early rectal carcinoma remains to be elucidated^[1].

In a long-term prospective study of 25 consecutive patients with MPCP treated with snare cautery polypectomy^[56], the author concluded that short-term outcomes after removal appeared to be similar to those with a nonmalignant polyp. He suggested that long-term surveillance should be considered in each patient, assuming reasonable life expectancy, because the risk of additional adenomas and metachronous colon cancer persists even after the initial five years of currently recommended surveillance. In addition to the small number of patients, the location of the lesions was limited to the sigmoid or descending colon, and both standard and high-definition colonoscopes were used without calculating the accuracy of polyp detection in separate subgroups. Personal or family history of intestinal neoplasia (such as previously resected adenomas) or underlying inflammatory bowel disease was excluded from the study.

A high carcinoembryonic antigen (CEA) value may be predictive of metastatic disease^[78-80]. There have been reported cases of MPCP with unfavorable histological criteria without initial local residual carcinoma or lymph node invasion but with distant metastasis even five years after surgery^[11,81], so close monitoring of such patients using CEA and imaging techniques seems prudent.

To our knowledge, to date, there are no particular guidelines including optimal treatment and surveillance of subgroups, such as synchronous CRCs, malignant pedunculated polyps, multiple malignant pedunculated polyps or malignant pedunculated polyps, associated with chronic inflammatory bowel disease.

UNRESOLVED ISSUES AND AREAS FOR FURTHER RESEARCH

There is a thin line between early cancer in pedunculated polyps and invasive cancer, due either to interobserver variation in detection rate by endoscopists or histologic interpretation by pathologists. Standard snare polypectomy is appropriate for pedunculated polyps with early cancer limited to the submucosa and favorable histology. The distance from the cancer to the margin of the resection excision is still under debate. These situations lead to a challenging evaluation of the natural history of the lesions.

Treatment plans and the best strategy to avoid postpolypectomy complications for colorectal malignant pedunculated polyps lack the evidence of randomized trials. Large randomized trials on this particular topic should be included in meta-analyses that develop further guidelines to provide relevant conclusions for patients' long-term

surveillance and outcomes. More long-term information focused on patients with endoscopically removed malignant polyps, including personal or family history of intestinal neoplasia, previously resected adenomas, or underlying inflammatory bowel disease^[82,83], would be valuable.

In addition to general unfavorable histological criteria, better stratification of patients with high-risk pedunculated polyps requiring surgery^[84], including those with high-grade tumor budding or invasive micropapillary components as reliable predictors of lympho-hematic metastases, is necessary. On the other hand, inadequate recognition of the pseudoinvasion pitfall as a benign condition can generate overdiagnosis and subsequent overtreatment of certain lesions. In this respect, a second histological opinion seems advisable for all cases of MPCP, especially when surgery is taken into consideration.

CONCLUSION

There are still unresolved issues requiring detailed recommendations according to the patient's and polyp's risk factors to avoid an overuse of surveillance procedures. Provided future novel imaging technologies and increased pathological recognition of high-risk markers for angiolymphatic invasion will be developed, it will be easier to decide on the optimal follow-up plan and therapy.

REFERENCES

- 1 **Bartel MJ**, Brahmabhatt BS, Wallace MB. Management of colorectal T1 carcinoma treated by endoscopic resection from the Western perspective. *Dig Endosc* 2016; **28**: 330-341 [PMID: 26718885 DOI: 10.1111/den.12598]
- 2 **Beaton C**, Twine CP, Williams GL, Radcliffe AG. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. *Colorectal Dis* 2013; **15**: 788-797 [PMID: 23331927 DOI: 10.1111/codi.12129]
- 3 **Aarons CB**, Shanmugan S, Bleier JI. Management of malignant colon polyps: current status and controversies. *World J Gastroenterol* 2014; **20**: 16178-16183 [PMID: 25473171 DOI: 10.3748/wjg.v20.i43.16178]
- 4 **Kashida H**, Kudo SE. Early colorectal cancer: concept, diagnosis, and management. *Int J Clin Oncol* 2006; **11**: 1-8 [PMID: 16508722 DOI: 10.1007/s10147-005-0550-5]
- 5 **Benson AB 3rd**, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Garrido-Laguna I, Grem JL, Grothey A, Hochster HS, HOFFE S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wutrick E, Gregory KM, Freedman-Cass DA. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw* 2018; **16**: 359-369 [PMID: 29632055 DOI: 10.6004/jnccn.2018.0021]
- 6 **Short MW**, Layton MC, Teer BN, Domagalski JE. Colorectal cancer screening and surveillance. *Am Fam Physician* 2015; **91**: 93-100 [PMID: 25591210]
- 7 **Geramizadeh B**, Marzban M, Owen DA. Malignant Colorectal Polyps; Pathological Consideration (A review). *Iran J Pathol* 2017; **12**: 1-8 [PMID: 29760747]
- 8 **Rex DK**, Hassan C, Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc* 2017; **86**: 253-263 [PMID: 28396276 DOI: 10.1016/j.gie.2017.03.1546]
- 9 **Gordon PH**, Nivatvongs S. Principles and practice of surgery for the colon, rectum, and anus. *Informa Healthcare* 2007: 452-459
- 10 **Gupta S**. Trouble in Paris (classification): polyp morphology is in the eye of the beholder. *Am J Gastroenterol* 2015; **110**: 188-191 [PMID: 25567171 DOI: 10.1038/ajg.2014.411]
- 11 **Bujanda L**, Cosme A, Gil I, Arenas-Mirave JI. Malignant colorectal polyps. *World J Gastroenterol* 2010; **16**: 3103-3111 [PMID: 20593495 DOI: 10.3748/wjg.v16.i25.3103]
- 12 **Park W**, Kim B, Park SJ, Cheon JH, Kim TI, Kim WH, Hong SP. Conventional endoscopic features are not sufficient to differentiate small, early colorectal cancer. *World J Gastroenterol* 2014; **20**: 6586-6593 [PMID: 24914381 DOI: 10.3748/wjg.v20.i21.6586]
- 13 **Backes Y**, Moons LM, Novelli MR, van Bergeijk JD, Groen JN, Seerden TC, Schwartz MP, de Vos Tot Nederveen Cappel WH, Spanier BW, Geesing JM, Kessels K, Kerkhof M, Siersema PD, Offerhaus GJ, Milne AN, Lacle MM. Diagnosis of T1 colorectal cancer in pedunculated polyps in daily clinical practice: a multicenter study. *Mod Pathol* 2017; **30**: 104-112 [PMID: 27713422 DOI: 10.1038/modpathol.2016.165]
- 14 **Haggitt RC**, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985; **89**: 328-336 [PMID: 4007423 DOI: 10.1016/0016-5085(85)90333-6]
- 15 **Kitajima K**, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; **39**: 534-543 [PMID: 15235870 DOI: 10.1007/s00535-004-1339-4]
- 16 **Matsuda T**, Fukuzawa M, Uraoka T, Nishi M, Yamaguchi Y, Kobayashi N, Ikematsu H, Saito Y, Nakajima T, Fujii T, Murakami Y, Shimoda T, Kushima R, Fujimori T. Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: a retrospective multicenter study. *Cancer Sci* 2011; **102**: 1693-1697 [PMID: 21627735 DOI: 10.1111/j.1349-7006.2011.01997.x]
- 17 **Nivatvongs S**, Rojanasakul A, Reiman HM, Dozois RR, Wolff BG, Pemberton JH, Beart RW Jr, Jacques LF. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. *Dis Colon Rectum* 1991; **34**: 323-328 [PMID: 1848810 DOI: 10.1007/BF02050592]
- 18 **Sohn DK**, Chang HJ, Park JW, Choi DH, Han KS, Hong CW, Jung KH, Kim DY, Lim SB, Choi HS, Jeong SY. Histopathological risk factors for lymph node metastasis in submucosal invasive colorectal carcinoma of pedunculated or semipedunculated type. *J Clin Pathol* 2007; **60**: 912-915 [PMID: 16997919 DOI: 10.1136/jcp.2006.043539]
- 19 **Kimura YJ**, Kudo SE, Miyachi H, Ichimasa K, Kouyama Y, Misawa M, Sato Y, Matsudaira S, Oikawa H, Hisayuki T, Mori Y, Kudo T, Ogata N, Kodama K, Wakamura K, Hayashi T, Katagiri A, Baba T, Hidaka E, Ishida F, Hamatani S. 'Head Invasion' Is Not a Metastasis-Free Condition in Pedunculated T1 Colorectal Carcinomas Based on the Precise Histopathological Assessment. *Digestion* 2016; **94**: 166-175 [PMID: 27832648 DOI: 10.1159/000450942]
- 20 **Lugli A**, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, El Zimaity H, Fléjou JF, Hansen TP, Hartmann A, Kakar S, Langner C, Nagtegaal I, Puppa G, Riddell R, Ristimäki A, Sheahan K, Smyrk T, Sugihara K, Terris B, Ueno H, Vieth M, Zlobec I, Quirke P. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. *Mod Pathol* 2017; **30**: 1299-1311 [PMID: 28548122 DOI: 10.1038/modpathol.2017.46]
- 21 **Koelzer VH**, Zlobec I, Lugli A. Tumor budding in colorectal cancer-ready for diagnostic practice? *Hum Pathol* 2016; **47**: 4-19 [PMID: 26718885 DOI: 10.1016/j.gie.2017.03.1546]

- 26476568 DOI: 10.1016/j.humpath.2015.08.007]
- 22 **Graham RP**, Vierkant RA, Tillmans LS, Wang AH, Laird PW, Weisenberger DJ, Lynch CF, French AJ, Slager SL, Raissian Y, Garcia JJ, Kerr SE, Lee HE, Thibodeau SN, Cerhan JR, Limburg PJ, Smyrk TC. Tumor Budding in Colorectal Carcinoma: Confirmation of Prognostic Significance and Histologic Cutoff in a Population-based Cohort. *Am J Surg Pathol* 2015; **39**: 1340-1346 [PMID: 26200097 DOI: 10.1097/PAS.0000000000000504]
 - 23 **Guzińska-Ustymowicz K**, Niewiarowska K, Pryczynicz A. Invasive micropapillary carcinoma: a distinct type of adenocarcinomas in the gastrointestinal tract. *World J Gastroenterol* 2014; **20**: 4597-4606 [PMID: 24782612 DOI: 10.3748/wjg.v20.i16.4597]
 - 24 **Eremia IA**, Ciobanu M, Tenea T, Comănescu MV, Crăitoiu S. Invasive papillary carcinoma of the mammary gland: histopathologic and immunohistochemical aspects. *Rom J Morphol Embryol* 2012; **53**: 811-815 [PMID: 23188445]
 - 25 **Zekioglu O**, Erhan Y, Ciris M, Bayramoglu H, Ozdemir N. Invasive micropapillary carcinoma of the breast: high incidence of lymph node metastasis with extranodal extension and its immunohistochemical profile compared with invasive ductal carcinoma. *Histopathology* 2004; **44**: 18-23 [PMID: 14717664 DOI: 10.1111/j.1365-2559.2004.01757.x]
 - 26 **Sonoo H**, Kameyama M, Inatugi N, Nonomura A, Enomoto Y. Pedunculated polyp of early sigmoid colon cancer with invasive micropapillary carcinoma. *Jpn J Clin Oncol* 2009; **39**: 523-527 [PMID: 19561116 DOI: 10.1093/jjco/hyp051]
 - 27 **Verdú M**, Román R, Calvo M, Rodón N, García B, González M, Vidal A, Puig X. Clinicopathological and molecular characterization of colorectal micropapillary carcinoma. *Mod Pathol* 2011; **24**: 729-738 [PMID: 21336262 DOI: 10.1038/modpathol.2011.1]
 - 28 **Mukai S**, Takakura Y, Egi H, Hinoi T, Saito Y, Tanimine N, Miguchi M, Adachi T, Shimomura M, Ohdan H. Submucosal invasive micropapillary carcinoma of the colon with massive lymph node metastases: a case report. *Case Rep Oncol* 2012; **5**: 608-615 [PMID: 23275774 DOI: 10.1159/000345566]
 - 29 **Hisamori S**, Nagayama S, Kita S, Kawamura J, Yoshizawa A, Sakai Y. Rapid progression of submucosal invasive micropapillary carcinoma of the colon in progressive systemic sclerosis: report of a case. *Jpn J Clin Oncol* 2009; **39**: 399-405 [PMID: 19287022 DOI: 10.1093/jjco/hyp015]
 - 30 **Cooper HS**. Pathologic issues in the treatment of endoscopically removed malignant colorectal polyps. *J Natl Compr Canc Netw* 2007; **5**: 991-996 [PMID: 17977505 DOI: 10.6004/jncn.2007.0083]
 - 31 **Chung EJ**, Lee JY, Choe J, Chang HS, Kim J, Yang DH, Ye BD, Byeon JS, Kim KJ, Yang SK, Kim JH, Myung SJ. Colonic Chicken Skin Mucosa is an Independent Endoscopic Predictor of Advanced Colorectal Adenoma. *Intest Res* 2015; **13**: 318-325 [PMID: 26576137 DOI: 10.5217/ir.2015.13.4.318]
 - 32 **Guan J**, Zhao R, Zhang X, Cheng Y, Guo Y, Wang L, Mi L, Liu F, Ma X, Li B. Chicken skin mucosa surrounding adult colorectal adenomas is a risk factor for carcinogenesis. *Am J Clin Oncol* 2012; **35**: 527-532 [PMID: 21654311 DOI: 10.1097/COC.0b013e31821dedf7]
 - 33 **Shatz BA**, Weinstock LB, Thyssen EP, Mujeeb I, DeSchryver K. Colonic chicken skin mucosa: an endoscopic and histological abnormality adjacent to colonic neoplasms. *Am J Gastroenterol* 1998; **93**: 623-627 [PMID: 9576459 DOI: 10.1111/j.1572-0241.1998.177_b.x]
 - 34 **Shepherd NA**, Griggs RK. Bowel cancer screening-generated diagnostic conundrum of the century: pseudoinvasion in sigmoid colonic polyps. *Mod Pathol* 2015; **28** Suppl 1: S88-S94 [PMID: 25560603 DOI: 10.1038/modpathol.2014.138]
 - 35 **Byun TJ**, Han DS, Ahn SB, Cho HS, Eun CS, Jeon YC, Sohn JH, Oh YH. Pseudoinvasion in an adenomatous polyp of the colon mimicking invasive colon cancer. *Gut Liver* 2009; **3**: 130-133 [PMID: 20431736 DOI: 10.5009/gnl.2009.3.2.130]
 - 36 **Panarelli NC**, Somarathna T, Samowitz WS, Kornacki S, Sanders SA, Novelli MR, Shepherd NA, Yantiss RK. Diagnostic Challenges Caused by Endoscopic Biopsy of Colonic Polyps: A Systematic Evaluation of Epithelial Misplacement With Review of Problematic Polyps From the Bowel Cancer Screening Program, United Kingdom. *Am J Surg Pathol* 2016; **40**: 1075-1083 [PMID: 26975041 DOI: 10.1097/PAS.0000000000000641]
 - 37 **Williams CB**, Saunders BP, Talbot IC. Endoscopic management of polypoid early colon cancer. *World J Surg* 2000; **24**: 1047-1051 [PMID: 11036280 DOI: 10.1007/s002680010144]
 - 38 **Cooper HS**, Deppisch LM, Gourley WK, Kahn EI, Lev R, Manley PN, Pascal RR, Qizilbash AH, Rickert RR, Silverman JF. Endoscopically removed malignant colorectal polyps: clinico-pathologic correlations. *Gastroenterology* 1995; **108**: 1657-1665 [PMID: 7768369 DOI: 10.1016/0016-5085(95)90126-4]
 - 39 **Lopez A**, Bouvier AM, Jooste V, Cottet V, Romain G, Faivre J, Manfredi S, Lepage C. Outcomes following polypectomy for malignant colorectal polyps are similar to those following surgery in the general population. *Gut* 2017 [PMID: 29074726 DOI: 10.1136/gutjnl-2016-312093]
 - 40 **ASGE Standards of Practice Committee**, Fisher DA, Shergill AK, Early DS, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Evans JA, Fanelli RD, Foley KQ, Fonkalsrud L, Hwang JH, Jue T, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD. Role of endoscopy in the staging and management of colorectal cancer. *Gastrointest Endosc* 2013; **78**: 8-12 [PMID: 23664162 DOI: 10.1016/j.gie.2013.04.163]
 - 41 **Nascimbeni R**, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002; **45**: 200-206 [PMID: 11852333 DOI: 10.1007/s10350-004-6147-7]
 - 42 **Mlynarsky L**, Zelber-Sagi S, Miller E, Kariv R. Endoscopic resection of large colorectal adenomas - clinical experience of a tertiary referral centre. *Colorectal Dis* 2018; **20**: 391-398 [PMID: 29105290 DOI: 10.1111/codi.13954]
 - 43 **Ma L**, Zhai Y, Chai N, Li H, Yan L, Li Z, Zhang X, Feng X, Linghu E. Insulated-tip knife endoscopic polypectomy for difficult pedunculated colorectal polyps: a prospective pilot study. *Int J Colorectal Dis* 2017; **32**: 287-290 [PMID: 27987015 DOI: 10.1007/s00384-016-2699-y]
 - 44 **Choi YS**, Lee JB, Lee EJ, Lee SH, Suh JP, Lee DH, Kim DS, Youk EG. Can endoscopic submucosal dissection technique be an alternative treatment option for a difficult giant (≥ 30 mm) pedunculated colorectal polyp? *Dis Colon Rectum* 2013; **56**: 660-666 [PMID: 23575407 DOI: 10.1097/DCR.0b013e318276d2b9]
 - 45 **Yang CW**, Yen HH, Chen YY, Soon MS. Use of dual knife for large pedunculated colorectal polyps. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 444-447 [PMID: 25198067 DOI: 10.1097/SLE.0000000000000097]
 - 46 **Boumitri C**, Mir FA, Ashraf I, Matteson-Kome ML, Nguyen DL, Puli SR, Bechtold ML. Prophylactic clipping and post-polypectomy bleeding: a meta-analysis and systematic review. *Ann Gastroenterol* 2016; **29**: 502-508 [PMID: 27708518 DOI: 10.20524/aog.2016.0075]
 - 47 **Choo WK**, Subhani J. Complication rates of colonic polypectomy in relation to polyp characteristics and techniques: a district hospital experience. *J Interv Gastroenterol* 2012; **2**: 8-11 [PMID: 22586542 DOI: 10.4161/jig.20126]
 - 48 **Kouklakis G**, Mpoumponaris A, Gatopoulou A, Efraimidou E, Manolas K, Lirantzopoulos N. Endoscopic resection of large pedunculated colonic polyps and risk of postpolypectomy bleeding with adrenaline injection versus endoloop and hemoclip: a prospective, randomized study. *Surg Endosc* 2009; **23**: 2732-2737 [PMID: 19430833 DOI: 10.1007/s00464-009-0478-3]
 - 49 **Kim DH**. Prediction and Prevention of Postpolypectomy Bleeding: Necessity of a Different Approach for Patients Using Antithrombotic Agents. *Clin Endosc* 2017; **50**: 217-218 [PMID: 28609814 DOI: 10.5946/ce.2017.056]
 - 50 **Buddingh KT**, Herngreen T, Haringsma J, van der Zwet WC, Vleggaar FP, Breumelhof R, Ter Borg F. Location in the right hemi-

- colon is an independent risk factor for delayed post-polypectomy hemorrhage: a multi-center case-control study. *Am J Gastroenterol* 2011; **106**: 1119-1124 [PMID: 21266961 DOI: 10.1038/ajg.2010.507]
- 51 **Moon HS**, Park SW, Kim DH, Kang SH, Sung JK, Jeong HY. Only the size of resected polyps is an independent risk factor for delayed postpolypectomy hemorrhage: a 10-year single-center case-control study. *Ann Coloproctol* 2014; **30**: 182-185 [PMID: 25210687 DOI: 10.3393/ac.2014.30.4.182]
 - 52 **Ferlitsch M**, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, Jover R, Langner C, Bronzwaer M, Nalankilli K, Fockens P, Hazzan R, Gralnek IM, Gschwanter M, Waldmann E, Jeschek P, Penz D, Heresbach D, Moons L, Lemmers A, Paraskeva K, Pohl J, Ponchon T, Regula J, Repici A, Rutter MD, Burgess NG, Bourke MJ. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017; **49**: 270-297 [PMID: 28212588 DOI: 10.1055/s-0043-102569]
 - 53 **Quintanilla E**, Castro JL, Rábago LR, Chico I, Olivares A, Ortega A, Vicente C, Carbó J, Gea F. Is the use of prophylactic hemoclips in the endoscopic resection of large pedunculated polyps useful? A prospective and randomized study. *J Interv Gastroenterol* 2012; **2**: 183-188 [PMID: 23687606 DOI: 10.4161/jig.23741]
 - 54 **Katsinelos P**, Chatzimavroudis G, Papaziogas B, Zavos C, Paroutoglou G, Pilpilidis I, Vasiladias T, Kountouras J. Endocliping-assisted resection of large colorectal polyps. *Surg Laparosc Endosc Percutan Tech* 2008; **18**: 19-23 [PMID: 18287977 DOI: 10.1097/SLE.0b013e3181576915]
 - 55 **Freeman HJ**. Prophylactic use of endoclips post-polypectomy: to bleed or not to bleed? *Dig Dis Sci* 2014; **59**: 1073-1074 [PMID: 24756317 DOI: 10.1007/s10620-014-3162-y]
 - 56 **Freeman HJ**. Long-term follow-up of patients with malignant pedunculated colon polyps after colonoscopic polypectomy. *Can J Gastroenterol* 2013; **27**: 20-24 [PMID: 23378979 DOI: 10.1155/2013/380389]
 - 57 **Parikh ND**, Zanooco K, Keswani RN, Gawron AJ. A cost-efficacy decision analysis of prophylactic clip placement after endoscopic removal of large polyps. *Clin Gastroenterol Hepatol* 2013; **11**: 1319-1324 [PMID: 23376322 DOI: 10.1016/j.cgh.2012.12.044]
 - 58 **Matsushita M**, Hajiro K, Takakuwa H, Kusumi F, Maruo T, Ohana M, Tominaga M, Okano A, Yunoki Y. Ineffective use of a detachable snare for colonoscopic polypectomy of large polyps. *Gastrointest Endosc* 1998; **47**: 496-499 [PMID: 9647375 DOI: 10.1016/S0016-5107(98)70251-2]
 - 59 **Ji JS**, Lee SW, Kim TH, Cho YS, Kim HK, Lee KM, Kim SW, Choi H. Comparison of prophylactic clip and endoloop application for the prevention of postpolypectomy bleeding in pedunculated colonic polyps: a prospective, randomized, multicenter study. *Endoscopy* 2014; **46**: 598-604 [PMID: 24830400 DOI: 10.1055/s-0034-1365515]
 - 60 **Mizukami T**, Hiroyuki I, Hibi T. Anchor clip technique helps in easy prevention of post-polypectomy hemorrhage of large colonic polyps. *Dig Endosc* 2010; **22**: 366-369 [PMID: 21175500 DOI: 10.1111/j.1443-1661.2010.01017.x]
 - 61 **Cariani G**. Combined technique (adrenaline injection plus endoloop) versus single technique (adrenaline injection) in the prevention of postpolypectomy bleeding in large pedunculated colonic polyps. *Am J Gastroenterol* 2007; **102**: 1137-1138 [PMID: 17489798 DOI: 10.1111/j.1572-0241.2007.01180_13.x]
 - 62 **Paspatis GA**, Paraskeva K, Theodoropoulou A, Mathou N, Vardas E, Oustamanolakis P, Chlouverakis G, Karagiannis I. A prospective, randomized comparison of adrenaline injection in combination with detachable snare versus adrenaline injection alone in the prevention of postpolypectomy bleeding in large colonic polyps. *Am J Gastroenterol* 2006; **101**: 2805; quiz 2913 [PMID: 17026560 DOI: 10.1111/j.1572-0241.2006.00855.x]
 - 63 **Park Y**, Jeon TJ, Park JY, Park SJ, Cheon JH, Kim TI, Kim WH, Hong SP. Comparison of clipping with and without epinephrine injection for the prevention of post-polypectomy bleeding in pedunculated colon polyps. *J Gastroenterol Hepatol* 2015; **30**: 1499-1506 [PMID: 25973838 DOI: 10.1111/jgh.12994]
 - 64 **Tullavardhana T**, Akranurakkul P, Ungkitphaiboon W, Songtish D. Efficacy of submucosal epinephrine injection for the prevention of postpolypectomy bleeding: A meta-analysis of randomized controlled studies. *Ann Med Surg (Lond)* 2017; **19**: 65-73 [PMID: 28652912 DOI: 10.1016/j.amsu.2017.05.035]
 - 65 **Kim HS**, Kim TI, Kim WH, Kim YH, Kim HJ, Yang SK, Myung SJ, Byeon JS, Lee MS, Chung IK, Jung SA, Jeon YT, Choi JH, Choi KY, Choi H, Han DS, Song JS. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. *Am J Gastroenterol* 2006; **101**: 1333-1341 [PMID: 16771958 DOI: 10.1111/j.1572-0241.2006.00638.x]
 - 66 **Lorenzo-Zúñiga V**, Moreno de Vega V, Doménech E, Mañosa M, Planas R, Boix J. Endoscopist experience as a risk factor for colonoscopic complications. *Colorectal Dis* 2010; **12**: e273-e277 [PMID: 19930145 DOI: 10.1111/j.1463-1318.2009.02146.x]
 - 67 **Dobrowolski S**, Dobosz M, Babicki A, Glowacki J, Nalecz A. Blood supply of colorectal polyps correlates with risk of bleeding after colonoscopic polypectomy. *Gastrointest Endosc* 2006; **63**: 1004-1009 [PMID: 16733117 DOI: 10.1016/j.gie.2005.11.063]
 - 68 **Jaruvongvanich V**, Prasitlumkun N, Assavapongpaiboon B, Suchartlikitwong S, Sanguankeo A, Upala S. Risk factors for delayed colonic post-polypectomy bleeding: a systematic review and meta-analysis. *Int J Colorectal Dis* 2017; **32**: 1399-1406 [PMID: 28779355 DOI: 10.1007/s00384-017-2870-0]
 - 69 **Jaruvongvanich V**, Assavapongpaiboon B, Wijarnpreecha K, Ungprasert P. Heparin-bridging therapy and risk of post-polypectomy bleeding: Meta-analysis of data reported by Japanese colonoscopists. *Dig Endosc* 2017; **29**: 743-748 [PMID: 28370508 DOI: 10.1111/den.12882]
 - 70 **Shibuya T**, Nomura O, Kodani T, Murakami T, Fukushima H, Tajima Y, Matsumoto K, Ritsuno H, Ueyama H, Inami Y, Ishikawa D, Matsumoto K, Sakamoto N, Osada T, Nagahara A, Ogihara T, Watanabe S. Continuation of antithrombotic therapy may be associated with a high incidence of colonic post-polypectomy bleeding. *Dig Endosc* 2017; **29**: 314-321 [PMID: 27809364 DOI: 10.1111/den.12760]
 - 71 **Veitch AM**, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Gut* 2016; **65**: 374-389 [PMID: 26873868 DOI: 10.1136/gutjnl-2015-311110]
 - 72 **Williams JG**, Pullan RD, Hill J, Horgan PG, Salmo E, Buchanan GN, Rasheed S, McGee SG, Haboubi N. Association of Coloproctology of Great Britain and Ireland. Management of the malignant colorectal polyp: ACPGBI position statement. *Colorectal Dis* 2013; **15** Suppl 2: 1-38 [PMID: 23848492 DOI: 10.1111/codi.12262]
 - 73 **Brooks DD**, Winawer SJ, Rex DK, Zauber AG, Kahi CJ, Smith RA, Levin B, Wender R; U.S. Multi-Society Task Force on Colorectal Cancer; American Cancer Society. Colonoscopy surveillance after polypectomy and colorectal cancer resection. *Am Fam Physician* 2008; **77**: 995-1002 [PMID: 18441865 DOI: 10.2307/4017009]
 - 74 **Aretz S**, Genuardi M, Hes FJ. Clinical utility gene card for: MUTYH-associated polyposis (MAP), autosomal recessive colorectal adenomatous polyposis, multiple colorectal adenomas, multiple adenomatous polyps (MAP) - update 2012. *Eur J Hum Genet* 2013; **21** [PMID: 22872101 DOI: 10.1038/ejhg.2012.163]
 - 75 **Kahi CJ**, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Lieberman D, Levin TR, Robertson DJ, Rex DK. Colonoscopy Surveillance after Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2016; **111**: 337-346; quiz 347 [PMID: 26871541 DOI: 10.1038/ajg.2016.22]
 - 76 **Rex DK**, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, Burt

- RW, Byers T, Fletcher RH, Hyman N, Johnson D, Kirk L, Lieberman DA, Levin TR, O'Brien MJ, Simmang C, Thorson AG, Winawer SJ. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. *CA Cancer J Clin* 2006; **56**: 160-167; quiz 185-186 [PMID: 16737948 DOI: 10.1053/j.gastro.2006.03.013]
- 77 **Kahi CJ**, Anderson JC, Rex DK. Screening and surveillance for colorectal cancer: state of the art. *Gastrointest Endosc* 2013; **77**: 335-350 [PMID: 23410695 DOI: 10.1016/j.gie.2013.01.002]
- 78 **Lou Z**, Meng RG, Zhang W, Yu ED, Fu CG. Preoperative carcinoembryonic antibody is predictive of distant metastasis in pathologically T1 colorectal cancer after radical surgery. *World J Gastroenterol* 2013; **19**: 389-393 [PMID: 23372362 DOI: 10.3748/wjg.v19.i3.389]
- 79 **Vasile I**, Mirea C, Vilcea ID, Paşalega M, Calotă F, Meşină C, Cheie M, Dumitrescu T, Mogoantă S, Tenea T, Radu V, Moraru E. Esophago-digestive anastomosis dehiscence. *Chirurgia (Bucur)* 2009; **104**: 281-286 [PMID: 19601459]
- 80 **Freeman HJ**. Early stage colon cancer. *World J Gastroenterol* 2013; **19**: 8468-8473 [PMID: 24379564 DOI: 10.3748/wjg.v19.i46.8468]
- 81 **Vilcea ID**, Vasile I, Tomescu P, Pasalega M, Meşină C, Calotă F, Mihaela C, Georgescu E, Ionescu M, Mirea C, Traşcă E, Tenea T, Mogoanta S. Loco-regional advanced colorectal cancer: diagnostic and therapeutic features. *Chirurgia (Bucur)* 2008; **103**: 189-194 [PMID: 18457097]
- 82 **Burada F**, Dumitrescu T, Nicoli R, Ciurea ME, Rogoveanu I, Ioana M. Cytokine promoter polymorphisms and risk of colorectal cancer. *Clin Lab* 2013; **59**: 773-779 [PMID: 24133905 DOI: 10.7754/Clin.Lab.2012.120713]
- 83 **Burada F**, Dumitrescu T, Nicoli R, Ciurea ME, Angelescu C, Mixich F, Ioana M. IL-1RN +2018T>C polymorphism is correlated with colorectal cancer. *Mol Biol Rep* 2013; **40**: 2851-2857 [PMID: 23192617 DOI: 10.1007/s11033-012-2300-x]
- 84 **Meşină C**, Vasile I, Ciobanu D, Calotă F, Gruia CL, Streba L, Mogoantă SŞ, Părvănescu H, Georgescu CV, Tarniţă DN. Collision tumor of recto-sigmoidian junction - case presentation. *Rom J Morphol Embryol* 2014; **55**: 643-647 [PMID: 25178338]

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Basic Study

Histological analysis of human pancreatic carcinoma following irreversible electroporation in a nude mouse model

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Abstract

AIM

To determine changes in the morphology and function of pancreatic cancer cells after irreversible electroporation (IRE) treatment, and to explore the clinical significance of IRE treatment for pancreatic cancer providing an experimental basis for the clinical application of IRE treatment.

METHODS

IRE was carried out in an athymic nude mouse model of pancreatic carcinoma generated with human pancreatic cancer cells 1. In therapy groups, IRE electrodes were inserted with 90 pulses per second at 800 V/cm applied to ablate the targeted tumor tissues. Histological assessment of the affected tissue was performed by hematoxylin and eosin staining (HE). Quantification of cell proliferation and apoptosis was performed by evaluating Ki67 and caspase-3 levels, respectively. Flow cytometry was used to assess cell apoptosis. Ultrasound

imaging was carried out to evaluate IRE treatment results. Pathological correlation studies showed IRE is effective for the targeted ablation of pancreatic tumors in an orthotopic mouse model.

RESULTS

IRE was efficacious in removing tumors in the orthotopic mouse model. The IRE-ablated zone displays characteristics of nude mouse models at different time-points as assessed by hematoxylin and eosin staining. Immunohistochemical analysis of samples from the pancreatic cancer models showed significantly enhanced caspase-3 cleavage and Ki67. Flow cytometry data corroborated the above findings that apoptosis in tumor cells was observed immediately on the first postoperative day, and with time the middle and late stages of apoptosis were observed. For ultrasound imaging studies, the IRE ablation zone became a hyperechoic area due to increasing inflammatory and immunologic cellular contents.

CONCLUSION

IRE is a promising new approach for pancreatic cancer, with many potential advantages over conventional ablation techniques.

Key words: Irreversible electroporation; Pancreatic carcinoma; Pathological evaluation; Transplantation model; Nude mouse

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Core tip: Patients with pancreatic cancer have a poor prognosis. It often quickly develops into locally advanced pancreatic cancer that is considered to be surgically unresectable. Irreversible electroporation represents a novel tumor ablation method that induces cell apoptosis with no thermal coagulation effects. This study aimed to assess the clinical significance of irreversible electroporation treatment in pancreatic cancer, and to provide an experimental basis for the clinical application of irreversible electroporation treatment.

Su JJ, Xu K, Wang PF, Zhang HY, Chen YL. Histological analysis of human pancreatic carcinoma following irreversible electroporation in a nude mouse model. *World J Gastrointest Oncol* 2018; 10(12): 476-486

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INTRODUCTION

Immunodeficient animals are obtained from genetic mutations or by artificial methods that cause one or more genes of the immune system to be defective.

Because such animals are immunodeficient, they are widely used in the fields of immunology, oncology, toxicology, and others. Currently, BALB/c mice are the most commonly used immunodeficient animals^[1]. A recent xenograft pancreatic cancer model employing human pancreatic cells was adopted^[2]. This constitutes a clinically relevant and reproducible animal model for assessing local and systemic treatments^[3]. Indeed, orthotopic models of pancreatic carcinoma mimic the main features of human disease, and are excellent tools for the biological characterization of this malignancy.

Pancreatic carcinoma is a malignant tumor with the characteristics of insidious onset, fast progression, high postoperative recurrence and overall 5-year survival rate below 5%^[4]. According to reports of the American Cancer Society, pancreatic carcinoma ranks fourth among deadliest cancers. Conventional therapeutic methods include surgical treatment and chemotherapy. However, the majority of cases cannot undergo surgery because they are diagnosed with advanced disease presenting distant metastasis; meanwhile, chemotherapeutics have low permeability and are limited by drug resistance^[5].

Considering the limited therapeutic options, irreversible electroporation (IRE) has been developed in recent years for the treatment of locally advanced pancreatic cancer^[6]. IRE represents a new modality that can be used independently for targeted tissue ablation, applying strong electrical fields instead of heat deposition or chemicals^[7]. Because IRE has a non-thermal mechanism of action, it can be used to target malignancies adjacent to vital structures (e.g., major vessels)^[8]. This study aimed to assess the efficacy of IRE in pancreatic cancer treatment using an orthotopic mouse model.

MATERIALS AND METHODS

Tumor cell line and culture

The human pancreatic cancer cells 1 (PANC-1) cell line was provided by American Type Culture Collection (Tumor Hospital of the Chinese Academy of Medical Sciences, China), and maintained in Dulbecco's modified Eagle's medium (DMEM; HyClone) with 10% FBS (Sigma), 100 U/mL penicillin, and 100 mg/mL streptomycin in a humid environment containing 5% CO₂. Cells were pelleted and re-suspended at 1×10^7 /mL in phosphate buffer solution (PBS, pH = 7.4). Prior to implantation, cell viability was assessed by Trypan blue staining (assessing the viability of the cultured cells for each tumor implantation procedure, > 95%). The tumor cells were kept on ice prior to injection into the pancreas.

Animal model

All animal experiments had approval from the Institutional Animal Care and Use Committee of Chinese

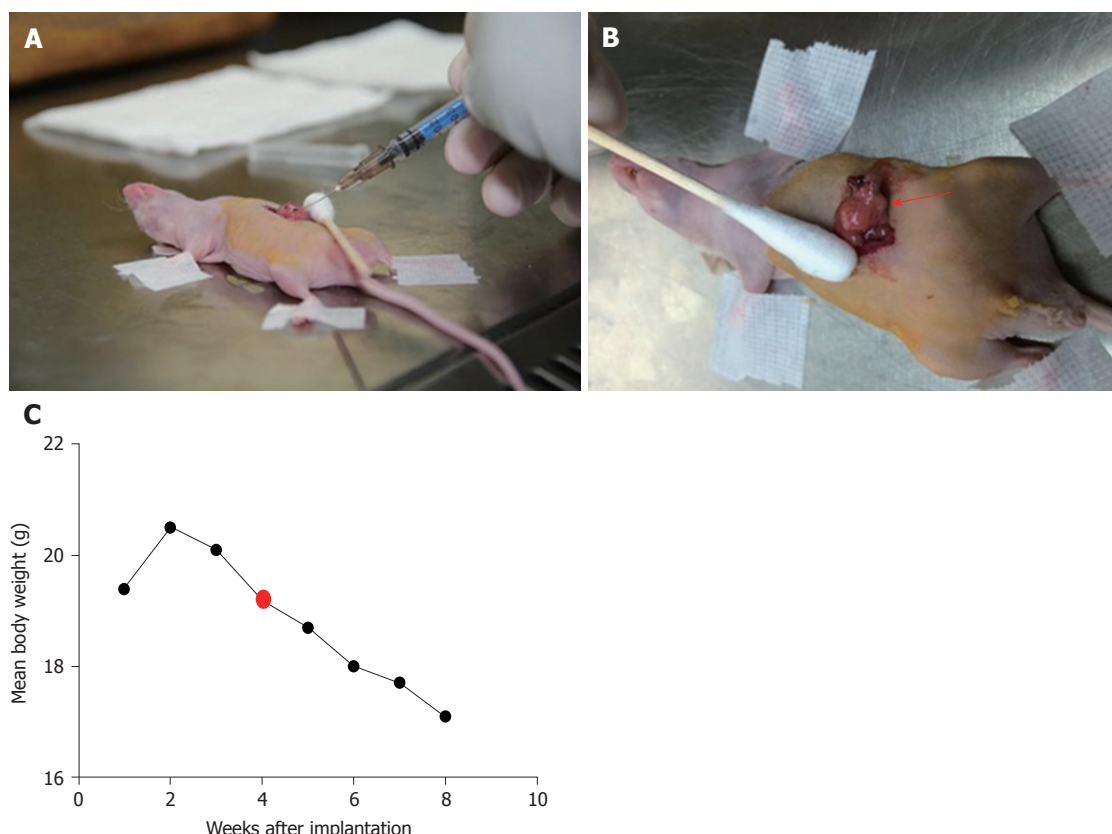


Figure 1 An orthotopic nude mouse with pancreatic cancer generated with human pancreatic cancer cells 1. A: The administered cells generated a bubble on the pancreatic surface; B: The median tumor area at the time of ablation approximated 1 cm²; C: Changes in body weights of tumor-bearing mice at different times after transplantation.

People's Liberation Army General Hospital. Fifty adult male BALB/c nude mice (Institute Of Medical Laboratory Animals, Chinese Academy Of Medical Sciences), initially weighing 18-20 g, were used in this study. The animals were housed in groups of five in facilities maintained at 22 °C ± 1 °C with 55 ± 10% relative humidity, under a 12 h – 12 h light/dark cycle for 1 wk before the experiments. Mice were anesthetized using inhaled 2%-3% isoflurane. Anesthesia depth was evaluated based on the lack of reflex to a toe pinch. The abdomen of each mouse was prepared with Anergian skin disinfectant. Each mouse was turned on the side to raise the left side of the abdomen. Using a sterile scalpel, 1.5 cm skin incisions (about 1 cm left lateral from the midline) were made; 1.5 cm incisions in the underlying abdominal muscle were also made. Then, 50 µL of the cell suspension was injected into the pancreatic tail. These cells generated a bubble on the pancreatic surface (Figure 1A). The injection site was inspected to ensure that no leakage occurred. The abdominal musculature and the external skin in each mouse were separately closed with an absorbable braided suture using a continuous stitch. After wound healing (7 d), the mice were anesthetized, and the external sutures were removed. Following the initial implantation, approximately 5-10 d were required to allow sufficient

tumor growth for pretreatment (diameter < 1.5 cm). The animals were externally examined frequently; in addition, ultra-high frequency, high-definition ultrasound (US) (Philips, CX50, Epiq 7, Seattle, WA, United States) assessment was performed every 3 d from 30 d after tumor cell injection (Figure 1B).

IRE procedures

Forty-four nude mice from the initial 45 implanted animals produced pancreatic cancer (0.5 ± 1.5 cm in diameter) suitable for subsequent IRE treatment procedures. Forty-nine animals were assigned to three groups, including the normal (5 mice with no tumor cell implantation; Group 1), sham-operation (Group 2; *n* = 22), and IRE (Group 3; *n* = 22) groups. Mice in groups 2 and 3 were subsequently euthanized for histological examination at different time-points (1 d, 3 d, and 7 d) after the original baseline scan.

IRE tumor ablation was performed with an experimental IRE generator (Nanoknife; Angio Dynamics, Queensbury, NY, United States). IRE electrodes were positioned in parallel, with spacing set to 0.5 cm, and inserted into the diseased pancreas at a final depth of 0.5 cm. Ablation parameters included a voltage of 800 V/cm at 90 µs and a pulse length of 100 milliseconds. A total of 90 pulses were applied per minute, with an

ablation rate of 90 pulses per second. The abdominal wall in mice was closed after the procedure. The abdominal cavity was opened, exposing the pancreas after 4 wk of modeling. The gross morphologies of the pancreas in various groups were: (1) control group, no obvious mass or tissue adhesion; and (2) IRE group, average tumor diameter of 0.8 cm, with the tumors having a hard texture. With regard to gross appearance, the tumors were round or nodular, and the tumor tissue was usually grayish white. Some of the tumors had mild adhesion to the surrounding tissue, while others invaded adjacent organs such as the stomach, duodenum and peritoneum. Early tumors showed no ascites (Figure 1B).

Tissue collection and immunohistochemistry

Tumor samples were harvested 1 d, 3 d, and 7 d after IRE from anesthetized animals, fixed with 10% formalin, and paraffin embedded. The sections were then submitted to hematoxylin and eosin (HE) staining for histopathological assessment on an Olympus BX43 microscope (Olympus, Japan). Histology slides were blinded and reviewed by a pathologist specialized in gastrointestinal oncology (> 10 years of experience). For immunohistochemistry, four-micron sections were incubated with antibodies against Ki67 (550609, 1:300, BD) and cleaved caspase-3 (Asp175) (9661S, 1:200, Cell Signaling Technology, United States). Ki67 staining was used as a marker of active proliferation, while caspase-3 signals reflected active apoptosis^[9]. Tumor cell proliferation was assessed in five high power fields under a microscope in each slide; the Ki67 index was employed for quantitation. Immunohistochemistry (IHC) staining for Ki67 and cleaved caspase-3 was scored as the percentage of positive cells.

Statistical analysis

Statistical analysis was carried out with SPSS v.22 for Mac (SPSS, United States). Data were presented as mean \pm SD. Groups were compared with variance tests (comparisons between untreated and treated mice). Differences were considered statistically significant with a *P*-value < 0.05.

RESULTS

A total of 44 of the 45 mice implanted with PANC-1 cells developed pancreatic cancer. One mouse was euthanized prior to the beginning IRE procedures because of suture failure, and one animal died after the IRE from improper operation. No severe postoperative complications occurred in the treated mice (Groups 2 and 3).

HE staining

Histological examination of tumor tissues was performed by a pathologist. As shown in Figure 2A,

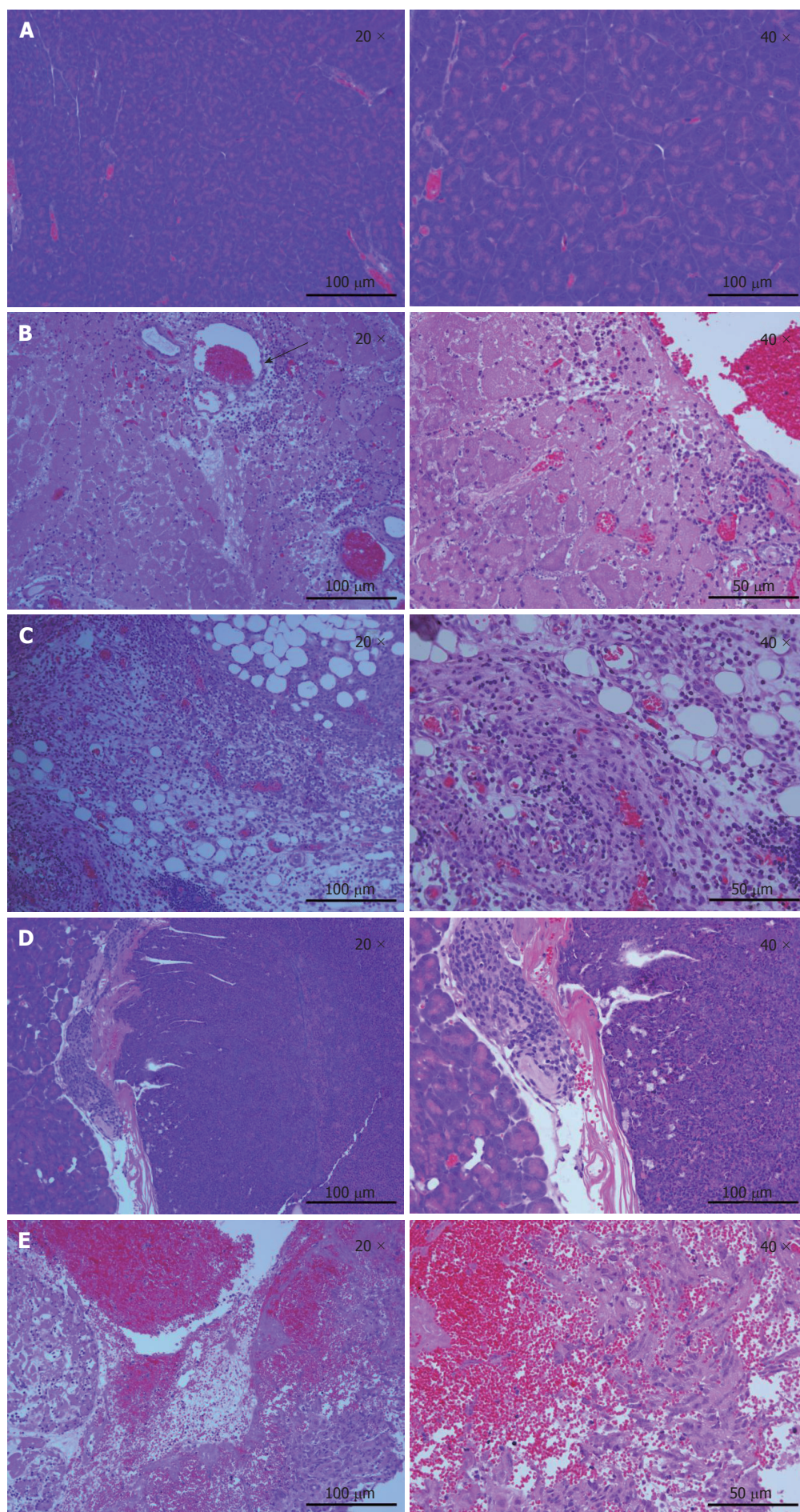
pancreas cells in the normal mouse had large nuclei surrounded by well-demarcated cytoplasm and well-defined cytoplasmic membrane. A total of 3 d post-IRE (Figure 2B), the ablation zone showed areas of acute, extensive, and severe pancreatic cell death. A seepage zone of erythrocytes was observed around the ablation zone. However, larger vessels in the ablated area appeared to be structurally well preserved. The normal pancreatic architecture was preserved. At 7 d after IRE ablation (Figure 2C), erythrocyte leakage continued to decrease. As shown in Figure 2E, most tumor cells were deformed and melded together. Large numbers of inflammatory cells began to permeate into the ablated area. At 3 d after IRE (Figure 2F), the ablation zone was characterized by edematous swelling of the interstitium and tumor tissue necrobiosis. Eosinophilia increased continually, with marked ablation zone inflammation. At 1 d post-IRE treatment (Figure 2G), complete cell death was achieved in the ablation zone, with a sharply delineated margin between ablated and non-ablated surrounding tissues. The majority of tumor cells were displaced by fibrosis, and mononuclear cells and chronic inflammation were observed.

Tumor IHC

To evaluate the effect of IRE on tumor tissues at different time points, *in vivo* IHC experiments were performed. Staining with antibodies targeting Ki67 and cleaved caspase-3 was performed to assess cell proliferation and apoptosis, respectively. Figure 3A is a representative IHC image in an untreated pancreatic parenchyma. In tumor tissues (Figure 3B), extensive caspase-3 activation was observed on the first postoperative day. IRE significantly increased cell proliferation (Ki67 staining) at 1 d post-treatment, but cell proliferation was decreased at 7 d post-treatment. Limited caspase-3 staining at 7 d post-IRE treatment was found in treated tumors, while most of the viable tumor tissues showed no caspase-3 activation (Figure 3C). Our results fully demonstrated overt tumor necrosis in the IRE group, especially the first day after treatment.

Flow cytometry

The propidium iodide staining assay was employed to assess cell cycle distribution. Tumor cells were fixed with 70% ethanol, washed, incubated in presence of 100 mg/mL RNase in PBS (30 min; 37 °C), and stained with 50 mg/mL propidium iodide in PBS. Cell cycle distribution was assessed on a Cell Lab Quanta SC flow cytometer (Beckman Coulter, United States). Meanwhile, Annexin V-fluorescein isothiocyanate Apoptosis Detection Kit (BioVision) was employed for apoptosis quantitation, as directed by the manufacturer. Spleens were extracted, weighed, and processed for analyses. For the cell cycle distribution assay, cells (5×10^5) were harvested, washed with PBS, and finally



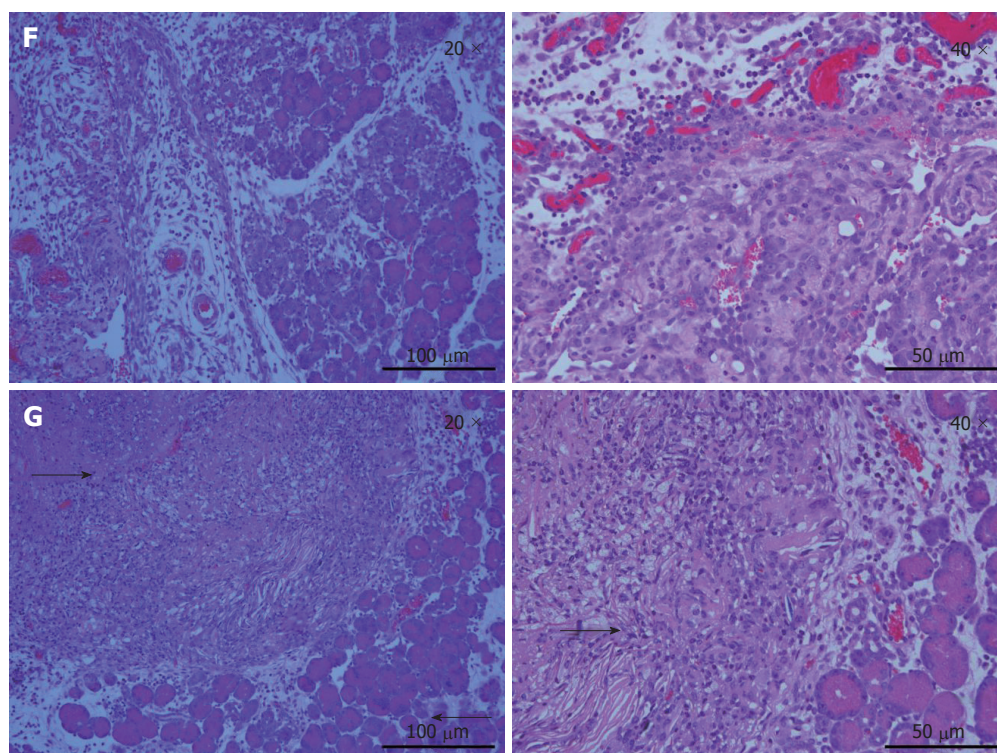


Figure 2 Hematoxylin and eosin staining of pancreatic cells in various groups. A: Histologically stained tissues of pancreatic parenchyma in untreated animals; B, C: Histology showed a normal pancreas after IRE, and a seepage area of erythrocytes was observed around the ablation zone (arrow). Additionally, larger amounts of erythrocytes were observed at 3 d post-IRE compared with 7 d post-IRE (black arrows represent the erythrocyte zone). The vascular structure was not damaged; D: Hematoxylin and eosin staining of tumor cells; E: Nuclear agglutination was observed 1 d post-IRE. The nucleus-to-cytoplasm ratio tended to increase; F: At 3 d post-therapy, a heterogeneous necrotizing tumor was present; G: Micrograph depicting the human pancreatic cancer cells 1 tumor xenograft 7 d post-IRE. A clear demarcation between the ablated (left side) and normal tumor (right side) tissues is depicted (arrows). Tumor cells were arranged more loosely in G compared with F ($\times 200$ or $\times 400$). IRE: Irreversible electroporation.

re-suspended in 500 mL binding buffer, followed by incubation with annexin V-fluorescein isothiocyanate (5 mL) and propidium iodide (5 mL) for 30 min at room temperature in the dark. After staining, cells were assessed on a flow cytometer. Flow cytometry data corroborated the above findings that apoptosis in tumor cells was observed immediately on the first postoperative day, and with time the middle and late stages of apoptosis were observed (Figure 4).

US imaging

For US studies, pre-ablation US (Philips, CX50, Epiq 7, Seattle, WA, United States) was performed to visualize the normal pancreatic anatomy, and US imaging was carried out to evaluate IRE treatment results. Image analysis was carried out by two radiologists with ≥ 10 years of experience in pancreatic US. Consensus was based on post-ablation discussion. In the normal group (Figure 5A and B), the position of the normal pancreatic parenchyma was accurately detected before and after the IRE treatment by US examination. In the tumor group (Figure 5C and 5D), tumor size was determined by US before and after IRE. Upon IRE treatment, US was repeated to acquire post-IRE images. These experiments successfully showed that IRE induced

rapid changes during ablation of the normal pancreatic tissue as well as tumor ablation, and these changes were apparent on US images^[10]. In the tumor tissue, the IRE ablation zone became a hyperechoic area due to increasing inflammatory and immunologic cellular contents.

DISCUSSION

Unresectable lesions amount to roughly 80% of pancreatic cancers at the time of diagnosis, and show a 5-year overall survival below 5%^[11]. This poor prognosis has historically reduced the enthusiasm for aggressive surgical resection^[12]. Recently, alternative tools for local therapy (e.g., radiation and various thermal and non-thermal ablation methods) have been assessed, but often produce discouraging outcomes^[13]. IRE represents a promising novel tool for tissue and tumor ablation^[6]. IRE destroys cells in the target region while preserving the collagen architecture of vascular, biliary, or neuronal structures^[14]. High electric voltage generating a large potential gradient to cause IRE has been assessed *in vitro* and *in vivo*^[8]. Such findings are interesting because IRE effectively causes cell death in the normal tissue as well as cancer cells^[15]. The main advantage of IRE is in the conservation of blood vessel and bowel wall

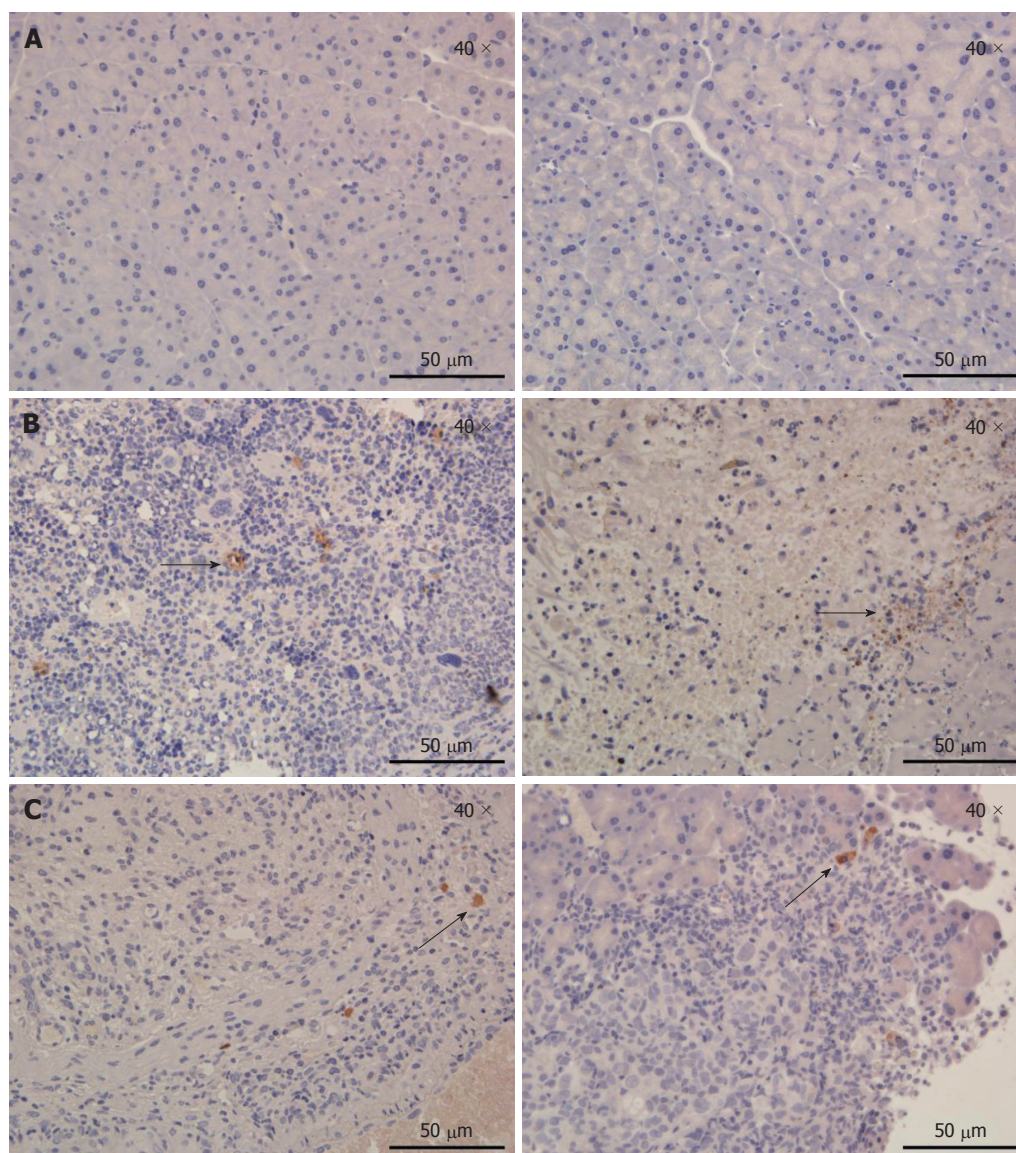


Figure 3 Tumor tissue sections at 1 d and 7 d after the irreversible electroporation treatment were stained for Ki67 and cleaved caspase-3. A: A representative immunohistochemistry image in an untreated pancreatic parenchyma; B: In tumor tissues, extensive caspase-3 activation was observed on the first postoperative day. Irreversible electroporation significantly increased cell proliferation (Ki67 staining) at 1 d post-treatment, but cell proliferation was decreased at 7 d post-treatment (arrows); C: Limited caspase-3 staining at 7 d post-irreversible electroporation treatment was found in treated tumors, while most of the viable tumor tissues showed no caspase-3 activation. The slides were imaged at 400 × by light microscopy.

integrity^[16]. The vascular structure in the ablation zone showed no damage and was only scarcely affected by the IRE treatment. In this study, we created a mouse model of orthotopic pancreatic carcinoma by treating BALB/c nude mice by transabdominal administration of PANC-1 cells. Orthotopic pancreatic cancer modeling was successfully achieved in forty-four nude mice. Studies on animal models demonstrated the efficacy of IRE for achieving anti-tumor effects in orthotopic mouse models of pancreatic cancer by HE staining, apoptosis-specific immunohistological analysis, flow cytometry, and US imaging.

HE staining (Figure 2) showed that the IRE-ablated zone (day 1) had an extensive necrotic area and the IRE ablation border zone had more infiltrated inflam-

matory cells compared with the ablation center zone. Large numbers of red blood cells were observed in the ablation area, which was probably due to IRE destroying microcirculation perfusion in the ablation area. Furthermore, there were large amounts of neutrophils with perivascular infiltration. Moreover, vessels in the ablation area showed an intact structure. We further demonstrated that extensive and severe cell death in the IRE ablation zone was completely different from that observed in the thermal ablation zone. Meanwhile, post-ablation inflammatory reactions were not the overall cause of necrosis resulting from the IRE treatment. At 7 d post-IRE, the tissue in the ablated area showed a uniform structure without cells. IRE caused an ablation of cells but left the cellular matrix intact, providing a

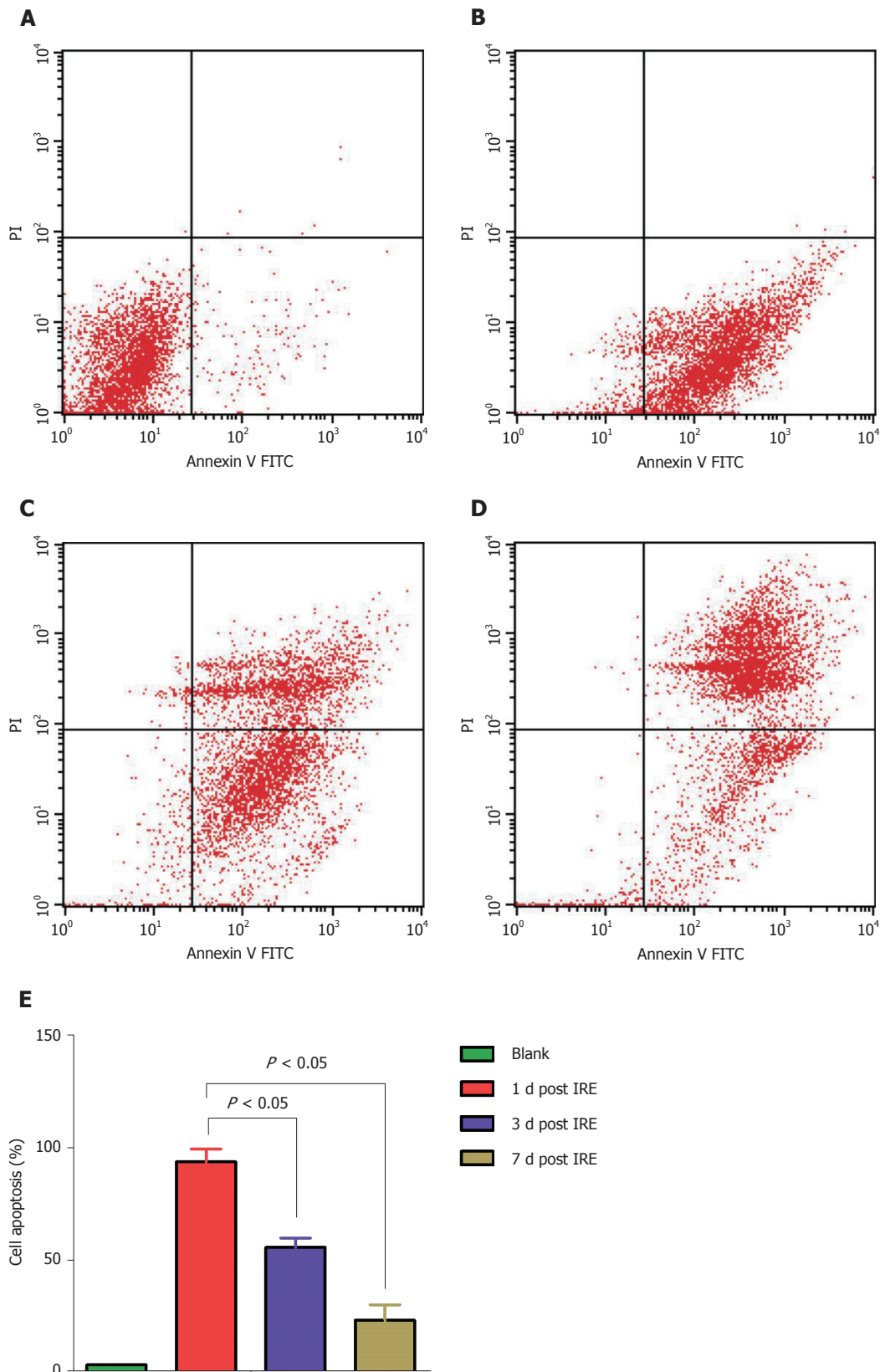


Figure 4 Apoptosis assay of mouse spleen cells before and after irreversible electroporation treatment using double-staining with annexin V-fluorescein isothiocyanate/propidium iodide. Apoptosis was quantified by flow cytometry. A: Control group; B: 1 d post-IRE; C: 3 d post-IRE; D: 7 d post-IRE; E: Percentages of apoptotic cells before and after the IRE intervention. Data are mean \pm SD ($n = 8$). IRE: irreversible electroporation.

good scaffold for new tissue formation^[17]. Due to tissue necrosis and cellulose formation in the ablated area,

the tissue structure was better visualized. We clearly observed that tissue dissolution and absorption occurred

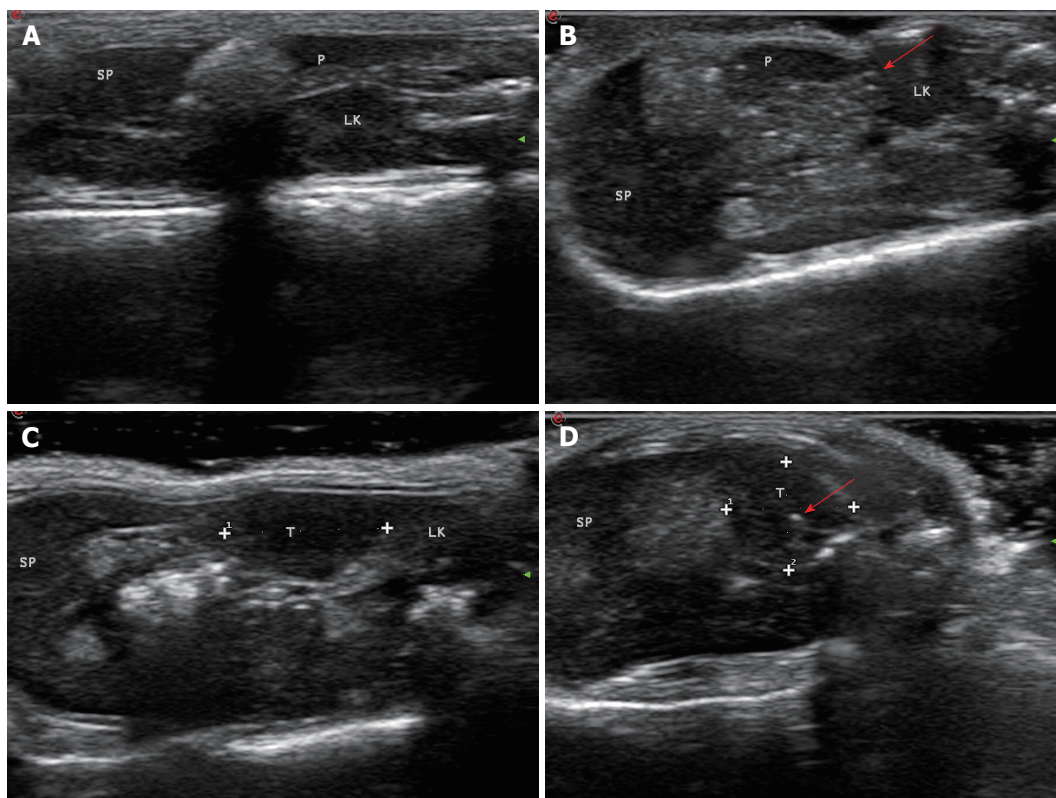


Figure 5 Evaluation of therapeutic effects of irreversible electroporation on tumors *in vivo* by ultrasound. A: A pre-irreversible electroporation ultrasound image showing the normal pancreatic parenchyma; B: The ablation zone showed hyperechoic signals with a comet tail sign in the normal pancreatic tissue (arrow); C: White dots indicate the region of the tumor; D: Ultrasound image showing that the irreversible electroporation ablation zone in the tumor tissue became hyperechoic (arrow). SP: Spleen; LK: Left kidney; P: Pancreas; T: Tumor.

between the necrotic area and the lacunae.

To further assess tissue cell proliferation and apoptosis occurring after the IRE treatment, we next performed IHC to evaluate the effect of IRE on tumor tissues. This study evaluated Ki67 staining and caspase-3 activity, which measure cell proliferation and apoptosis, respectively, in the region between the two electrodes; as shown above, these two measurements showed a positive correlation. The results showed that cell death in the IRE-ablation area was reflected by increased amounts of caspase-3 compared with the adjacent normal tissue on the first day after IRE ablation (Figure 3B). At 7 d postoperatively, very few apoptotic cells were stained, indicating that IRE induced cell death by apoptosis rather than coagulative thermal necrosis. Figure 3B shows blood vessel cells that were not stained, suggesting that large blood vessels are not affected by IRE in the ablation area. This may be an advantage for IRE to create an effective ablation of the undesirable tumor without damaging the underlying architecture of the healthy pancreatic parenchyma.

Furthermore, we used flow cytometry to examine cell cycle distribution and the apoptotic rate. To assess cell apoptosis efficiency, mouse spleen cells in the treatment group were analyzed by flow cytometry at different time-points (Figure 4). No overt cell apoptosis in the control group (Figure 4A) was observed. However,

cells treated by IRE (Figure 4B) had an apoptotic rate of 93.71%, which was markedly elevated compared with the control value (3.37%, $P < 0.05$), suggesting that the IRE treatment is highly effective. Cells in the middle and late stages of apoptosis increased with time (Figure 4C and 4D). As expected, cell apoptosis rates of the therapy groups were much higher than that of the control group. Meanwhile, significant differences were obtained in apoptotic rates at different time points (Figure 4E). These results indicated that the IRE treatment is effective for targeted ablation of pancreatic tumors in an orthotopic mouse model.

The above experiments successfully demonstrated that IRE induces changes detectable on US imaging. Pre-IRE US imaging showed the tumor appearing peripherally hyperechoic compared with the normal pancreatic parenchyma. This study showed that IRE ablation produced greater alterations to echogenicity in tumors compared with normal tissues. The above US findings demonstrated that ablated tissues in the normal pancreas and tumors became more hyperechoic. The US images obtained during IRE showed the hypoechoic ablation region as being mixed with the hyperechoic region in close proximity to the probes used. As shown in Figure 5B, both hyperechoic probe tips of the dual probe system in the ablated zone had a minimal amount of hyperechoic microbubbles. US

images showed that the area of hypoechogenicity became largely hyperechogenic due to increased inflammatory and immunologic cellular contents in the ablated zone. We also demonstrated that the treated areas correlated with pathological measurements. Such changes in echogenicity provide strong evidence that perioperative US is feasible in monitoring IRE.

The efficacy of IRE treatment was also evaluated by monitoring body weights in mice for 7 d (Figure 1C). The therapy groups displayed more pronounced body weights over time compared with control mice, which may be due to decreased tumor sizes in the treatment groups.

Another significant finding was that IRE had a safer and shorter operation procedure compared with traditional techniques, such as the radiofrequency and microwave ablation methods. This compares to routine thermal ablation methods requiring > 30-60 min for ablating a tumor of comparable size^[18]. A reduced operation time in IRE indicates less complications and improved safety for patients compared with conventional means.

In conclusion, this study systematically assessed the efficacy of IRE ablation, and demonstrated that the IRE-ablated zone displays characteristics of nude mouse models at different time-points as assessed by HE staining. IRE is a promising new approach for pancreatic cancer with many potential advantages over conventional ablation techniques. Follow-up US images demonstrated tumor size reduction suggesting that US may be used for ablation zone evaluation.

ARTICLE HIGHLIGHTS

Research background

Irreversible electroporation (IRE) is a medical technique that utilizes high voltage pulses to create permanent nanopores in the cell membrane, which in turn induces apoptosis of the targeted cells. Although there are benefits of IRE, many adverse events should be taken into consideration before its use. We aimed to assess the efficacy of IRE ablation in nude mouse models providing an experimental basis for the clinical application of IRE treatment.

Research motivation

Animal models of pancreatic cancer were successfully established and were successfully treated by IRE treatment. Tumor cell proliferation and apoptosis were detected by different methods, which proved that this treatment was effective.

Research objectives

The main objectives aimed to determine changes in the morphology and function of pancreatic cancer cells after IRE treatment providing an experimental basis for the clinical application of IRE treatment.

Research methods

Animal models of pancreatic cancer were successfully treated by IRE treatment. Histological assessment of the affected tissue was performed by hematoxylin and eosin staining. Quantification of cell proliferation and apoptosis was performed by evaluating Ki67 and caspase-3 levels, respectively. Flow cytometry was used to assess cell apoptosis. Ultrasound imaging was carried out to evaluate IRE treatment results. Pathological correlation studies showed

IRE is effective for the targeted ablation of pancreatic tumors in an orthotopic mouse model. Ultrasound imaging was repeatedly carried out to evaluate IRE treatment results.

Research results

This study systematically assessed the efficacy of IRE ablation and demonstrated that the main advantage of IRE is in the conservation of blood vessel and bowel wall integrity. Clinical data of patients after the application of IRE treatment is needed to prove that IRE treatment is effective in treating patients with pancreatic cancer.

Research conclusions

IRE ablation is safe and effective for treatment of pancreatic cancer in a mouse model. The implication of this study for future clinical practice is that advanced pancreatic cancer patients can use IRE ablation as an effective treatment.

Research perspectives

The future direction of research is the extensive safety application of IRE ablation in patients. The best method for future research is to study the practical application of IRE ablation in patients.

REFERENCES

- 1 **Ingman WV**, Jones RL. Cytokine knockouts in reproduction: the use of gene ablation to dissect roles of cytokines in reproductive biology. *Hum Reprod Update* 2008; **14**: 179-192 [PMID: 18063609 DOI: 10.1093/humupd/dmm042]
- 2 **Philips P**, Li Y, Li S, St Hill CR, Martin RC. Efficacy of irreversible electroporation in human pancreatic adenocarcinoma: advanced murine model. *Mol Ther Methods Clin Dev* 2015; **2**: 15001 [PMID: 26029712 DOI: 10.1038/mtm.2015.1]
- 3 **Philips P**, Li Y, Martin RC 2nd. Low-energy DC current ablation in a mouse tumor model. *Methods Mol Biol* 2014; **1121**: 257-265 [PMID: 24510830 DOI: 10.1007/978-1-4614-9632-8_23]
- 4 **Li D**, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004; **363**: 1049-1057 [PMID: 15051286 DOI: 10.1016/s0140-6736(04)15841-8]
- 5 **Czito BG**, Willett CG, Clark JW, Fernandez Del Castillo C. Current perspectives on locally advanced pancreatic cancer. *Oncology (Williston Park)* 2000; **14**: 1535-1545; discussion 1546, 1549-1552 [PMID: 11125940]
- 6 **Al-Sakere B**, André F, Bernat C, Connault E, Opolon P, Davalos RV, Rubinsky B, Mir LM. Tumor ablation with irreversible electroporation. *PLoS One* 2007; **2**: e1135 [PMID: 17989772 DOI: 10.1371/journal.pone.0001135]
- 7 **Onik G**, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate ablation. *Technol Cancer Res Treat* 2007; **6**: 295-300 [PMID: 17668936 DOI: 10.1177/153303460700600405]
- 8 **Edd JF**, Horowitz L, Davalos RV, Mir LM, Rubinsky B. In vivo results of a new focal tissue ablation technique: irreversible electroporation. *IEEE Trans Biomed Eng* 2006; **53**: 1409-1415 [PMID: 16830945 DOI: 10.1109/tbme.2006.873745]
- 9 **Yagi T**, Hardin JA, Valenzuela YM, Miyoshi H, Gores GJ, Nyberg SL. Caspase inhibition reduces apoptotic death of cryopreserved porcine hepatocytes. *Hepatology* 2001; **33**: 1432-1440 [PMID: 11391532 DOI: 10.1053/jhep.2001.24560]
- 10 **Appelbaum L**, Ben-David E, Sosna J, Nissenbaum Y, Goldberg SN. US findings after irreversible electroporation ablation: radiologic-pathologic correlation. *Radiology* 2012; **262**: 117-125 [PMID: 22106355 DOI: 10.1148/radiol.11110475]
- 11 **Linecker M**, Pfammatter T, Kambakamba P, DeOliveira ML. Ablation Strategies for Locally Advanced Pancreatic Cancer. *Dig Surg* 2016; **33**: 351-359 [PMID: 27216160 DOI: 10.1159/000445021]
- 12 **Artinyan A**, Soriano PA, Prendergast C, Low T, Ellenhorn JD, Kim J. The anatomic location of pancreatic cancer is a prognostic factor for survival. *HPB (Oxford)* 2008; **10**: 371-376 [PMID: 18982154]

DOI: 10.1080/13651820802291233]

- 13 **Hajj C**, Goodman KA. Pancreatic cancer and SBRT: A new potential option? *Rep Pract Oncol Radiother* 2015; **20**: 377-384 [PMID: 26549996 DOI: 10.1016/j.rpor.2015.05.008]
- 14 **Heger M**, van der Wal AC, Storm G, van Gemert MJ. Potential therapeutic benefits stemming from the thermal nature of irreversible electroporation of solid cancers. *Hepatobiliary Pancreat Dis Int* 2015; **14**: 331-333 [PMID: 26063038 DOI: 10.1016/S1499-3872(15)60370-8]
- 15 **Davalos RV**, Msir IL, Rubinsky B. Tissue ablation with irreversible electroporation. *Ann Biomed Eng* 2005; **33**: 223-231 [PMID: 15771276 DOI: 10.1007/s10439-005-8981-8]
- 16 **Leen E**, Picard J, Stebbing J, Abel M, Dhillon T, Wasan H. Percutaneous irreversible electroporation with systemic treatment for locally advanced pancreatic adenocarcinoma. *J Gastrointest Oncol* 2018; **9**: 275-281 [PMID: 29755766 DOI: 10.21037/jgo.2018.01.14]
- 17 **Maor E**, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. *Technol Cancer Res Treat* 2007; **6**: 307-312 [PMID: 17668938 DOI: 10.1177/153303460700600407]
- 18 **Friedman M**, Mikityansky I, Kam A, Libutti SK, Walther MM, Neeman Z, Locklin JK, Wood BJ. Radiofrequency ablation of cancer. *Cardiovasc Intervent Radiol* 2004; **27**: 427-434 [PMID: 15383844 DOI: 10.1007/s00270-004-0062-0]

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Retrospective Study

Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms

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Abstract

AIM

To compare the outcomes of endoscopic submucosal dissection (ESD) for gastric neoplasms using Clutch Cutter (ESD-C) or other knives (ESD-O).

METHODS

This was a single-center retrospective study. Gastric neoplasms treated by ESD between April 2016 and October 2017 at Kitakyushu Municipal Medical Center were reviewed. Multivariate analyses and propensity score matching were used to reduce biases. Covariates included factors that might affect outcomes of ESD, including age, sex, underlying disease, anti-thrombotic drugs use, tumor location, tumor position, tumor size, tumor depth, tumor morphology, tumor histology, ulcer (scar), and operator skill. The treatment outcomes were compared among two groups. The primary outcome was ESD procedure time. Secondary outcomes were *en bloc*, complete, and curative resection rates, and adverse events rates including perforation and delayed bleeding.

RESULTS

A total of 155 patients were included in this study; 44 pairs were created by propensity score matching. Background characteristics were quite similar among two groups after matching. Procedure time was significantly shorter for ESD-C (median; 49 min) than for ESD-O (median; 88.5 min) ($P < 0.01$). However, there was no significant difference in treatment outcomes between ESD-C and ESD-O including *en bloc* resection rate (100% in both groups), complete resection rate (100% in both groups), curative resection rate (86.4% *vs* 88.6%, $P = 0.730$), delayed bleeding (2.3% *vs* 6.8%, $P = 0.62$) and perforation (0% in both groups).

CONCLUSION

ESD-C achieved shorter procedure time without an increase in complication risk. Therefore, ESD-C could become an effective ESD option for gastric neoplasms.

Key words: Endoscopic submucosal dissection; Clutch Cutter; Gastric neoplasm; Knife; Propensity score

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Core tip: Propensity score matching was performed to compare the outcomes of endoscopic submucosal

dissection (ESD) for gastric neoplasms using Clutch Cutter or other knives in this single-center retrospective study. Forty-four pairs were matched in this study. ESD using Clutch Cutter achieved shorter procedure time without an increase in complication risk (median procedure time; 49 min *vs* 88.5 min, $P < 0.01$). Therefore, ESD using Clutch Cutter could become an effective ESD option for gastric neoplasms.

Hayashi Y, Esaki M, Suzuki S, Ihara E, Yokoyama A, Sakisaka S, Hosokawa T, Tanaka Y, Mizutani T, Tsuruta S, Iwao A, Yamakawa S, Irie A, Minoda Y, Hata Y, Ogino H, Akiho H, Ogawa Y. Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms. *World J Gastrointest Oncol* 2018; 10(12): 487-495

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is the standard treatment for gastrointestinal tract tumors including gastric neoplasms, achieving a higher rate of *en bloc* resection and low rates of local recurrence even for large and ulcerated lesions, as compared with endoscopic mucosal resection (EMR)^[1]. However, more advanced technical skills and greater experience are needed in ESD because of the longer procedure time and high risk of complications including bleeding and perforation^[1]. Although various types of endo-knife including needle-type knife and insulated-tip knife were invented and used in ESD, this remains a challenging procedure and there is no consensus on the best knife to be used^[2-5].

Clutch Cutter (DP2618DT, Fujifilm Medical, Tokyo, Japan; Figure 1) was invented as a scissor-type device for ESD, which allows for grasping of the targeted tissue and its subsequent cut with an electrosurgical unit^[6]. This procedure is similar to the technique of a standard bite biopsy, which is a common procedure during routine endoscopy. Furthermore, Clutch Cutter allows re-grasping of the tissue anytime during ESD, which may prevent miscutting and perforation. Therefore, Clutch Cutter may contribute to easier and safer ESD than other endo-knives. ESD with Clutch Cutter (ESD-C) may then become an option of endo-knife for ESD. Favorable outcomes of ESD-C have been reported, including in a large single-center study with single arm trial^[7-9]. However, few reports exist showing the comparison between scissors-type and non-scissors-type knives in the technical outcomes of ESD, which have been limited to non-experts in inclusion criteria^[10,11]. The advantage of scissor-type knife in ESD is controversial at present because comparative studies are still lacking.

We retrospectively compared the technical outcomes of ESD-C for gastric neoplasms with those of ESD



Figure 1 Clutch Cutter is a scissor-type device for endoscopic submucosal dissection.

with other knives (ESD-O) by using propensity score matching analysis, which compensated for differences in extraneous factors including baseline characteristics^[2]. We hypothesize that the outcomes using ESD-C will be superior to those of ESD-O.

MATERIALS AND METHODS

Study design and ethical approval

This was designed as a retrospective, observational cohort study, which was conducted based on the ESD databases at a single-center, Kitakyushu Municipal Medical Center (Fukuoka, Japan). These cases represented a consecutive and unselected cohort. The protocol of this study was developed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kitakyushu Municipal Medical Center on November 2017 (No. 201711050).

Patients

We enrolled 191 consecutive patients with gastric neoplasms treated by ESD between April 2016 and October 2017 at the Kitakyushu Municipal Medical Center. Three patients were excluded from analysis for previously having undergone gastric surgery. Furthermore, 33 patients were excluded because two or more lesions were simultaneously resected. Finally, 155 patients were analyzed in this study. We classified the patients into two groups: one group included patients treated by ESD-C and the other group included patients treated by ESD-O. Either IT Knife2 (KD-611L, Olympus, Tokyo, Japan) or Splash M-Knife (DN-D2718A; HOYA Corp., Pentax, Tokyo, Japan) was mainly used in the patients enrolled between April 2016 and March 2017, while Clutch Cutter was mainly used in the patients enrolled between April 2017 and October 2017. The flow chart of the patients enrolled in the present study is shown in Figure 2.

ESD procedure

All patients were admitted at Kitakyushu Municipal

Medical Center. All ESD procedures were carried out using a GIF-Q260J (Olympus, Tokyo, Japan) with a CO₂ insufflation system. VIO 300D (ERBE Elektromedizin, GmbH, Tübingen, Germany) was used as the electrical power source. The ESD procedure was described in detail in previous reports^[7,12,13]. In brief, marking dots were made 2 mm outside the lesion. A mixture of 4% hyaluronic acid and normal saline with a small amount of indigo carmine and epinephrine (0.001 mg/mL) was injected into the submucosa. After lifting the lesion, mucosal incision was conducted circumferentially using cutting and coagulation (Figure 3A). Once the circumferential mucosal incision was completed, submucosal dissection of the lesion was performed using cutting and coagulation (Figure 3B). Injection was added during dissection when needed. Prophylactic coagulation for visible vessels or hemostasis for active bleeding was conducted using endo-knives or hemostatic forceps (Figure 3C). When using Clutch Cutter, cutting was conducted by Endo Cut Mode (effect 1, duration 4, interval 1), while coagulation was conducted by Soft Coagulation Mode (80-100 W, effect; 5-6 in VIO300D) or Forced Coagulation Mode (30 W, effect 2). In this study, operators with an experience of performing at least 50 ESD procedures were defined as experts, while those who had performed less than 50 ESD procedures were defined as trainees. As a result, 4 operators were defined as experts and 5 as trainees in this study. All experts were familiar with using each device since they had used each device at least 10 times before this study.

Histology evaluation

ESD specimens were immediately stretched and fixed in 10% buffered formalin. The specimens were serially sectioned perpendicularly at 2-3 mm intervals. Then, histological type, depth of invasion, tumor size, lymphatic/vascular invasion, and resection margin were assessed. The pathological curability of the specimens was evaluated based on the Japanese Gastric Cancer Classification^[14].

Outcome

The primary outcome of this study was the procedure time during ESD, which was defined as the time from the start of marking to the completion of dissection. *En bloc* resection rate, complete resection rate, curative resection rate, and the rate of complications (delayed bleeding and perforation) were evaluated as secondary outcomes. *En bloc* resection was defined as resection in one piece. Complete resection was defined as *en bloc* resection with the lateral and vertical resection margins free of neoplasm. Curative resection was evaluated according to the guideline^[15]. Delayed bleeding was defined as clinical evidence of bleeding after ESD, requiring endoscopic hemostasis or blood transfusion. Perforation was diagnosed if mesenteric fat or the

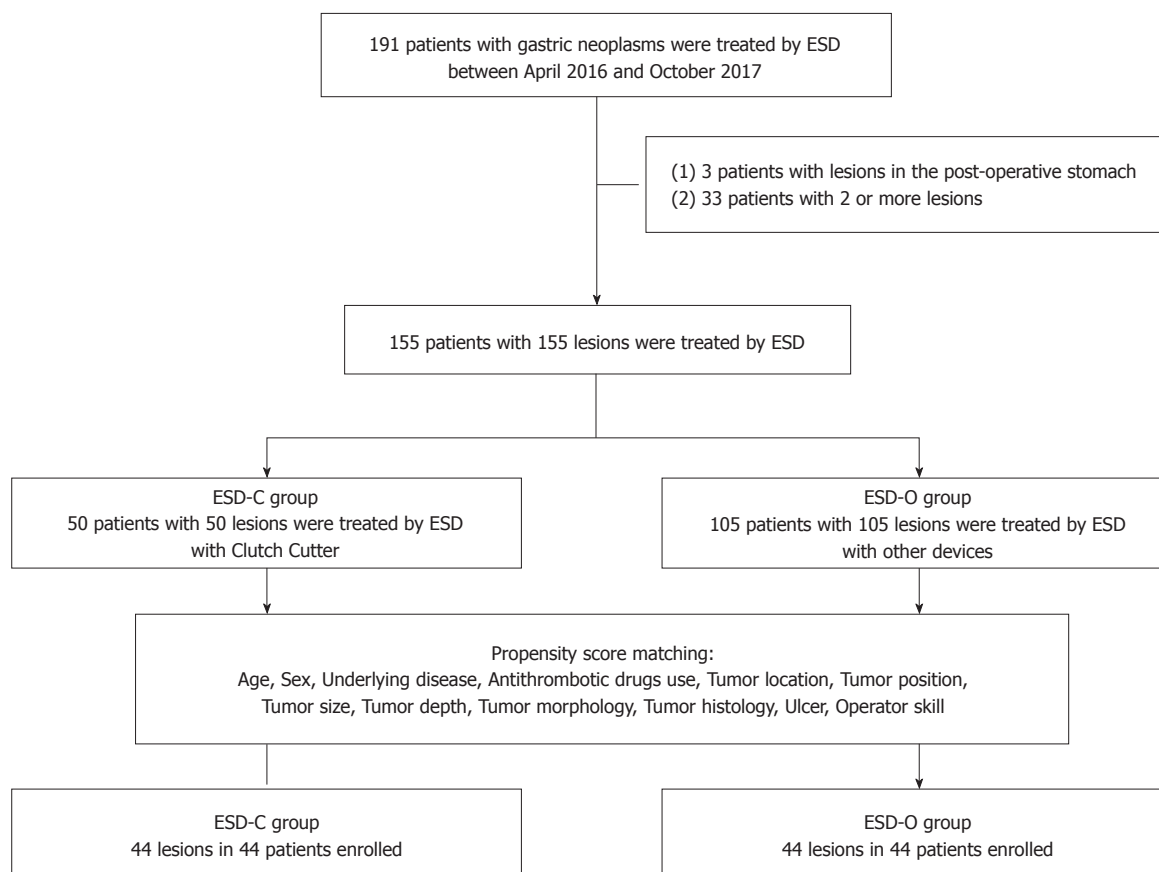


Figure 2 Flowchart of patients and lesions enrolled in this study. ESD: Endoscopic submucosal dissection; ESD-C: Endoscopic submucosal dissection using Clutch Cutter; ESD-O: Endoscopic submucosal dissection using other knives.

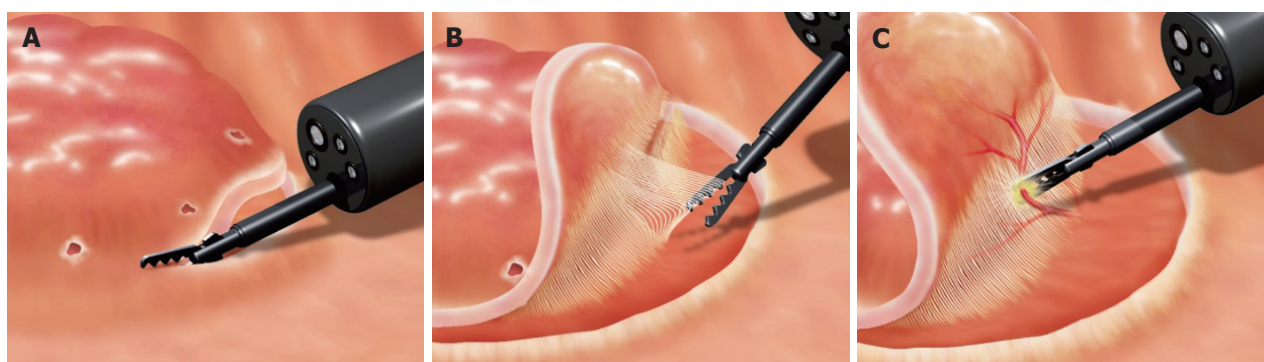


Figure 3 Procedures of endoscopic submucosal dissection. A: Mucosal incision using Clutch Cutter; B: Submucosal dissection using Clutch Cutter; C: Prophylactic coagulation for visible vessels using Clutch Cutter.

intra-abdominal space was observed during ESD procedure or free air was detected on chest and abdominal radiographs or computed tomography scans after ESD. All patients were given a proton pump inhibitor or potassium competitive acid blocker for a minimum of 4 wk.

Statistics

Background characteristics were not equal among two groups. Previous studies have reported some factors associated with the difficulty or complication of the

ESD procedure, which may affect outcomes of this study^[16-22]. Therefore, we adopted propensity score matching analysis to reduce bias. Logistic regression of the following factors with ESD device (Clutch Cutter vs other endo-knives) and calculation of propensity score were conducted: age (≥ 75 vs < 75 years old), sex (male vs female), underlying disease (presence vs none), anti-thrombotic drugs use (continuation vs not receiving or discontinuation), tumor location (upper third of the stomach vs middle or lower third), tumor position (lessor curvature of the stomach vs others),

tumor size (> 20 mm vs ≤ 20 mm), tumor depth (mucosa vs submucosa), tumor morphology (flat or depressed vs others), tumor histology (differentiated type vs undifferentiated type), ulcer (scar) (presence vs absence), and operator skill (expert vs trainee). Underlying disease included cardiomyopathy, liver cirrhosis, and chronic kidney disease. Nearest neighbor matching in a 1:1 ratio from the ESD-C and ESD-O groups was made in calipers (0.12) with a width equal to 0.25 of the standard deviation of the logit of the propensity score. Baseline characteristics and outcomes were analyzed using Fisher's exact test for categorical data, the Mann-Whitney U test for continuous data with non-normal distributions, and a *t* test for continuous data with normal distribution. $P < 0.05$ was considered statistically significant for all tests. All statistical analyses were performed using JMP Pro13.0 software (SAS Institute, Cary, NC, United States).

RESULTS

Propensity score matching

The area under the receiver operating characteristic curve, *i.e.*, C statistic, was estimated to be 0.681, which indicated good predictive power. Propensity score matching created 44 pairs in this study. We compared two groups by using the absolute standardized differences (ASD) before and after matching to assess the propensity score balance. After matching, all ASDs ranged within $1.96\sqrt{2/n}$, indicating that the characteristics were well-balanced^[23].

Characteristics before and after propensity score matching

The background characteristics of 155 patients enrolled in this study are shown in Table 1. Patients in the ESD-C group had a significantly higher rate of undifferentiated adenocarcinoma than those in the ESD-O group (10.0% vs 0.95%; $P = 0.014$). The median tumor size of patients in ESD-C group was significantly smaller than that of patients in the ESD-O group (13.5 mm vs 18.0 mm; $P = 0.027$).

Matching factors between two groups after propensity score matching are shown in Table 2. No significant differences were found in any matching factors.

Technical outcomes after propensity score matching

Treatment outcomes after matching are shown in Table 3. A significantly shorter procedure time was observed for ESD-C than for ESD-O in the adjusted comparison (49.0 min vs 88.5 min; $P < 0.001$). *En bloc* resection rates and complete resection rates were 100% in both groups. All ESDs were completed without perforation. Curative resection rates were similar between the two groups. The delayed bleeding rates of ESD-C tended to be lower than those of ESD-O, but these rates did not reach statistical significance (2.3% vs 6.8%, $P = 0.62$).

DISCUSSION

The present study is the first to show that the technical outcomes of ESD-C are superior to those of ESD-O for the endoscopic treatment of gastric neoplasms regardless of technical expertise, as shown by the propensity score matching analysis.

Currently, a wide variety of ESD devices is available. These devices are roughly classified into two types: scissor-type knives or non-scissor-type knives. The scissor-type knives commonly used in ESD include Clutch Cutter, SB knife, and SB knife Jr, while non-scissor-type knives mainly include IT Knife2, Dual knife, Flush knife, and Splash M-Knife. However, it is yet to be determined which type of knife is superior, scissor-type or non-scissor-type.

It has been reported that the scissor-type knives reduced the technical difficulty of gastrointestinal ESD for unexperienced as well as expert endoscopists^[24,25]. Rescue usage of the SB Jr knife has been reported to increase the self-completion rate of ESD of colorectal neoplasms using the Flush knife (63% in the SB Jr knife group vs 39% in the Flush knife only group; $P = 0.03$), without increasing the procedure time (59 min vs 51 min; $P = 0.14$)^[11]. In other studies, however, ESD-C was reported to be a time-consuming procedure compared with ESD with non-scissor-type knives, especially when performed by unexperienced endoscopists^[26,27]. Therefore, we carried out this study using a propensity score matching analysis to determine which was superior, ESD-C or ESD-O. We found that ESD-C achieved significantly shorter procedure time than ESD-O, indicating that ESD-C is a time-saving rather than a time-consuming procedure. Clutch Cutter might reduce the technical difficulties in gastric ESD similarly to those in colorectal ESD, which might have contributed to the reduction in procedure time. The scissors-type knives were invented several years after the invention of non-scissors-type knives^[4-6]. In general, ESD experts tended to use non-scissors-type knives rather than scissors-type knives. In previous studies on the usefulness of ESD-C, the ESD-C procedures were conducted mainly by trainees rather than experts. In this study, however, ESD procedures were performed by 4 experts and 5 trainees. After propensity score matching, up to 68.2% of ESD procedures were conducted by experts, which might explain the discrepancy in the outcomes between the present and previous studies. ESD with scissor-type knives is being widely used not only by trainees but also by experts.

Both delayed bleeding and perforation are major complications of ESD. In the present study, delayed bleeding occurred in only 1 case with ESD-C while in 3 cases with ESD-O after propensity score matching, although the results were not statistically significant. Moreover, the delayed bleeding rate was 2.0% in ESD-C before propensity score matching (data not shown),

Table 1 Characteristics of enrolled patients before propensity score matching

	ESD-C <i>n</i> = 50	ESD-O <i>n</i> = 105	<i>P</i> value	ASD
Age, yr				
Mean ± SD	73.1 ± 8.55	72.75 ± 8.04	0.806 ²	0.0422
Median (range)	74.0 (46–91)	73.0 (52–91)	0.580 ³	
Sex (<i>n</i>)				
Male	39	71	0.256 ¹	0.2350
Female	11	34		
Underlying disease, positive, <i>n</i> (%)	18 (36.0)	29 (27.6)	0.350 ¹	0.1810
Anti-thrombotic drugs (<i>n</i>)				
None or discontinuation	48	102	0.658 ¹	0.0623
Continuation	2	3		
Tumor location (<i>n</i>)				
Upper third	9	17	0.820 ¹	0.0481
Middle or lower third	41	88		
Tumor position (<i>n</i>)				
Lesser	21	57	0.731 ¹	0.2670
Others	29	48		
Morphology (<i>n</i>)				
Flat or depressed	29	63	0.862 ¹	0.0407
Others	21	42		
Histology (<i>n</i>)				
Undifferentiated	5	1	0.014 ^{1,4}	0.4060
Others	45	104		
Tumor size (mm)				
Mean ± SD	16.89 ± 12.65	20.90 ± 13.30	0.076 ²	0.3090
Median (range)	13.5 (3–67)	18.0 (3–82)	0.027 ^{3,4}	
Tumor depth (<i>n</i>)				
Mucosa	44	91	1.000 ¹	0.0401
Submucosa	6	14		
Ulceration positive, <i>n</i> (%)	7 (14.0)	22 (21.0)	0.381 ¹	0.1840
Operator skill				
Experts	34	73	0.854 ¹	0.0329
Trainees	16	32		

¹*P* value was calculated using Fisher's exact test; ²*P* value was calculated using a *t* test; ³*P* value was calculated using the Mann-Whitney *U* test; ⁴Significant value. ESD-C: Endoscopic submucosal dissection with Clutch Cutter; ESD-O: Endoscopic submucosal dissection with another end-knife; SD: Standard deviation; ASD: Absolute standardized difference.

Table 2 Matching factors between two groups after propensity score matching

	ESD-C <i>n</i> = 44	ESD-O <i>n</i> = 44	<i>P</i> value	ASD
Variable matching between groups				
Age, yr; mean ± SD	73.16 ± 8.59	71.11 ± 8.81	0.273 ²	0.2360
Sex: Male/female	8/36	6/38	0.772 ¹	0.1250
Underlying disease: No/yes	28/16	29/15	1 ¹	0.0476
Anti-thrombotic drugs: No/yes	2/42	3/41	1 ¹	0.0983
Tumor location: Upper third/others	7/37	2/42	0.250 ¹	0.3810
Tumor position: Lesser/others	19/25	21/23	0.831 ¹	0.0914
Morphology: Flat or depressed/others	25/19	28/16	0.663 ¹	0.1400
Histology: Undifferentiated/others	0/44	0/44	-	0
Tumor size, mm: mean ± SD	16.89 ± 12.65	20.90 ± 13.30	0.076 ²	0.3090
Tumor depth: Mucosa/submucosa	Jun-38	Jun-38	1 ¹	0
Ulceration, positive	6 (13.6%)	4 (9.1%)	0.739 ¹	0.1440
Operator skill: Expert/trainee	14/30	14/30	1 ¹	0

¹*P* value was calculated using Fisher's exact test; ²*P* value was calculated using a *t* test for continuous data. ESD-C: Endoscopic submucosal dissection with Clutch Cutter; ESD-O: Endoscopic submucosal dissection with another end-knife; SD: Standard deviation; ASD: Absolute standardized difference.

which was lower than previously reported delayed bleeding rates^[15]. Although it was unknown why delayed bleeding occurs, during ESD-C, hemostasis was conducted by grasping and coagulation, similar to the procedure by hemostatic forceps, which may contribute to the reduction in the delayed bleeding rate. On the

other hand, no perforation occurred in ESD-C before propensity score matching in this study. By contrast, perforation occurred in one case of ESD-O before matching (data not shown), although this case was excluded after propensity score matching. Although the number of patients undergoing ESD-C was smaller than

Table 3 Treatment outcomes between two groups after propensity score matching *n* (%)

	ESD-C <i>n</i> = 44	ESD-O <i>n</i> = 44	<i>P</i> value
Procedure time, min			< 0.001 ^{2,3}
Mean ± SD	63.1 ± 41.90	98.41 ± 51.77	
Median (range)	49 (9–190)	88.5 (26–290)	
<i>En bloc</i> resection	44 (100)	44 (100)	-
Complete resection	44 (100)	44 (100)	-
Curative resection	38 (86.4)	39 (88.6)	0.730 ¹
Perforation	0 (0)	0 (0)	-
Delayed bleeding	1 (2.3)	3 (6.8)	0.620 ¹

¹*P* value was calculated using Fisher's exact test; ²*P* value was calculated using the Mann-Whitney *U* test; ³Significant value. ESD-C: Endoscopic submucosal dissection with Clutch Cutter; ESD-O: Endoscopic submucosal dissection with another end-knife; SD: Standard deviation.

that of patients undergoing ESD-O, ESD-C might be a safer procedure than ESD-O. In ESD-C, tissue grasping and lifting were conducted before coagulation or cutting, which could reduce heat conduction to the muscular layer, contributing to the decreased risk of perforation. In terms of safety, it was reported that ESD-C could be preferred over ESD-O for elderly patients with some comorbidities^[28]. In the present study, over 90% (46/50 before matching, 41/44 after matching) of patients were aged 65 years or older; furthermore, over 40% (22/50 before matching, 20/44 after matching) of patients were aged 75 years or older. No patient experienced worsening of general condition or developed any severe complications. However, further studies are required to clarify whether ESD-C is safer than ESD-O. In addition, ESD-C has been recently used not only for ESD but also for other endoscopic procedures such as endoscopic treatment of Zenker's diverticulum and endoscopic necrosectomy for pancreatic necrosis^[29–31]. In the future, Clutch Cutter could be widely applied in additional endoscopic procedures.

This study had several limitations. First, this was a single-center retrospective study. Therefore, the sample size was relatively small. There might be a selection bias because lesions in the ESD-C group were significantly smaller than those in the ESD-O group and had significantly higher rate of undifferentiation in histology evaluation. Second, only 9 endoscopists conducted ESD. Therefore, a multicenter trial should be carried out to validate this outcome. Third, in some ESD procedures conducted by trainees, experts occasionally assisted in the procedure, which might affect the outcomes of this study. Fourth, we grouped other devices together, including needle-type and insulated-tip knives, for comparison with Clutch Cutter. Future studies are needed to compare each knife individually with Clutch Cutter. Fifth, there was a possibility of an institutional learning curve. We cannot compensate for this bias because the Clutch Cutter was used mainly in the latter phase of this study; other devices were used mainly in former phase of this study, which may also affect outcomes.

In conclusion, ESD-C achieved shorter procedure time than ESD-O without an increase in complication rates. Therefore, ESD-C could become one of the

best endoscopic procedure options in ESD for gastric neoplasms.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is the standard treatment for early gastric neoplasms with negligible lymph node metastasis. However, it is a complex and difficult procedure. Many types of endo-knives have been invented and developed to improve the ESD procedure.

Research motivation

The Clutch Cutter is a novel scissor-type endo-knife, which may contribute to facilitating the ESD procedure. However, few studies have compared the technical outcomes of each knife.

Research objectives

The aim of this study was to compare the technical outcomes between ESD with the Clutch Cutter and ESD with other devices.

Research methods

Patients with early gastric neoplasms treated by ESD at Kitakyushu Municipal Medical Center between April 2016 and October 2017 were reviewed. ESD was performed using the Clutch Cutter (ESD-C group) or other devices (ESD-O group). Propensity score matching analysis was conducted to compensate for confounding differences between the two groups that may affect the outcomes. After matching, the technical outcomes of ESD were compared among the two groups.

Research results

A total of 155 patients were included and 44 pairs were matched. ESD with the Clutch Cutter achieved a significantly shorter procedure time (median, 49 min vs 88.5 min, *P* < 0.001). The other technical outcomes and complication rates were similar among the two groups.

Research conclusions

The Clutch Cutter contributed to shortening the ESD's procedure time. ESD with the Clutch Cutter could be an effective option in ESD with endo-knives for early gastric neoplasms.

Research perspectives

This was a single-center, retrospective study with a relatively small number of ESD cases. Therefore, further large-scale, randomized, prospective studies are needed.

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REFERENCES

- Park YM**, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. *Surg Endosc* 2011; **25**: 2666-2677 [PMID: 21424201 DOI: 10.1007/s00464-011-1627-z]
- Esaki M**, Suzuki S, Hayashi Y, Yokoyama A, Abe S, Hosokawa T, Ogino H, Akiho H, Ihara E, Ogawa Y. Splash M-knife versus Flush Knife BT in the technical outcomes of endoscopic submucosal dissection for early gastric cancer: a propensity score matching analysis. *BMC Gastroenterol* 2018; **18**: 35 [PMID: 29486717 DOI: 10.1186/s12876-018-0763-5]
- Bhatt A**, Abe S, Kumaravel A, Vargo J, Saito Y. Indications and Techniques for Endoscopic Submucosal Dissection. *Am J Gastroenterol* 2015; **110**: 784-791 [PMID: 25623656 DOI: 10.1038/ajg.2014.425]
- Kodashima S**, Fujishiro M, Yahagi N, Kakushima N, Ichinose M, Omata M. Endoscopic submucosal dissection for gastric neoplasia: experience with the flex-knife. *Acta Gastroenterol Belg* 2006; **69**: 224-229 [PMID: 16929621]
- Ohkuwa M**, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; **33**: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]
- Akahoshi K**, Akahane H, Murata A, Akiba H, Oya M. Endoscopic submucosal dissection using a novel grasping type scissors forceps. *Endoscopy* 2007; **39**: 1103-1105 [PMID: 18072064 DOI: 10.1055/s-2007-966842]
- Akahoshi K**, Motomura Y, Kubokawa M, Gibo J, Kinoshita N, Osada S, Tokumaru K, Hosokawa T, Tomoeda N, Otsuka Y, Matsuo M, Oya M, Koga H, Nakamura K. Endoscopic Submucosal Dissection for Early Gastric Cancer using the Clutch Cutter: a large single-center experience. *Endosc Int Open* 2015; **3**: E432-E438 [PMID: 26528497 DOI: 10.1055/s-0034-1392509]
- Akahoshi K**, Kubokawa M, Gibo J, Osada S, Tokumaru K, Yamaguchi E, Ikeda H, Sato T, Miyamoto K, Kimura Y, Shiratsuchi Y, Akahoshi K, Oya M, Koga H, Ihara E, Nakamura K. Endoscopic submucosal dissection of gastric adenomas using the clutch cutter. *World J Gastrointest Endosc* 2017; **9**: 334-340 [PMID: 28744346 DOI: 10.4253/wjge.v9.i7.334]
- Akahoshi K**, Honda K, Motomura Y, Kubokawa M, Okamoto R, Osoegawa T, Nakama N, Kashiwabara Y, Higuchi N, Tanaka Y, Oya M, Nakamura K. Endoscopic submucosal dissection using a grasping-type scissors forceps for early gastric cancers and adenomas. *Dig Endosc* 2011; **23**: 24-29 [PMID: 21198913 DOI: 10.1111/j.1443-1661.2010.01037.x]
- Nagai K**, Uedo N, Yamashina T, Matsui F, Matsuura N, Ito T, Yamamoto S, Hanaoka N, Takeuchi Y, Higashino K, Ishihara R, Iishi H. A comparative study of grasping-type scissors forceps and insulated-tip knife for endoscopic submucosal dissection of early gastric cancer: a randomized controlled trial. *Endosc Int Open* 2016; **4**: E654-E660 [PMID: 27556074 DOI: 10.1055/s-0042-105870]
- Yamashina T**, Takeuchi Y, Nagai K, Matsuura N, Ito T, Fujii M, Hanaoka N, Higashino K, Uedo N, Ishihara R, Iishi H. Scissor-type knife significantly improves self-completion rate of colorectal endoscopic submucosal dissection: Single-center prospective randomized trial. *Dig Endosc* 2017; **29**: 322-329 [PMID: 27977890 DOI: 10.1111/den.12784]
- Akahoshi K**, Akahane H, Motomura Y, Kubokawa M, Itaba S, Komori K, Nakama N, Oya M, Nakamura K. A new approach: endoscopic submucosal dissection using the Clutch Cutter® for early stage digestive tract tumors. *Digestion* 2012; **85**: 80-84 [PMID: 22269283 DOI: 10.1159/000334647]
- Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512 [PMID: 12297765 DOI: 10.1067/mge.2002.128108]
- Yokoyama T**, Kamada K, Tsurui Y, Kashizuka H, Okano E, Ogawa S, Obara S, Tatsumi M. Clinicopathological analysis for recurrence of stage Ib gastric cancer (according to the second English edition of the Japanese classification of gastric carcinoma). *Gastric Cancer* 2011; **14**: 372-377 [PMID: 21590318 DOI: 10.1007/s10120-011-0051-3]
- Ono H**, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y, Ichinose M, Matsui T. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; **28**: 3-15 [PMID: 26234303 DOI: 10.1111/den.12518]
- Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]
- Kim JH**, Nam HS, Choi CW, Kang DH, Kim HW, Park SB, Kim SJ, Hwang SH, Lee SH. Risk factors associated with difficult gastric endoscopic submucosal dissection: predicting difficult ESD. *Surg Endosc* 2017; **31**: 1617-1626 [PMID: 27495343 DOI: 10.1007/s00464-016-5149-6]
- Imagawa A**, Okada H, Kawahara Y, Takenaka R, Kato J, Kawamoto H, Fujiki S, Takata R, Yoshino T, Shiratori Y. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy* 2006; **38**: 987-990 [PMID: 17058162 DOI: 10.1055/s-2006-944716]
- Libânio D**, Costa MN, Pimentel-Nunes P, Dinis-Ribeiro M. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. *Gastrointest Endosc* 2016; **84**: 572-586 [PMID: 27345132 DOI: 10.1016/j.gie.2016.06.033]
- Choi JJ**, Kim CG, Chang HJ, Kim SG, Kook MC, Bae JM. The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. *Gastrointest Endosc* 2005; **62**: 860-865 [PMID: 16301026 DOI: 10.1016/j.gie.2005.04.033]
- Yoshida M**, Kakushima N, Mori K, Igarashi K, Kawata N, Tanaka M, Takizawa K, Ito S, Imai K, Hotta K, Ishiwatari H, Matsubayashi H, Ono H. Learning curve and clinical outcome of gastric endoscopic submucosal dissection performed by trainee operators. *Surg Endosc* 2017; **31**: 3614-3622 [PMID: 28039646 DOI: 10.1007/s00464-016-5393-9]
- Hong KH**, Shin SJ, Kim JH. Learning curve for endoscopic submucosal dissection of gastric neoplasms. *Eur J Gastroenterol Hepatol* 2014; **26**: 949-954 [PMID: 25045843 DOI: 10.1097/MEG.0000000000000156]
- Austin PC**. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**: 3083-3107 [PMID: 19757444 DOI: 10.1002/sim.3697]
- Akahoshi K**, Akahane H. A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms. *World J Gastrointest Endosc* 2010; **2**: 90-96 [PMID: 21160708 DOI: 10.4253/wjge.v2.i3.90]
- Oka S**, Tanaka S, Takata S, Kanao H, Chayama K. Usefulness and safety of SB knife Jr in endoscopic submucosal dissection for colorectal tumors. *Dig Endosc* 2012; **24** Suppl 1: 90-95 [PMID: 22533760 DOI: 10.1111/j.1443-1661.2012.01255.x]
- Akahoshi K**, Okamoto R, Akahane H, Motomura Y, Kubokawa M, Osoegawa T, Nakama N, Chaen T, Oya M, Nakamura K. Endoscopic submucosal dissection of early colorectal tumors using a grasping-type scissors forceps: a preliminary clinical study. *Endoscopy* 2010; **42**: 419-422 [PMID: 20340070 DOI: 10.1055/s-0029-1243973]
- Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H,

- Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928 [PMID: 19802773 DOI: 10.1055/s-0029-1215129]
- 28 **Otsuka Y**, Akahoshi K, Yasunaga K, Kubokawa M, Gibo J, Osada S, Tokumaru K, Miyamoto K, Sato T, Shiratsuchi Y, Oya M, Koga H, Ihara E, Nakamura K. Clinical outcomes of Clutch Cutter endoscopic submucosal dissection for older patients with early gastric cancer. *World J Gastrointest Oncol* 2017; **9**: 416-422 [PMID: 29085568 DOI: 10.4251/wjgo.v9.i10.416]
- 29 **Ishaq S**, Sultan H, Siau K, Kuwai T, Mulder CJ, Neumann H. New and emerging techniques for endoscopic treatment of Zenker's diverticulum: State-of-the-art review. *Dig Endosc* 2018; **30**: 449-460 [PMID: 29423955 DOI: 10.1111/den.13035]
- 30 **González N**, Debenedetti D, Taullard A. Endoscopic retreatment of Zenker's diverticulum using novel endoscopic scissors - The Clutch Cutter device. *Rev Esp Enferm Dig* 2017; **109**: 669 [PMID: 28689425 DOI: 10.17235/reed.2017.4789/2016]
- 31 **Neumann H**, Löffler S, Rieger S, Kretschmer C, Nägel A. Endoscopic therapy of Zenker's diverticulum using a novel endoscopic scissor - the Clutch Cutter device. *Endoscopy* 2015; **47** Suppl 1 UCTN: E430-E431 [PMID: 26397855 DOI: 10.1055/s-0034-1392658]

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Retrospective Study

Stents combined with iodine-125 implantation to treat main portal vein tumor thrombus

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Abstract**AIM**

To evaluate the efficacy of main portal vein stents combined with iodine-125 (¹²⁵I) to treat main portal vein tumor thrombus.

METHODS

From January 1, 2010 to January 1, 2015, 111 patients were diagnosed with liver cancer combined with main portal vein tumor thrombus. They were non-randomly assigned to undergo treatment with transarterial chemoembolization (TACE)/transarterial embolization (TAE) + portal vein stents combined with ¹²⁵I implantation (Group A) and TACE/TAE + portal vein

stents only (Group B). After the operation, scheduled follow-up was performed at 6, 12 and 24 mo. The recorded information included clinical manifestations, survival rate, and stent restenosis rate. Kaplan–Meier curves, log-rank test and Cox regression were used for data analyses.

RESULTS

From January 1, 2010 to January 1, 2015, 54 and 57 patients were allocated to Groups A and B, respectively. The survival rates at 6, 12 and 24 mo were 85.2%, 42.6% and 22.2% in Group A and 50.9%, 10.5% and 0% in Group B. The differences were significant [log rank $P < 0.05$, hazard ratio (HR): 0.37, 95%CI: 0.24–0.56]. The rates of stent restenosis were 18.5%, 55.6% and 83.3% in Group A and 43.9%, 82.5% and 96.5% in Group B. The differences were significant (log rank $P < 0.05$, HR: 0.42, 95%CI: 0.27–0.63). Cox regression identified that treatment was the only factor affecting survival rate in this study.

CONCLUSION

Main portal vein stents combined with ^{125}I can significantly improve survival rate and reduce the rate of stent restenosis.

Key words: Iodine-125; Liver cancer; Stent; Main portal vein tumor thrombus; Transarterial chemoembolization/transarterial embolization

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Core tip: This study evaluated the efficacy of stents combined with iodine-125 (^{125}I) to treat main portal vein tumor thrombus and its complications. ^{125}I was placed between the stent and tumor thrombus, and not in the form of particle strands. In this way, the quantity and position of ^{125}I could be flexibly adjusted. Transarterial chemoembolization or transarterial embolization was used as basic treatment. Patients with liver cancer and main portal vein tumor thrombus were non-randomly assigned to undergo portal vein stents combined with ^{125}I implantation or portal vein stents only. Portal vein stent combined with ^{125}I significantly improved survival rate and reduced stent restenosis.

Wu YF, Wang T, Yue ZD, Zhao HW, Wang L, Fan ZH, He FL, Liu FQ. Stents combined with iodine-125 implantation to treat main portal vein tumor thrombus. *World J Gastrointest Oncol* 2018; 10(12): 496–504

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INTRODUCTION

Liver cancer is a common malignant tumor^[1], and it decreases patient quality of life^[2,3]. Tumor thrombus

in the main portal vein indicates late-stage disease. The treatment for portal vein tumor thrombus includes surgery and radiotherapy^[4,5]. However, the overall effect is limited. In recent years, radioactive iodine-125 (^{125}I) particles have been used to treat portal vein tumor thrombus to effectively decrease tumor thrombus volume and improve patient survival rates^[6]. However, ^{125}I was implanted in particle strands in those studies. This limits the amount of ^{125}I implanted and the ability to reposition the ^{125}I , which restrains the clinical use of ^{125}I . We studied the clinical effect of ^{125}I combined with main portal vein stents when the ^{125}I was placed between the tumor thrombus and the stents. This method avoids the above disadvantages and has never been previously reported.

MATERIALS AND METHODS

Study design

This was a nonrandomized controlled trial in which we compared transarterial chemoembolization (TACE)/transarterial embolization (TAE) + main portal vein stents combined with ^{125}I implantation and TACE/TAE + main portal vein stents only for the treatment of liver cancer with main portal vein tumor thrombus and portal hypertension.

Criteria

Inclusion criteria were as follows: (1) Liver cancer according to histological, cytological, or clinical diagnostic standards that conformed to the rules of diagnosis and treatment of primary hepatocellular carcinoma, 2011; (2) Main stem tumor thrombus of portal vein confirmed through biopsy (70%) or imaging, without tumor thrombus in the branches; (3) Clear indication of percutaneous liver puncture and main portal vein stent implantation; (4) Clear TACE or TAE treatment indication; (5) Age 18–70 years; and (6) No serious complications of portal hypertension, and only a small amount of ascites without bleeding or other complications. Exclusion criteria were: (1) Patients with serious disorders of the heart, lung, kidney, brain, or other important organs; (2) Active infection; (3) Women in pregnancy or lactation; (4) Life expectancy < 3 mo; and (5) Patients who could not cooperate with treatment and observation.

Patients

One hundred and eleven patients with main portal vein tumor thrombus were non-randomly assigned to undergo treatment with TACE/TAE + main portal vein stents combined with ^{125}I implantation or TACE/TAE + main portal vein stents alone from January 1, 2010 to January 1, 2015. There were 73 cases of hepatitis B cirrhosis, 21 cases of hepatitis C cirrhosis, seven cases of alcoholic cirrhosis, three cholestatic cirrhosis cases, three autoimmune liver cirrhosis cases and four cases of cirrhosis from other causes. Twenty-three patients

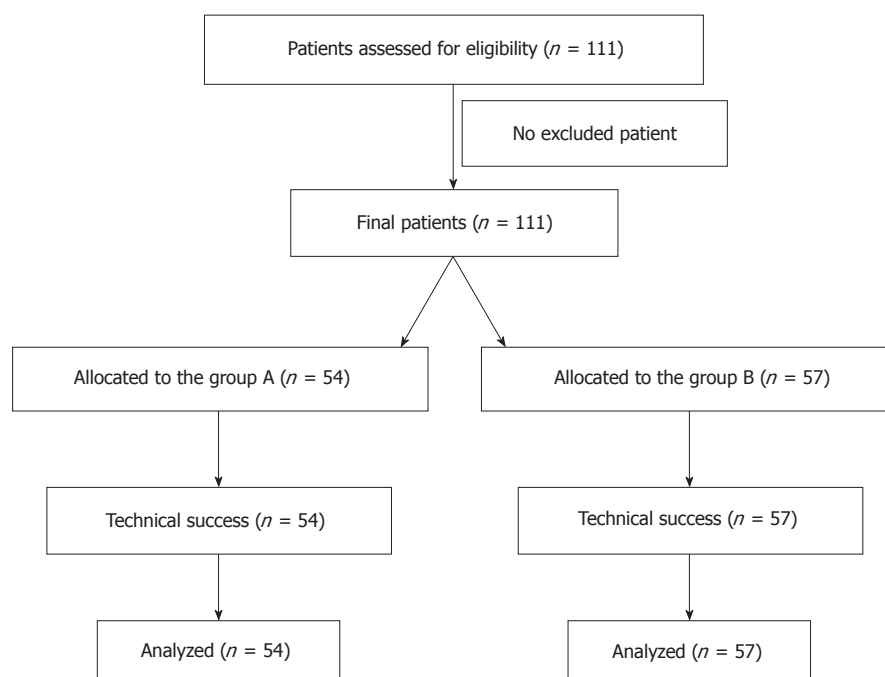


Figure 1 Study design and flow chart.

were diagnosed with primary carcinoma of the liver by percutaneous liver biopsy, whereas 88 patients were diagnosed by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), serum α -fetoprotein levels and hepatic artery angiography. Imaging examination confirmed main portal vein tumor thrombus in all patients. According to the preoperative Child–Pugh classification, there were 49 cases of Class A, 62 cases of Class B, and zero class C cases. There were 20 patients with mild ascites and 91 without ascites. The flow chart is shown in Figure 1. Comparison between the two groups is shown in Table 1 and Figure 2.

Preoperative preparation

Before the operation, liver function tests, blood coagulation tests, routine blood tests, electrocardiography, CT, and/or MRI, color Doppler ultrasonography, and esophageal radiography were performed. In addition, gastroscopy was performed when necessary. Patients' coagulation function was corrected to the normal range. The operation-related concerns were explained to the patients and their family members, and they were asked to give signed informed consent. This study was approved by the Institutional Review Board of Beijing Shijitan Hospital and conducted in accordance with all current ethical guidelines.

Percutaneous transhepatic and portal vein stent implantation

Patients were assigned to receive percutaneous transhepatic and portal vein covered stents (Fluency, Bard, Tempe, AZ, United States) with local anesthesia at the puncture site. A puncture device (NPAS-100; Cook, Indianapolis, IN, United States), which included a

puncture needle, venous sheath and guide wire, was passed from the right hypochondriac region to the portal vein. After that, a pigtail catheter was advanced through the NPAS-100 to the distal end of the splenic vein or superior mesenteric vein to measure the portal vein pressure and conduct venography. The pigtail catheter was removed, and the stent was implanted through the vein sheath. A 10-mm covered stent was implanted. Portal vein pressure measurements before and after stent placement allowed assessment of the success of the procedure. The hepatic puncture passage was blocked during catheter removal to avoid intra-peritoneal or thoracic hemorrhage.

¹²⁵I implantation

In Group A, the patients received treatment with percutaneous transhepatic and portal vein covered stent implantation, like the patients in Group B. After measurement of portal vein pressure and conduction of venography, the pigtail catheter was removed, and a guide wire was inserted through the venous sheath of the NPAS-100. Because the NPAS-100 had one guide wire, there were two guide wires in the main portal vein. The venous sheath was drawn out and inserted into the portal vein again along one of the guide wires. Another guide wire was placed between the tumor thrombus and venous sheath. Stents were implanted through the venous sheath. A catheter was inserted through the guide wire that was between the tumor thrombus and venous sheath. The catheter between the stent and the tumor thrombus was linked to the particle release gun. The catheter was slowly retracted, and ¹²⁵I (Tong Fu, Beijing, China) was simultaneously

Table 1 Baseline characteristics, *n* (%)

	Group A (<i>n</i> = 54)	Group B (<i>n</i> = 57)	<i>P</i> value
Gender			0.693
Male	35 (64.8)	39 (68.4)	
Female	19 (35.2)	18 (31.6)	
Average age (yr)	43.6 ± 6.9	44.3 ± 5.2	0.697
Pathogenesis			0.788
Hepatitis B	35 (64.8)	38 (66.7)	
Hepatitis C	9 (16.7)	12 (21)	
Alcoholic	5 (9.3)	2 (3.5)	
Cholestasis	2 (3.7)	1 (1.8)	
Autoimmunity	1 (1.8)	2 (3.5)	
Others	2 (3.7)	2 (3.5)	
Child-Pugh classification			0.705
A	25 (46.3)	24 (42.1)	
B	29 (53.7)	33 (57.9)	
C	0 (0)	0 (0)	
Albumin (g/L)	34.5 ± 7.5	31.5 ± 11.5	0.880
Alanine aminotransferase (U/L)	62.5 ± 46.5	49.5 ± 37.5	0.396
Glutamyl transpeptidase (U/L)	73 ± 66	74 ± 62	0.647
Na ⁺	143.5 ± 8.5	140 ± 7	0.104
K ⁺	4.12 ± 1.08	4.75 ± 1.05	0.883
Direct bilirubin (μmol/L)	29.8 ± 25.2	24.5 ± 18.5	0.299
Aspartate aminotransferase (U/L)	39 ± 30	49 ± 39	0.349
MELD score	11.96 ± 1.68	12.76 ± 2.47	0.145
Ascites			0.624
Yes	11 (20.4)	9 (15.8)	
No	43 (79.6)	48 (84.2)	
Size of liver cancer (cm)			0.788
≤ 5	14 (25.9)	17 (29.8)	
5-8	31 (57.4)	29 (50.9)	
> 8	9 (16.7)	11 (19.3)	
No. of liver tumors			0.834
1	28 (51.9)	32 (56.1)	
2 or 3	19 (35.2)	17 (29.8)	
> 3	7 (12.9)	8 (14.1)	

MELD: Model for end-stage liver disease; Child-Pugh classification: Score for liver function.

released through the catheter up to the portal vein trunk and tumor thrombus. The radioactive particles were arranged as neatly as possible in all tumor thrombi. After implantation, portal vein pressure was measured and venography was conducted. These particles could emit characteristic electrons and photons through the recession of the electron capture surface. The electrons were absorbed by the titanium alloy wall of the sealed seeds of ¹²⁵I. The photons mainly emitted X rays of 27.4 and 31.4 keV as well as γ rays of 35.5 keV. The pictures taken during the operation are shown in Figure 3.

TACE/TAE

Patients in Group A were treated with TACE according to the position of the lesion and its blood supply. The embolization agent was 3–30 mL iodinated oil. The chemotherapeutics included 10–20 mg pirarubicin and 5–15 mg hydroxycamptothecine. Patients in Group B were treated with TAE to reduce damage to liver function. The embolization agent was 5–25 mL iodinated oil.

For the basic technical operation, a needle was passed from the right or left femoral artery to the hepatic artery followed by hepatic arteriography. A catheter was placed in the direct blood supply artery of the tumor

as close to the focus as possible, and embolization and infusion of chemotherapeutic drugs were performed. The interval and number of treatments depended on tumor size, arterial status and liver function status. The interval was usually once every 1–6 mo. In Group A, 25 and 29 patients were treated with TACE and TAE, respectively, while 24 and 33 patients in Group B were treated with TACE and TAE, respectively, with no significant difference in patient numbers (*P* = 0.705).

Patients with lesions ≤ 5 cm in size and with a rich blood supply underwent TACE or TAE first and radiofrequency ablation after 3–5 d. Patients whose lesion was > 5 cm underwent TACE or TAE once or several times and then radiofrequency ablation when the imaging showed that the lesions no longer had blood supply from the hepatic artery or when the catheter could not enter the artery supplying the lesion. Finally, all patients underwent radiofrequency ablation (WHK-IB; Weaver Electronics, Beijing, China).

Postoperative routine observation and treatment

Low molecular weight heparin (5000 IU, twice daily) was subcutaneously injected for 5 d, and then warfarin was administered for one year. Coagulation function of

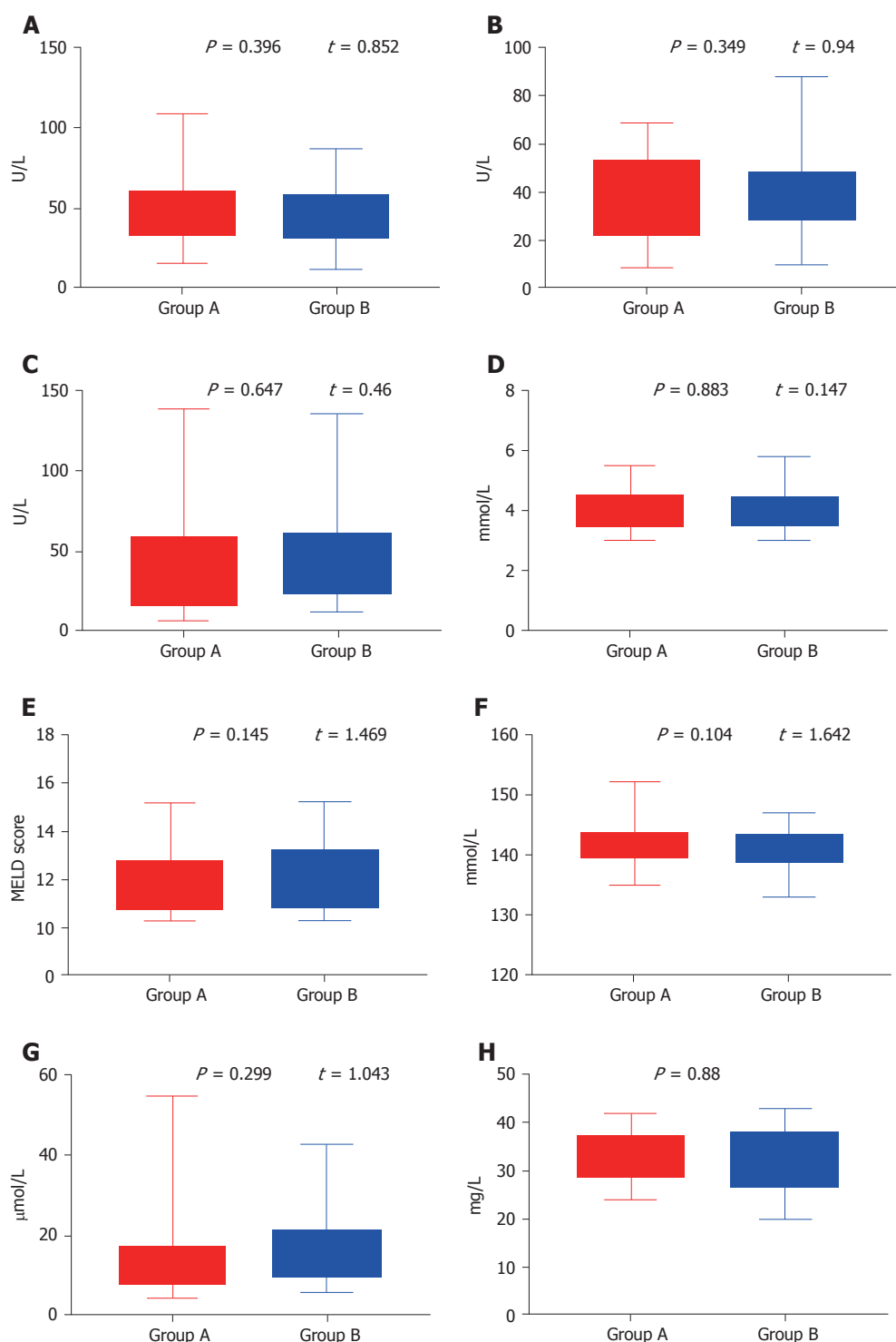


Figure 2 Boxplots of liver function. A: Alanine aminotransferase; B: Aspartate aminotransferase; C: Glutamyl transpeptidase; D: K⁺; E: Model for end-stage liver disease score; F: Na⁺; G: Direct bilirubin; H: Albumin (H) in Group A (red bars) and Group B (blue bars) were compared with Student's *t* test. MELD: Model for end-stage liver disease score.

each patient was examined every 15 d to ensure that the International Normalized Ratio ranged from 2 to 3.

Follow-up

Scheduled follow-up was performed at 6, 12 and 24 mo postoperatively. The recorded information included clinical manifestations, survival rate, physical exami-

nation, stent restenosis evaluation (through ultrasound and endoscopy) and laboratory tests. Telephone follow-up was performed to record patient conditions and details of relevant clinical events.

Statistical analysis

Continuous variables are presented as mean ± median

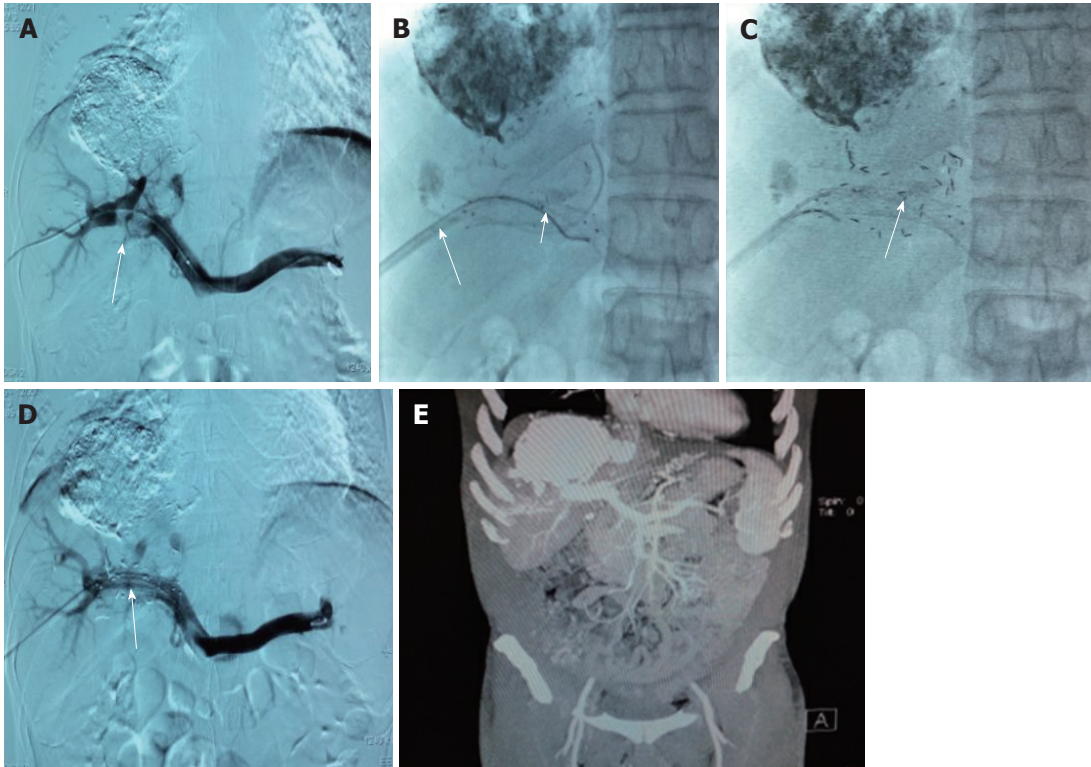


Figure 3 Pictures taken during operation of a 55-year-old male patient with hepatitis B cirrhosis and primary liver cancer with main portal vein tumor thrombus. The patient was treated with percutaneous liver puncture and ^{125}I implantation combined with portal vein stent implantation. A: Percutaneous transhepatic portal venography showing proximal and left branch of portal vein tumor thrombus (long white arrow); B: X-ray showing vein stent (short white arrow), catheter between the stent and tumor thrombus (long white arrow); C: X-ray showing ^{125}I between the stent and tumor thrombus (long white arrow); D: Postoperative portal vein angiography showing patency of stent blood flow (long white arrow); E: 18 mo after the operation, enhanced computed tomography showed that blood flow in the splenic vein, superior mesenteric vein, portal vein and stent was good.

and were compared by independent-sample or paired-sample t test. Categorical and ordinal variables are presented as frequencies or percentages and compared using χ^2 test. Time-to-event outcomes were evaluated with Kaplan–Meier curves and log-rank tests. Cox regression model was used to identify independent predictors. Unbalanced factors between groups were treated as covariates. Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM, Chicago, IL, United States) and GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, United States). Follow-up investigators and statisticians had access to all of the data and vouched for the integrity of the data analyses.

RESULTS

Portosystemic pressure gradient before and after operation

The portosystemic pressure gradient (PPG) in Group A decreased from 26.9 ± 6.22 to 13.6 ± 6.4 mmHg ($t = 18.11$, $P < 0.05$) after operation. The PPG before and after operation were significantly different. The PPG in Group B decreased from 26.77 ± 6.25 to 15.1 ± 7.2 mmHg ($t = 17.1$, $P < 0.05$). The PPG before and after operation were significantly different (Table 2). The pre-operative PPG was not significantly different

between the two groups ($t = 1.52$, $P = 0.132$). The post-operative PPG was also not significantly different between the two groups ($t = 1.20$, $P = 0.234$) (Figure 4).

Time-to-event outcomes

The rates of stent restenosis at 6, 12 and 24 mo were 18.5%, 55.6% and 83.3% in Group A and 43.9%, 82.5% and 96.5% in Group B, which differed significantly [log rank $P < 0.05$, hazard ratio (HR): 0.42, 95%CI: 0.27–0.63] (Figure 5A and Table 3). The rates of survival at 6, 12 and 24 mo were 85.2%, 42.6% and 22.2%, respectively in Group A and 50.9%, 10.5% and 0%, respectively in Group B, which differed significantly (log rank $P < 0.05$, HR: 0.37, 95%CI: 0.24–0.56) (Figure 5B and Table 3)

Cox regression

Cox regression showed that pathogenesis, tumor number and serum albumin had no significant effect on survival rate. Treatment was the only factor that affected survival rate (Table 4).

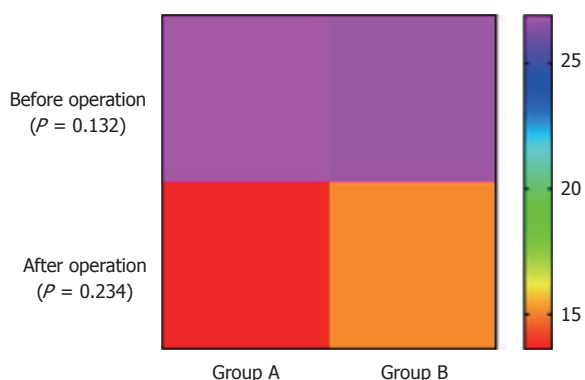
DISCUSSION

With a rapid increase in the number of patients with liver cancer, the incidence of portal vein tumor thrombus is gradually increasing. ^{125}I was reported to have a

Table 2 Differences of portosystemic pressure gradient in the two groups before and after operation

	PPG before operation (mmHg)	PPG after operation (mmHg)	<i>t</i>	df	<i>P</i> value
Group A	26.9 ± 6.22	13.6 ± 6.4	18.11	53	< 0.0001
Group B	26.77 ± 6.25	15.1 ± 7.2	17.10	56	< 0.0001

PPG: Portosystemic pressure gradient.

**Figure 4** Heat map of comparison of portosystemic pressure gradient measurements before and after operation between Groups A and B. Student's *t* test was used to compare portosystemic pressure gradient at each time point, and no difference was found between the two groups.

good therapeutic effect^[7]. However, ¹²⁵I implantation has been in the form of particle strands. This has some disadvantages, such as implantation of a limited number of particles. In addition, the position of ¹²⁵I cannot be adjusted. No one has studied the clinical effect of ¹²⁵I combined with main portal vein stents in which the ¹²⁵I is placed between the tumor thrombus and stents. This procedure could make it easier to adjust the position and amount of ¹²⁵I. Thus, in the present study, we compared TACE/TAE + main portal vein stents combined with ¹²⁵I implantation and TACE/TAE + main portal vein stents alone for the treatment of liver cancer patients with main portal vein tumor thrombus and portal hypertension. Overall, our study suggested a benign outcome: (1) ¹²⁵I combined with stents implanted in the main portal vein significantly improved survival rate and reduced stent restenosis rate; (2) stents implanted in the main portal vein reduced portal vein pressure and relieved clinical symptoms; and (3) TACE/TAE + main portal vein stents combined with ¹²⁵I implantation was safe and feasible.

The incidence of portal vein tumor thrombus is high, and its treatment includes surgical resection, chemotherapy, and stent^[8-10]. Stent implantation of the main portal vein can quickly reduce portal vein pressure, relieve clinical symptoms and improve quality of life^[11,12]. In recent years, portal vein stenting combined with ¹²⁵I implantation has achieved significant effects in treating main portal vein tumor thrombus. Sun *et al.*^[13] conducted a study to evaluate the effect of ¹²⁵I. In their study, the median survival was 147 d. The cumulative survival rates and stent patency rates at 90, 180, and 360 d were 94.1%, 61.8%, and 32.4% and 97.1% (33/34), 76.9% (24/34), and 29.4% (10/34), respectively^[13]. However,

in previous studies, ¹²⁵I particles were implanted in the form of particle strands, which has some drawbacks. It is important to find a better method. In our study, the survival rate in Group A was higher than in Group B, and the stent restenosis rate was lower in Group A than in Group B. Cox regression was used to evaluate the effects of various factors on survival and stent restenosis. It showed that pathogenesis, tumor number and serum albumin had no significant effect on survival rate. Treatment was the only factor influencing survival rate. TACE/TAE + main portal vein stents combined with ¹²⁵I implantation can improve patient survival rate and reduce stent restenosis rate.

Our study had several limitations. First, the radiation dose was not uniformly distributed. Second, the number of patients was small, which may have influenced the accuracy of the results.

In summary, TACE/TAE + main portal vein stents combined with ¹²⁵I implantation is effective in treating main portal vein tumor thrombus and its complications, improving quality of life and reducing mortality.

ARTICLE HIGHLIGHTS

Research background

Tumor thrombus in the main portal vein indicates late-stage disease. Treatment for portal vein tumor thrombus includes surgery, chemotherapy, radiotherapy, targeted therapy, and proton beam radiation. In recent years, radioactive iodine-125 (¹²⁵I) particles have been used to treat portal vein tumor thrombus. However, seed implantation in recent studies had some disadvantages. We carried out the present study to explore a new method of seed implantation.

Research motivation

Previously, ¹²⁵I was implanted in the form of particle strands. This limits the number of ¹²⁵I particles implanted, and their position cannot be adjusted. In this study, we performed ¹²⁵I seed implantation combined with stent implantation, placing the particles between the stent and tumor thrombus. The stent could hold the ¹²⁵I particles, and the method can be widely used in clinical application.

Research objectives

¹²⁵I has been shown to be effective in treating portal vein thrombosis. The main objective of this study was to determine the efficacy of stents combined with ¹²⁵I implantation in the treatment of liver cancer accompanied by main portal vein tumor thrombus, as well as the technical feasibility of this method of seed implantation.

Research methods

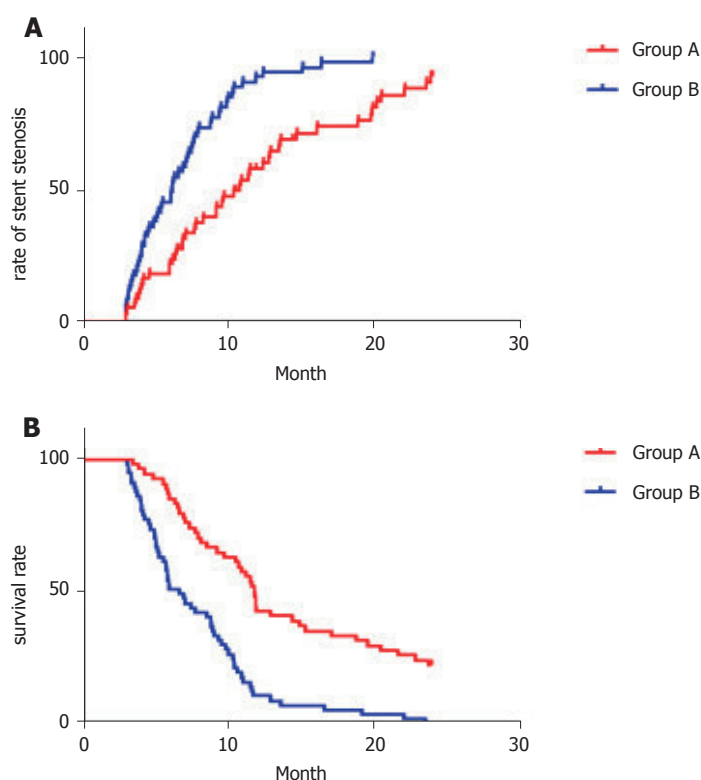
Patients were non-randomly assigned to undergo treatment with transarterial chemoembolization (TACE)/transarterial embolization (TAE) + portal vein stents combined with ¹²⁵I implantation (Group A) or TACE/TAE + portal vein stents only (Group B). It could show differences in treatment and outcomes between the two groups. After operation, scheduled follow-up was performed at 6, 12 and 24 mo. Follow-up included postoperative and preoperative portosystemic pressure gradient, postoperative stenting stenosis rate, and survival rate. Time-to-event outcomes were evaluated with Kaplan-Meier curves and log-rank test. Cox

Table 3 Time-to-event outcomes

	Group A (n = 54)	Group B (n = 57)	P value
Rate of stent stenosis			< 0.05
6 mo	18.5	43.9	
12 mo	55.6	82.5	
24 mo	83.3	96.5	
Survival rate			< 0.05
6 mo	85.2	50.9	
12 mo	42.6	10.5	
24 mo	22.2	0	

Table 4 Multivariate analysis of factors associated with postoperative outcomes

	Hazard ratio	95%CI	P value
Pathogenesis	1.227	0.773–1.948	0.385
Albumin (g/L)	1.266	0.829–1.932	0.275
Alanine aminotransferase (U/L)	1.222	0.798–1.872	0.357
Glutamy1 transpeptidase (U/L)	0.821	0.509–1.224	0.419
Direct bilirubin (μmol/L)	2.262	0.270–18.96	0.452
Aspartate aminotransferase (U/L)	1.270	0.800–2.017	0.311
No. of liver tumors	1.238	0.232–19.41	0.330

**Figure 5** Kaplan–Meier curves of postoperative stent restenosis (A) and survival (B).

regression model was used to identify independent predictors. Kaplan–Meier curves and log-rank test clearly demonstrated the differences in survival rate and restenosis rate between the two groups, as well as the efficacy of ^{125}I in the treatment of main portal vein tumor thrombus. Cox analysis could take various factors into account to make the results more convincing.

Research results

Compared with stents alone, stents combined with ^{125}I implantation had a good therapeutic effect in liver cancer with main portal vein tumor thrombus. This method reduced the restenosis rate and improved survival rate. Stents

combined with ^{125}I implantation were safe and reliable in clinical application. In this study, the ^{125}I was placed between the stent and tumor thrombus and the stent could hold the particles. Using this method of ^{125}I implantation, the number and position of the particles could be adjusted, which is more flexible in clinical application. However, as the size of the liver cancer shrinks, the particles may drift to other parts of the body via blood flow, and this needs further study.

Research conclusions

Stents combined with ^{125}I implantation have a good therapeutic effect in the treatment of liver cancer with main portal vein tumor thrombus. The ^{125}I was

placed between the stent and the tumor thrombus, and the stent could hold the particles. The new method can avoid the drawbacks of particle strands and can be widely used in the clinic. Stents combined with ^{125}I implantation have a good therapeutic effect in the treatment of liver cancer with main portal vein tumor thrombus. The method is technically safe and reliable. Tumor thrombus in the main portal vein indicates late-stage disease. ^{125}I is an effective treatment for main portal vein thrombosis. Compared with stents alone, stents combined with ^{125}I implantation can reduce restenosis rates and improve survival rate. It is technically safe and reliable. ^{125}I has made great achievements in the treatment of main portal vein tumor thrombus, but there are drawbacks in the method of ^{125}I implantation, and new methods should be explored.

Research perspectives

Liver cancer with portal vein thrombosis seriously affects patient quality of life and should be treated in a timely manner. Stents combined with ^{125}I implantation have a good therapeutic effect in liver cancer with main portal vein tumor thrombus. Appropriate patients were selected for seed implantation treatment according to the inclusion criteria. The particle drift rate of the patients was followed up at 6, 12 and 24 mo after the operation.

REFERENCES

- 1 Li L, Wang H. Heterogeneity of liver cancer and personalized therapy. *Cancer Lett* 2016; **379**: 191-197 [PMID: 26213370 DOI: 10.1016/j.canlet.2015.07.018]
- 2 Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. *Int J Cancer* 2016; **139**: 1534-1545 [PMID: 27244487 DOI: 10.1002/ijc.30211]
- 3 Ryerson AB, Ehemann CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, Henley SJ, Holtzman D, Lake A, Noone AM, Anderson RN, Ma J, Ly KN, Cronin KA, Penberthy L, Kohler BA. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016; **122**: 1312-1337 [PMID: 26959385 DOI: 10.1002/cncr.29936]
- 4 Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol* 2010; **17**: 2073-2080 [PMID: 20131013 DOI: 10.1245/s10434-010-0940-4]
- 5 Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, Ishihara T, Mayahara H, Fukumoto T, Ku Y, Yamaguchi M, Sugimoto K, Sasaki R. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. *J Radiat Res* 2016; **57**: 512-523 [PMID: 27053259 DOI: 10.1093/jrr/rrw028]
- 6 Tan T, Xiao Y, Zhou S, Ma C, Zhang Z. Y-configuration stent combined with iodine-125 seeds strand for the treatment of hepatocellular carcinoma with tumor thrombosis in portal vein branches: A case report. *Medicine* (Baltimore) 2017; **96**: e8660 [PMID: 29145293 DOI: 10.1097/MD.00000000000008660]
- 7 Sun H, Zhang M, Liu R, Liu Y, Hou Y, Wu C. Endovascular implantation of ^{125}I seed combined with transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. *Future Oncol* 2018; **14**: 1165-1176 [PMID: 29334777 DOI: 10.2217/fon-2017-0354]
- 8 Luo JJ, Zhang ZH, Liu QX, Zhang W, Wang JH, Yan ZP. Endovascular brachytherapy combined with stent placement and TACE for treatment of HCC with main portal vein tumor thrombus. *Hepatol Int* 2016; **10**: 185-195 [PMID: 26341514 DOI: 10.1007/s12072-015-9663-8]
- 9 Han K, Kim JH, Ko GY, Gwon DI, Sung KB. Treatment of hepatocellular carcinoma with portal venous tumor thrombosis: A comprehensive review. *World J Gastroenterol* 2016; **22**: 407-416 [PMID: 26755886 DOI: 10.3748/wjg.v22.i1.407]
- 10 Zhang YF, Le Y, Wei W, Zou RH, Wang JH, OuYang HY, Xiao CZ, Zhong XP, Shi M, Guo RP. Optimal surgical strategy for hepatocellular carcinoma with portal vein tumor thrombus: a propensity score analysis. *Oncotarget* 2016; **7**: 38845-38856 [PMID: 27072577 DOI: 10.18632/oncotarget.8642]
- 11 Higaki I, Hirohashi K, Kubo S, Tanaka H, Tsukamoto T, Omura T, Kinoshita H. Portal vein stenting to treat portal vein tumor thrombus in hepatocellular carcinoma. *Osaka City Med J* 2000; **46**: 99-104 [PMID: 11252736]
- 12 Lu J, Guo JH, Zhu HD, Zhu GY, Chen L, Teng GJ. Safety and Efficacy of Irradiation Stent Placement for Malignant Portal Vein Thrombus Combined with Transarterial Chemoembolization for Hepatocellular Carcinoma: A Single-Center Experience. *J Vasc Interv Radiol* 2017; **28**: 786-794.e3 [PMID: 28396192 DOI: 10.1016/j.jvir.2017.02.014]
- 13 Sun JH, Zhou T, Zhu T, Zhang Y, Nie C, Ai J, Zhou G, Zhang A, Dong MJ, Wang WL, Zheng SS. Portal Vein Stenting Combined with Iodine-125 Seeds Endovascular Implantation Followed by Transcatheter Arterial Chemoembolization for Treatment of Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus. *Biomed Res Int* 2016; **2016**: 3048261 [PMID: 27999793 DOI: 10.1155/2016/3048261]

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Clinical Trials Study

Multicenter phase II trial of modified FOLFIRINOX in gemcitabine-refractory pancreatic cancer

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Author contributions: Chung MJ, Lee SH and Bang S led the

study design; the study was managed by Lee SH and Bang S; Kang H and Chung MJ performed the data analysis; Chung MJ, Kang H, Kim HG, Hyun JJ, Lee JK, Lee KH, Noh MH, Kang DH, Lee SH and Bang S interpreted the data; Chung MJ, Kang H and Bang S wrote the manuscript; all versions of the manuscript were reviewed by Chung MJ, Kang H, Kim HG, Hyun JJ, Lee JK, Lee KH, Noh MH, Kang DH and Lee SH; all authors approved the final manuscript; Chung MJ and Kang H contributed equally to this work as primary authors; Lee SH and Bang S contributed equally to this work as corresponding authors.

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Clinical trial registration statement: This trial is registered with ClinicalTrials.gov, number NCT02440958.

Informed consent statement: Written, informed consent was obtained from each participant after potential treatment complications had been fully explained.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

CONSORT 2010 statement: The guidelines of the CONSORT 2010 Statement have been adopted in this article.

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Abstract

AIM

To evaluate the efficacy and safety of modified FOLFIRINOX as a second-line treatment for gemcitabine (GEM)-refractory unresectable pancreatic cancer (PC).

METHODS

This study was a prospective, multicenter, one-arm, open-label, phase II trial. Patients with unresectable PC, who showed disease progression during GEM-based chemotherapy were enrolled. All patients were administered FOLFIRINOX with reduced irinotecan and oxaliplatin (RIO; irinotecan 120 mg/m² and oxaliplatin 60 mg/m²), which was set according to the phase I study of FOLFIRINOX. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events were evaluated. Additionally, changes in quality of life (QoL) were assessed using a questionnaire on QoL.

RESULTS

Between August 2015 and May 2016, a total of 48 patients were enrolled. The median follow-up time was 259 d with a median of 8.5 cycles. The ORR and DCR were 18.8% and 62.5%, respectively, including one patient who showed complete remission. The median PFS was 5.8 mo [95% confidence interval (CI): 3.7-7.9] and median OS was 9.0 mo (95%CI: 6.4-11.6). Neutropenia (64.6%) was the most common grade 3-4 adverse event, followed by febrile neutropenia (16.7%). Although 14.6% of patients experienced grade 3 fatigue, most non-hematologic AEs were under grade 2. In the QoL analysis, the global health status score before treatment was not different from the score at the last visit after treatment (45.43 ± 22.88 *vs* 48.66 ± 24.14, *P* = 0.548).

CONCLUSION

FOLFIRINOX with RIO showed acceptable toxicity and promising efficacy for GEM-refractory unresectable PC. However, this treatment requires careful observation of treatment-related hematologic toxicities.

Key words: Pancreatic cancer; FOLFIRINOX; Clinical Trial, Phase II; Chemotherapy; Gemcitabine refractory

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Core tip: For gemcitabine (GEM)-refractory unresectable pancreatic cancer (PC), there are limited options of second-line chemotherapy regimen. To find new treatment option for GEM-refractory unresectable PC, we conducted a multicenter phase II trial, which evaluated the efficacy and safety of uniquely modified FOLFIRINOX with reduced irinotecan and oxaliplatin. In our results, FOLFIRINOX with reduced irinotecan and oxaliplatin showed acceptable toxicity and promising efficacy. With careful observation of treatment-related hematologic toxicities, this chemotherapy regimen is a promising option for patients with GEM-refractory PC after first-line treatment failure.

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INTRODUCTION

Pancreatic cancer (PC) is among the major causes of cancer-related deaths in the United States^[1]. In South Korea, PC is the eighth highest-diagnosed cancer and the fifth most common cause of cancer-related death^[2]. Metastatic pancreatic cancer (MPC) accounts for 60% of all cases; the median survival of patients with MPC is 3-6 mo. Systemic chemotherapy is pivotal for treating such patients; however, effective regimens remain limited. Recently, two first-line combination regimens-FOLFIRINOX [a combination of oxaliplatin, folinic acid (FA), irinotecan, and 5-fluorouracil (5-FU)] and nanoparticle albumin-bound (nab) paclitaxel in combination with GEM-prolonged survival compared to gemcitabine (GEM) monotherapy and became standard treatments^[3,4]. However, the median progression-free survival (PFS) of these new treatment regimens was only 6.4 and 5.5 mo, respectively.

Proper second-line treatment can improve survival of patients with locally advanced pancreatic cancer (LAPC) or MPC who fail first-line treatment. Although some previous phase III trials showed survival improvement with their study regimens, the standard treatment remains unclear^[5-7].

Patients who received first-line FOLFIRINOX or nab-paclitaxel plus GEM may benefit from a novel second-line treatment, although toxicity should also be considered.

FOLFIRINOX, a standard first-line treatment, has been proposed as a second-line treatment for patients with good performance status who failed GEM-based chemotherapy. However, as the condition of many patients deteriorates after first-line chemotherapy, second-line therapy requires administration at attenuated doses and/or schedules, even in patients who maintain a preserved comorbidity profile.

Standard FOLFIRINOX has limited broad use as a second-line therapy because of toxicity; it includes irinotecan (180 mg/m²), oxaliplatin (85 mg/m²), 5-FU (400 mg/m² administered as a bolus followed by 2400 mg/m² administered as a 46-h continuous infusion), and leucovorin (400 mg/m²) every 2 wk^[3]. Several FOLFIRINOX trials have investigated reducing dosages while maintaining efficacy^[8-10]. However, studies focused on the efficacy and safety of a modified dose of FOLFIRINOX for patients with GEM-refractory PC are still rare. Therefore, we conducted a prospective, multicenter, one-arm, open-label, phase II trial using a modified FOLFIRINOX with reduced oxaliplatin and irinotecan (RIO) to minimize adverse events (AEs). Our aim was to evaluate the efficacy and safety of FOLFIRINOX with (RIO) in patients with unresectable PC who had earlier been treated with a GEM-based regimen until disease progression.

MATERIALS AND METHODS

Study population

This study was a prospective, multicenter, one-arm, open-label, phase II trial and conducted in eight Korean university hospitals. The inclusion criteria for this study were patients between 19 and 75 years old; Eastern Cooperative Oncology Group performance status ≤ 2 ; cytologically or histologically proven unresectable pancreatic adenocarcinoma that progressed after first-line GEM-based chemotherapy; adequate bone marrow function (white blood cell count $\geq 3500/\mu\text{L}$, absolute neutrophil count $\geq 1500/\mu\text{L}$, and platelet count $\geq 100000/\mu\text{L}$); adequate hepatic function (total bilirubin $\leq 1.5 \times$ the upper limit of the normal range [ULN], serum aspartate and alanine transaminase $\leq 3 \times$ ULN, and alkaline phosphatases $\leq 3 \times$ ULN or $\leq 5 \times$ ULN in case of liver metastasis); adequate renal function (serum creatinine ≤ 1.5 mg/dL); and adequate cardiopulmonary function. Patients were excluded if they had a concurrent malignancy other than PC; a serious, uncontrollable medical condition; or a psychiatric disorder. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each participant after potential treatment complications had been fully explained. The institutional review boards at all participating institutions approved this study. This trial is registered with ClinicalTrials.gov, number NCT02440958.

Study endpoints

The primary endpoints were objective response rate [ORR; complete remission (CR) + partial response (PR)] and disease control rate (DCR; CR + PR + stable disease (SD)). The secondary endpoints were PFS, overall survival (OS), changes in quality of life (QoL), and safety. OS was calculated from the date of enrollment until death from any cause. In the absence of an event, data were censored on the last day of survival confirmation. PFS was calculated from the initiation of treatment until either imaging-confirmed disease progression or death from any cause; in their absence, data for such patients were censored on the day of their last imaging procedure.

Determination of study drug dose

In the phase I study of FOLFIRINOX, febrile neutropenia, prolonged (≥ 7 d) severe neutropenia, and severe non-hematologic AEs were not reported at a dose level of 120 mg/m² irinotecan and 60 mg/m² oxaliplatin^[11]. Based on these data, we set the study drug regimen – FOLFIRINOX with RIO – to 120 mg/m² irinotecan (66.6% of standard dose) and 60 mg/m² oxaliplatin (70.5% of standard dose) with standard dose of bolus and infusional 5-FU.

Treatment protocol and dose adjustments

Oxaliplatin was first administered as a 2-h intravenous infusion (IVF); 1 h later, irinotecan was administered as a 90-min IVF. Leucovorin (400 mg/m²) was administered as a 90-min IVF immediately after oxaliplatin and irinotecan. The 5-FU dose was a 400 mg/m² bolus followed by 2400 mg/m² administered over 46 h of IVF. Each cycle of FOLFIRINOX with RIO was administered every 2 wk and repeated until either evidence of progressive disease (PD), significant clinical deterioration, or withdrawal of patient consent. All patients routinely received palonosetron 30 min before the initiation of chemotherapy as a prophylactic anti-emetic agent. Atropine was administered to patients with irinotecan-caused cholinergic reactions. High-dose loperamide was administered for delayed diarrhea, followed by prophylactic oral fluoroquinolones if diarrhea continued for over 48 h. Granulocyte colony-stimulating factor (G-CSF) was administered for severe neutropenia. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) before each cycle. In the event of predefined hematologic or non-hematologic AEs, protocol-specified treatment modifications or delays were performed to minimize additional treatment-related AEs.

For each patient, the study lasted up to 15 cycles with drugs donated by the pharmaceutical manufacturers; patients who completed these cycles without PD were admitted to a post-study phase and continued chemotherapy according to the study protocol at their

own expense. Treatment was discontinued if PD or intolerable toxicity was observed, if the patient withdrew from the study, or at the physician's discretion.

Data assessment

Pre-treatment evaluations included taking a complete medical history, physical examination, and laboratory tests. Evaluations were performed within 2 wk before, and every 2 wk during treatment. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1) based on high-resolution computed tomography scans every 8 wk. QoL was assessed every 8 wk using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)^[12] and its supplement for patients with pancreatic cancer (QLQ-PAN26)^[13]. Additionally, changes in body weight and pain scale were checked every 2 wk. The Korean version of the questionnaire, officially translated and distributed by EORTC, was used. All patients filled-out and submitted the questionnaire by themselves on the day of visit. QoL changes between baseline and the last visit were analyzed, considering that the participation period varied among patients. Scores of all QoL scales range from 0 to 100; a higher score indicates a better functional status or a worse symptom.

Statistical analysis

When this clinical trial was being designed, the previously reported ORR of second-line chemotherapy for unresectable PC with GEM failure ranged from 0% to 11.4%^[5,14–17]. With this background, this trial was performed according to a Simon optimal two-stage design ($P_0 = 0.100$, $P_1 = 0.250$, $\alpha = 0.050$, and $\beta = 0.200$; P_0 and P_1 are the response proportions of a poor and good drug, respectively)^[18,19]. In the first stage, accepting a type I error of 10% and a power of 80%, 46 patients were planned for enrollment. If three or fewer of the 22 enrolled patients demonstrated an objective response, we would terminate the experiment at that stage based on the regimen's low efficacy. Otherwise, the regimen would be recommended for further testing and accrual would continue to 46 patients (assuming a 15% dropout rate).

All patients who received the study regimen at least once were included in the intention-to-treat (ITT) and toxicity analysis populations. All efficacy assessments were based on the ITT analyses. PFS and OS were estimated using Kaplan-Meier methods with 95% confidence interval (CIs). When comparing data (QoL questionnaire, weight, and pain scale) between baseline and last visit, the paired *t*-test was used for normally distributed data while the Wilcoxon signed rank test was used for non-normally distributed data. All statistical analyses were performed using IBM SPSS (version 23.0, IBM Corp., Armonk, NY, United States). A *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients

Between August 2015 and May 2016, 48 patients were enrolled. The median age at the time of enrollment was 63.5 years [interquartile range (IQR), 57.5–69.0 years]. All patients had cytologically or histologically confirmed adenocarcinoma according to the inclusion criteria. Also, all patients had LAPC or MPC including 38 patients (79.2%) with accompanying distant metastasis (Table 1). Close to 80% of the patients received GEM plus erlotinib as their first-line GEM-based treatment. Because GEM plus nab-paclitaxel became available in January 2016 in Korea, only one patient was administered this regimen prior to the study.

Treatment exposure

A flowchart of the 48 patients' treatments is shown in Supplementary Figure 1; at the time of analysis, 38 of these patients had died while two patients remained on FOLFIRINOX with RIO. Treatment was discontinued prior to completing 15 cycles in 33 patients, including 14 who showed PD, 10 who had treatment delays for unresolved infections ($n = 2$) or grade 3/4 toxicities ($n = 8$), five who declined further treatment, two who died after treatment (one of septic shock and the other of unknown reasons at another location), one who had acute cerebral infarction, and one who showed radiologic CR. All patients combined received a total of 493 cycles of chemotherapy. The median follow-up time was 259 d (IQR, 103.3–427.8 d), and the median number of chemotherapy cycles per patient was 8.5 (IQR, 3.0–16.5), with a median treatment duration of 145 d (IQR, 30.5–286.3 d). The relative dose intensity (proportion of the administered accumulated dose relative to the planned accumulated dose) of bolus 5-FU, infusional 5-FU, combined bolus plus infusional 5-FU, irinotecan, and oxaliplatin was $93.60\% \pm 15.86\%$, $93.60\% \pm 15.86\%$, $93.60\% \pm 15.86\%$, $95.65\% \pm 8.16\%$, and $95.65\% \pm 8.16\%$, respectively.

Tumor responses and survival

Tumor responses and survival analysis are shown in Table 2. The ORR and DCR of all patients were 18.8% and 62.5%, respectively. The DCR was 80% in ten LAPC patients, but no CR or PR was reported. Among 38 MPC patients (79.2% of all patients), the ORR and DCR were 23.7% and 57.9%, respectively. A sixty-year-old female patient, who progressed to multiple liver metastasis after GEM monotherapy, achieved radiologic CR after 12 cycle of FOLFIRINOX with RIO. After twelfth cycle, the patient had not experienced disease recurrence on serial radiologic studies without chemotherapy for a year, until peritoneal seeding and liver metastasis were confirmed.

The median PFS was 5.8 mo (95%CI: 3.7–7.9 mo) and the median OS was 9.0 mo (95%CI: 6.4–11.6 mo) for all patients (Figure 1). The PFS rates at 6, 12, and

Table 1 Baseline characteristics

Characteristics of the patients		<i>n</i> = 48	Percent
Age (yr)	median (IQR)	63.5 (57.5-69.0)	
	40-49	4	8.3
	50-59	10	20.8
	60-69	25	52.1
	70-79	9	18.8
Sex	Male	23	47.9
	Female	25	52.1
ECOG-PS	0	22	45.8
	1	24	50
	2	2	4.2
Duration since diagnosis (mo)	median (IQR)	7.0 (3.0-12.0)	
Location of pancreatic cancer	Head	18	37.5
	Body and tail	17	35.4
	Recurrence after resection	13	27.1
Number of metastatic site	0	10	20.8
	1	18	37.5
	2	14	29.2
	≥ 3	6	12.5
Metastatic sites (> 5%)	Liver	28	58.3
	Peritoneum	16	33.3
	Distant lymph node	8	16.7
	Lung	6	12.5
Level of CA 19-9	Normal	10	20.8
	> ULN	38	79.2
Prior GEM CTx	GEM monotherapy	6	12.5
	GEM + Erlotinib	38	79.2
	GEM + Capecitabine	2	4.2
	GEM + Cisplatin	1	2.1
	GEM + Nab-paclitaxel	1	2.1
Period of prior CTx (mo)	median (IQR)	4.1 (1.9-7.8)	
Prior treatment other than CTx	Operation	13	27.1
	CCRT	6	12.5

IQR: Interquartile range; ECOG-PS: Eastern Cooperative Oncology Group-performance status; CA 19-9: Carbohydrate antigen 19-9; GEM: Gemcitabine; ULN: Upper limit of the normal range; CCRT: Concurrent chemo-radiotherapy; CTx: Chemotherapy.

18 mo were 47.9%, 27.1%, and 6.3%, respectively, while the OS rates at 6, 12, and 18 mo were 60.4%, 37.5% and 10.4%, respectively. Eighteen patients (37.5%) survived more than 1 year. The estimated OS from the beginning of first-line treatment was 17.1 mo (95%CI: 10.6–23.6 mo). The median PFS and OS were respectively 5.4 and 8.4 mo for MPC patients, and 8.8 and 12.5 mo for LAPC patients. Analysis of changes in laboratory tests between before and after therapy showed that the median CA19-9 significantly decreased from 366.3 (1–16351) to 311.7 (2–16287) U/mL ($P = 0.041$).

Safety analysis

AEs that occurred in more than 5% of the 48 patients are listed in Table 3. Common AEs observed in more than 20% of patients were neutropenia (68.8%), fatigue (22.9%), nausea and vomiting (66.7%), diarrhea (35.4%), oral mucositis (31.3%), anorexia (20.8%), and fever (20.8%). Of a total of 511 AEs, 358 (70.1%) were considered related to therapy, and 163 (31.9%) were severe AEs (grade 3 or 4). The most common severe AE was neutropenia (64.6%), followed by febrile neutropenia and fatigue (16.7% for both). None of

the patients experienced severe nausea/vomiting or constipation. One patient died of septic shock related to grade 4 neutropenia after treatment.

Changes in QoL

The average body weight was 58.9 ± 9.81 kg at baseline and 59.0 ± 9.83 kg at the last visit. The average pain scale (Visual Analogue Scale) at baseline and the last visit were 2.12 ± 2.31 and 1.90 ± 2.15 , respectively. There were no significant changes in body weight and pain scale ($P = 0.93$ and $P = 0.71$, respectively). QoL questionnaires were available for 31 patients. The global health status scores of the EORTC QLQ-C30 did not worsen after treatment ($P = 0.548$). In general, most functional scores were not significantly decreased except role and cognitive functioning ($P = 0.044$ and $P = 0.015$, respectively) (Supplementary Table 1). Among symptom scores, fatigue and dyspnea were significantly worse than those in the pre-treatment period ($P = 0.021$ and $P = 0.038$, respectively). Among separate QLQ-PAN26 questions, worsening of dry mouth was observed ($P = 0.011$). In patients who achieved disease control ($n = 29$), the global health status score did not worsen after treatment,

Table 2 Tumor responses and survivals (intention-to-treat population)

	All (<i>n</i> = 48)	LAPC (<i>n</i> = 10)	MPC (<i>n</i> = 38)
Response, <i>n</i> (%)			
CR	1 (2.1)	0 (0.0)	1 (2.6)
PR	8 (16.7)	0 (0.0)	8 (21.1)
SD	21 (43.8)	8 (80.0)	13 (34.2)
PD	7 (14.6)	1 (10.0)	6 (15.8)
Could not be evaluated	11 (22.9)	1 (10.0)	10 (26.3)
ORR	9 (18.8)	0 (0.0)	9 (23.7)
DCR	30 (62.5)	8 (80.0)	22 (57.9)
Survival, mo (95%CI)			
Median PFS	5.8 (3.7-7.9)	8.8 (6.0-11.6)	5.4 (2.9-7.9)
Median OS (from 2 nd -line CTx)	9.0 (6.4-11.6)	12.5 (4.9-20.1)	8.4 (5.4-11.4)
Median OS (from 1 st -line CTx)	17.1 (10.6-23.6)	19.1 (13.8-24.4)	16.8 (8.8-24.8)

LAPC: Locally advanced pancreatic cancer; MPC: Metastatic pancreatic cancer; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate; CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival; CTx: Chemotherapy.

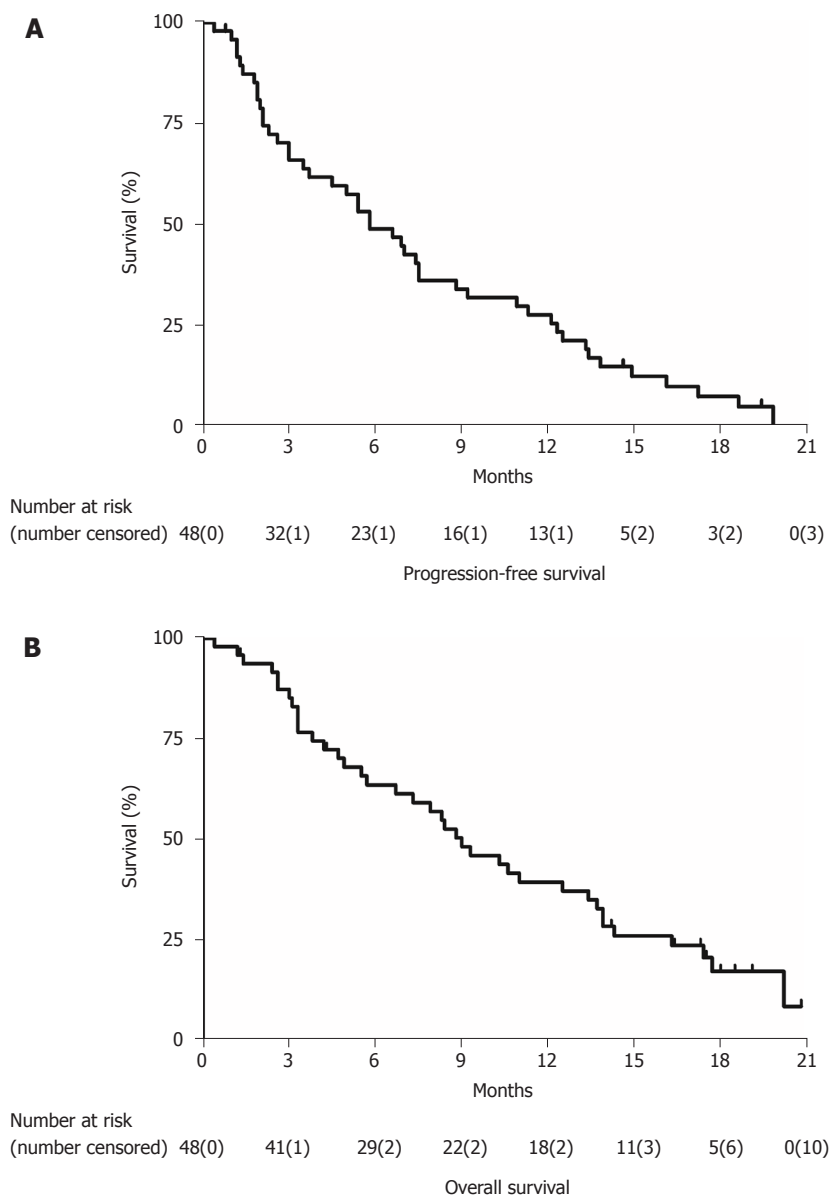


Figure 1 Kaplan-Meier analysis of survival data. A: The estimated median progression-free survival was 5.8 mo (95%CI: 3.7-7.9); B: The estimated median overall survival was 9.0 mo (95%CI: 6.4-11.6).

Table 3 Adverse events ($\geq 5\%$)

N = 48	n (%)	Intensity according to the NCI-CTCAE v4.03			
		Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic					
Fatigue	11 (22.9)	3 (6.3)	0	8 (16.7)	-
Nausea and vomiting	32 (66.7)	17 (35.4)	15 (31.3)	0	0
Diarrhea	17 (35.4)	7 (14.6)	9 (18.8)	1 (2.1)	0
Constipation	8 (16.7)	4 (8.3)	4 (8.3)	0	0
Oral mucositis	15 (31.3)	4 (8.3)	10 (20.8)	1 (2.1)	0
Anorexia	10 (20.8)	9 (18.8)	0	1 (2.1)	0
Peripheral neuropathy	7 (14.6)	6 (12.5)	0	1 (2.1)	0
Biliary tract infection	3 (6.3)	0	0	3 (6.1)	0
Fever	10 (20.8)	1 (2.1)	9 (18.8)	0	0
Hematologic					
Neutropenia	33 (68.8)	0	2 (4.2)	11 (22.9)	20 (41.7)
Thrombocytopenia	6 (12.5)	0	1 (2.1)	1 (2.1)	4 (8.3)
Febrile neutropenia	8 (16.7)	-	-	5 (10.4)	3 (6.3)

NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events.

but some individual items including cognitive function, fatigue, digestive symptoms, and dry mouth were significantly worsened. Only one item (future worries) was significantly improved (Supplementary Table 2). In patients who completed 15 cycles, constipation and pancreatic pain were significantly improved by the end of treatment; only digestive symptoms were aggravated (Supplementary Table 3).

DISCUSSION

FOLFIRINOX with RIO showed an acceptable toxicity profile and promising efficacy as a second-line treatment for GEM-refractory unresectable PC. Although severe neutropenia occurred in almost 65% of participants, other severe AEs, particularly non-hematologic AEs, were infrequently reported. Moreover, the global health status scores of the EORTC QLQ-C30 were not changed significantly after treatment.

Second-line chemotherapy may be considered for many patients^[20]. At present, there is no recognized standard for patients with unresectable PC who experience PD after first-line chemotherapy, and PFS is consistently < 4 mo in patients receiving second-line chemotherapy. A meta-analysis showed that median OS was 6.0 mo with chemotherapy versus 2.8 mo with best supportive care^[21]. Patients whose cancers progress after first-line therapy have difficulty undergoing second-line chemotherapy since they are often older, unwell, and at risk of rapid deterioration^[22].

Only a few prospective trials have shown encouraging results with oxaliplatin plus 5-FU using various doses and schedules^[5,6,14,17,23]. Two phase III trials produced conflicting results. The CONKO-003 trial comparing 5-FU plus FA (FF) and oxaliplatin plus FF (OFF) showed survival benefits of second-line OFF in patients with unresectable GEM-refractory PC^[6]. In contrast, the PANCREOX trial evaluating the modified FOLFOX6 (mFOLFOX6) found no difference in PFS, while the OS

of mFOLFOX6 was inferior to that of FF^[24].

Research on irinotecan plus 5-FU as second-line chemotherapy for PC was also performed^[15,25]. The NAPOLI-1 phase III trial comparing nanoliposomal irinotecan (nal-IRI) alone or combined with FF showed that the combination of nal-IRI and FF was more effective than FF alone, but caused more frequent severe AEs^[7].

A recent comparative systematic review of four randomized trials evaluating oxaliplatin- or irinotecan-containing regimens as post-GEM therapies for patients with unresectable PC showed significant dissimilarity between them; therefore, it is unclear which regimen is best-suited for patients with unresectable PC previously treated with GEM^[26]. Table 4 summarizes clinical trials of second-line treatment for GEM-pre-treated unresectable PC. Our results using second-line FOLFIRINOX with RIO showed results that were superior to those in most previous trials.

Toxicities associated with standard FOLFIRINOX have prompted trials evaluating modifications of FOLFIRINOX^[8-10]. These previous studies of FOLFIRINOX modifications suggested that upfront dose attenuations of standard FOLFIRINOX can improve tolerability without reducing efficacy. A recent phase II trial showed that the efficacy of first-line FOLFIRINOX with reduced doses of the 5-FU bolus and irinotecan was comparable to that of the standard regimen; furthermore, neutropenia, vomiting, and fatigue were significantly reduced^[10]. However, only a few studies have evaluated FOLFIRINOX for patients with unresectable PC after failure of GEM-based chemotherapy; patients' performance statuses are likely to deteriorate after first-line treatment; necessitating second-line dose reductions as in our study. A Japanese phase II trial used modified FOLFIRINOX reducing only irinotecan for 18 MPC patients^[27]. Findings of that trial were consistent with our results except the PFS, which was longer in the present study (2.8 mo vs 5.8 mo).

FOLFIRINOX and nab-paclitaxel plus GEM are two

Table 4 Clinical trials of second-line treatment for gemcitabine pre-treated unresectable pancreatic cancer

Author (yr)	Type of study	Regimen	Patients, n	KPS ≥ 90 or ECOG ≤ 1, %	MPC, %	ORR, %	DCR, %	PFS/TTP, mo	OS, mo
Yoo <i>et al</i> ^[15] 2009	II	Modified FOLFOX	30	97	100	7	17	6.0 wk	14.9 wk
		Modified FOLFIRI3	31	100	100	0	23	8.3 wk	16.6 wk
Novarino <i>et al</i> ^[14] 2009	II	Oxaliplatin/5-FU/LV	23	73.9	69.6	0	23.5	11.6 wk ¹	17.1 wk
Pelzer <i>et al</i> ^[5] 2011	III	BSC	23	52.2	69.6	0	NA	NA	2.3
		Oxaliplatin/5-FU/LV (OFF)	23	47.8	73.9	0	NA	NA	4.8 (P = 0.008)
Chung <i>et al</i> ^[23] 2013	II	FOLFOX4	44	NA	100	11.4	40.9	9.9 wk ¹	31.1 wk
Oettle <i>et al</i> ^[6] 2014	III	5-FU/LV (FF)	84	47.6	88.1	NA	NA	2	3.3
		Oxaliplatin/5-FU/LV (OFF)	84	53.9	88.2	NA	NA	2.9 (P = 0.019)	5.9 (P = 0.01)
Zaanen <i>et al</i> ^[17] 2014	Prospective cohort	FOLFOX ²	27	44.4	100	0	36.4	1.7	4.3
Wang-Gillam <i>et al</i> ^[7] 2016	III	5-FU/LV	119	48	100	1	NA	1.5	4.2
		Nal-IRI/5-FU/LV	117	59	100	16	NA	3.1 (P < 0.001)	6.1 (P = 0.01)
		Nal-IRI	151	57	100	6	NA	2.7 (P = 0.1)	4.9 (P = 0.94)
Gill <i>et al</i> ^[24] 2016	III	Modified FOLFOX6	54	88.9	92.6	13.2	44.7	3.1	6.1
		Infusional 5FU/LV	54	94.3	94.4	8.5 (P = 0.36)	55.3	2.9 (P = 0.99)	9.9 (P = 0.02)
Present study	II	FOLFIRINOX with RIO	48 (MPC: 38)	95.8	79.2	18.8 (MPC: 23.7)	62.5 (MPC: 57.9)	5.8 (MPC: 5.4)	9 (MPC: 8.4)

¹Time to progression; First line therapy was GEM alone or FOLFIRI.3 alternating with GEM. KPS: Karnofsky Performance Scale; ECOG: Eastern Cooperative Oncology Group performance status; MPC: Metastatic pancreatic cancer; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival; 5-FU: 5-fluorouracil; LV: Leucovorin; NA: Not available; II: Phase II study; III: Phase III study; BSC: Best supportive care; Nal-IRI: Nanoliposomal irinotecan; RIO: Reduced dosage of irinotecan and oxaliplatin.

Table 5 Comparison with previous studies focused on FOLFIRINOX as a second-line therapy

Study characteristics			Patients characteristics			Treatment outcomes					Grade ≥ 3 AE (%)				
Author (yr)	Type	Dose modification	Patients, n	Age, median (range)	ECOG	Cancer status (%)	ORR, %	DCR, %	PFS, mo	OS, mo	NP	Febrile NP	Fatigue	Nausea	Diarrhoea
Assaf <i>et al</i> ^[29] 2011	Retro	Standard	27	63 (45-83)	1-3	MPC (100)	18.5	62.9	3	8.5	56	3.7	NA	11	11
Lee <i>et al</i> ^[30] 2013	Retro	Standard	18	57 (44-68)	0-1	MPC (88.9) LAPC (11.1)	27.8	55.6	2.8	8.4	38.9	11.1	NA	38.9	0
Kobayashi <i>et al</i> ^[27] 2017	II	Irinotecan 56% or 67%	18	63 (46-68)	0-1	MPC (100)	22.2	61.1	2.8	9.8	66.7	5.6	NA	0	0
Present study	II	Irinotecan 67% Oxaliplatin 71%	48	64 (40-79)	0-2	MPC (79.2) LAPC (20.8)	All: 18.8 MPC: 23.7 LAPC: 0.0	All: 62.5 MPC: 57.9 LAPC: 80.0	All: 5.8 MPC: 5.4 LAPC: 8.8	All: 9.0 MPC: 8.4 LAPC: 12.5	64.6	16.7	16.7	0	2.1

AE: Adverse event; ECOG: Eastern Cooperative Oncology Group performance status; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; OS: Overall survival; NP: Neutropenia; WHO-PS: World Health Organization performance status; II: Phase II study; Retro: Retrospective study; MPC: Metastatic pancreatic cancer; LAPC: Locally advanced pancreatic cancer; NA: Not available.

of the most effective first-line treatments for MPC, but the appropriate sequence of administration is unclear. A previous study in France concluded that nab-paclitaxel plus GEM appears to be effective, with a manageable toxicity profile, after FOLFIRINOX failure in patients with MPC^[28]. However, studies evaluating the reverse sequence of administration have not been performed to date. Only three studies have been performed evaluating second-line FOLFIRINOX following first-line GEM-based treatment (Table 5)^[27,29,30]. To our knowledge, this study is the first prospective multicenter phase II trial, which evaluated the efficacy and safety of FOLFIRINOX in GEM-refractory PC using

unique dose modification called “FOLFIRINOX with RIO”.

In our study, the relatively higher incidences of severe neutropenia may be related to the patients’ deteriorated physical status after first-line chemotherapy and the lack of prophylactic G-CSF support. For non-hematologic AEs, no grade 3 or 4 vomiting was observed, unlike in the PRODIGE 4/ACCORD 11 trial^[3]. This improved non-hematologic tolerability may be related to the routine administration of prophylactic palonosetron during every cycle of treatment. Peripheral neuropathy was also significantly reduced compared with the previous study, likely because of oxaliplatin dose reduction. In comparison with nal-IRI plus 5-FU regimen of the NAPOLI-1 trial, the preferred second-line therapy for MPC in current guidelines^[31,32], most severe non-hematologic AEs of the present study occurred at lower rates (diarrhea, 13% vs 2.1%; vomiting, 11% vs 0%; anorexia, 4% vs 2.1%)^[7]. However, the rate of severe neutropenia was much higher in the present study (27% vs 64.6%).

Considering QoL, some functional scales such as role and cognitive functioning were significantly reduced in our patients, and some symptom scales such as fatigue and dyspnea were significantly worsened. However, these changes were predictable given our patients’ ages and performance statuses. Global QoL indicators did not significantly deteriorate; moreover, the “physical functioning” QoL score (regarded as one of the strongest prognostic values^[33]) did not significantly worsen throughout treatment.

This study had several limitations. First, it was a non-randomized, single arm trial with a relatively small sample size. A prospective randomized trial including sufficient patients is warranted to provide the clinical recommendation about the treatment sequence for MPC. Second, we included patients with LAPC and MPC who were treated with various prior GEM-based regimens. This heterogeneity in patient population and first-line chemotherapy regimens needs to be improved in future research.

In conclusion, FOLFIRINOX with RIO showed encouraging results in terms of efficacy, with an acceptable safety profile. In addition to nal-IRI plus 5-FU regimen, FOLFIRINOX with RIO may be considered as a treatment option in patients with GEM-refractory unresectable PC. Because the condition of such patients can quickly deteriorate owing to rapid disease progression and treatment toxicity, this regimen may provide acceptable tolerability for patients in terms of patient QoL. However, the presence of hematologic toxicities should be carefully observed, nevertheless, and the routine use of G-CSF should be considered to minimize the risk of hematologic toxicities.

pancreatic cancer (PC) who fail first-line treatment with gemcitabine (GEM)-based regimen. Although some previous phase III trials showed survival improvement with their study regimens, the standard second-line treatment remains unclear.

Research motivation

FOLFIRINOX, a standard first-line treatment for PC, has been proposed as a second-line treatment regimen; however, concerns about relatively high toxicity limited broad use of FOLFIRINOX as a second-line therapy.

Research objectives

We evaluated the efficacy and safety of modified dose of FOLFIRINOX as a second-line treatment for GEM-refractory unresectable PC.

Research methods

In this prospective, multicenter, one-arm, open-label, phase II trial, unresectable PC patients, who showed disease progression during GEM-based therapy were enrolled. All patients were administered FOLFIRINOX with reduced irinotecan and oxaliplatin (RIO; irinotecan 120 mg/m² and oxaliplatin 60 mg/m²), which was set according to the previous phase I study of FOLFIRINOX, with the standard dose of 5-fluorouracil (5-FU). The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse events, and changes in quality of life (QoL) were evaluated.

Research results

A total of 48 patients were enrolled in eight Korean centers. The ORR and DCR were 18.8% and 62.5%, respectively, including one patient who showed complete remission. The median PFS was 5.8 mo [95% confidence interval (CI): 3.7-7.9] and median OS was 9.0 mo (95%CI: 6.4-11.6). Neutropenia (64.6%) was the most common grade 3-4 adverse event. Although 14.6% of patients experienced grade 3 fatigue, most non-hematologic AEs were under grade 2. In the QoL analysis, the global health status score before treatment was not different from the score at the last visit after treatment (45.43 ± 22.88 vs 48.66 ± 24.14, *P* = 0.548).

Research conclusions

FOLFIRINOX with RIO showed acceptable tolerability for patients in terms of patient QoL and may be considered as a treatment option in patients with GEM-refractory unresectable PC. However, the presence of hematologic toxicities should be carefully observed and the routine use of granulocyte colony-stimulating factor should be considered to minimize the risk of hematologic toxicities.

Research perspectives

Prospective study with larger population comparing the efficacy and safety between FOLFIRINOX with RIO and 5-FU plus leucovorin needs to be conducted.

REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; **67**: 7-30 [PMID: 28055103 DOI: 10.3322/caac.21387]
- 2 National Cancer Information Center (Republic of Korea). Cancer Statistics in Korea. Ministry of Health and Welfare, Korea Central Cancer Registry, National Cancer Center, 2017. Available from: URL: https://ncc.re.kr/main.ncc?uri=english/sub04_Statistics
- 3 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bannoun J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
- 4 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, Harris M, Reni M,

ARTICLE HIGHLIGHTS

Research background

Proper second-line treatment can improve survival of patients with unresectable

- Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
- 5 **Pelzer U**, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H, Oettle H. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011; **47**: 1676-1681 [PMID: 21565490 DOI: 10.1016/j.ejca.2011.04.011]
- 6 **Oettle H**, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, Görner M, Mölle M, Greten TF, Lakner V, Bischoff S, Sinn M, Dörken B, Pelzer U. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; **32**: 2423-2429 [PMID: 24982456 DOI: 10.1200/JCO.2013.53.6995]
- 7 **Wang-Gillam A**, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartzmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD, Chen LT; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016; **387**: 545-557 [PMID: 26615328 DOI: 10.1016/S0140-6736(15)00986-1]
- 8 **Mahaseeth H**, Brucher E, Kauh J, Hawk N, Kim S, Chen Z, Kooby DA, Maithel SK, Landry J, El-Rayes BF. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013; **42**: 1311-1315 [PMID: 24152956 DOI: 10.1097/MPA.0b013e31829e2006]
- 9 **Ghorani E**, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience. *Oncology* 2015; **89**: 281-287 [PMID: 26372905 DOI: 10.1159/000439171]
- 10 **Stein SM**, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staugaard C, Indukala D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 2016; **114**: 737-743 [PMID: 27022826 DOI: 10.1038/bjc.2016.45]
- 11 **Ychou M**, Conroy T, Seitz JF, Gourgou S, Hua A, Mery Mignard D, Kramar A. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol* 2003; **14**: 481-489 [PMID: 12598357 DOI: 10.1093/annonc/mdg119]
- 12 **Aaronson NK**, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-376 [PMID: 8433390 DOI: 10.1093/jnci/85.5.365]
- 13 **Fitzsimmons D**, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, Beger HG, Birk D, Büchler MW, Dervenis C, Fernandez Cruz L, Friess H, Grahm AL, Jeekel J, Laugier R, Meyer D, Singer MW, Tihanyi T. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *Eur J Cancer* 1999; **35**: 939-941 [PMID: 10533475 DOI: 10.1016/S0959-8049(99)00047-7]
- 14 **Novarino A**, Satolli MA, Chiappino I, Giacobino A, Bellone G, Rahimi F, Milanesi E, Bertetto O, Ciuffreda L. Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. *Am J Clin Oncol* 2009; **32**: 44-48 [PMID: 19194124 DOI: 10.1097/COC.0b013e31817be5a9]
- 15 **Yoo C**, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, Lee SS, Seo DW, Lee SK, Kim MH, Han DJ, Kim SC, Lee JL. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer* 2009; **101**: 1658-1663 [PMID: 19826418 DOI: 10.1038/sj.bjc.6605374]
- 16 **Chung MJ**, Park JY, Bang S, Park SW, Song SY. Phase II clinical trial of ex vivo-expanded cytokine-induced killer cells therapy in advanced pancreatic cancer. *Cancer Immunol Immunother* 2014; **63**: 939-946 [PMID: 24916038 DOI: 10.1007/s00262-014-1566-3]
- 17 **Zaanen A**, Trouilloud I, Markoutsaki T, Gauthier M, Dupont-Gossart AC, Lecomte T, Aparicio T, Artru P, Thiriot-Bidault A, Joubert F, Fanica D, Taieb J. FOLFOX as second-line chemotherapy in patients with pretreated metastatic pancreatic cancer from the FIRM study. *BMC Cancer* 2014; **14**: 441 [PMID: 24929865 DOI: 10.1186/1471-2407-14-441]
- 18 **Simon R**. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**: 1-10 [PMID: 2702835 DOI: 10.1016/0197-2456(89)90015-9]
- 19 **Conroy T**, Paillot B, François E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A, Deplanque G. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol* 2005; **23**: 1228-1236 [PMID: 15718320 DOI: 10.1200/jco.2005.06.050]
- 20 **Nagrial AM**, Chin VT, Sjoquist KM, Pajic M, Horvath LG, Biankin AV, Yip D. Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials. *Crit Rev Oncol Hematol* 2015; **96**: 483-497 [PMID: 26481952 DOI: 10.1016/j.critrevonc.2015.07.007]
- 21 **Rahma OE**, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. *Ann Oncol* 2013; **24**: 1972-1979 [PMID: 23670093 DOI: 10.1093/annonc/mdl166]
- 22 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]
- 23 **Chung JW**, Jang HW, Chung MJ, Park JY, Park SW, Chung JB, Song SY, Bang S. Folfex4 as a rescue chemotherapy for gemcitabine-refractory pancreatic cancer. *Hepatogastroenterology* 2013; **60**: 363-367 [PMID: 23858557]
- 24 **Gill S**, Ko YJ, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfikar M, Zalewski P, Do T, Cano P, Lam WYH, Dowden S, Grassin H, Stewart J, Moore M. PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. *J Clin Oncol* 2016; **34**: 3914-3920 [PMID: 27621395 DOI: 10.1200/JCO.2016.68.5776]
- 25 **Gebbia V**, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-Fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. *Am J Clin Oncol* 2010; **33**: 461-464 [PMID: 20142727 DOI: 10.1097/COC.0b013e3181b4e3b0]
- 26 **Vogel A**, Ciardiello F, Hubner RA, Blanc JF, Carrato A, Yang Y, Patel DA, Ektare V, de Jong FA, Gill S. Post-gemcitabine therapy for patients with advanced pancreatic cancer - A comparative review of randomized trials evaluating oxaliplatin- and/or irinotecan-containing regimens. *Cancer Treat Rev* 2016; **50**: 142-147 [PMID: 27676174 DOI: 10.1016/j.ctrv.2016.09.001]
- 27 **Kobayashi N**, Shimamura T, Tokuhisa M, Goto A, Endo I, Ichikawa Y. Effect of FOLFIRINOX as second-line chemotherapy for metastatic pancreatic cancer after gemcitabine-based chemotherapy failure. *Medicine (Baltimore)* 2017; **96**: e6769 [PMID: 28489753 DOI: 10.1097/MD.00000000000006769]
- 28 **Portal A**, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardière C, Hammel P, Lecomte T, Dréanic J, Coriat R, Bachet JB, Dubreuil O, Marthey L, Dahan L, Tchoundjeu B, Locher C, Lepère C, Bonnetain F, Taieb J. Nab-paclitaxel plus gemcitabine

- for metastatic pancreatic adenocarcinoma after FOLFIRINOX failure: an AGEO prospective multicentre cohort. *Br J Cancer* 2015; **113**: 989-995 [PMID: 26372701 DOI: 10.1038/bjc.2015.328]
- 29 **Assaf E**, Verlinde-Carvalho M, Delbaldo C, Grenier J, Sellam Z, Pouessel D, Bouaita L, Baumgaertner I, Sobhani I, Tayar C, Paul M, Culine S. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. *Oncology* 2011; **80**: 301-306 [PMID: 21778770 DOI: 10.1159/000329803]
 - 30 **Lee MG**, Lee SH, Lee SJ, Lee YS, Hwang JH, Ryu JK, Kim YT, Kim DU, Woo SM. 5-Fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with advanced pancreatic cancer who have progressed on gemcitabine-based therapy. *Chemotherapy* 2013; **59**: 273-279 [PMID: 24457620 DOI: 10.1159/000356158]
 - 31 **Sohal DP**, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, Uronis HE, Ramanathan RK, Crane CH, Engebretson A, Ruggiero JT, Copur MS, Lau M, Urba S, Laheru D. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; **34**: 2784-2796 [PMID: 27247222 DOI: 10.1200/JCO.2016.67.1412]
 - 32 **Ducreux M**, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** Suppl 5: v56-v68 [PMID: 26314780 DOI: 10.1093/annonc/mdv295]
 - 33 **Gourgou-Bourgade S**, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013; **31**: 23-29 [PMID: 23213101 DOI: 10.1200/JCO.2012.44.4869]

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Small intestinal hemangioma: Endoscopic or surgical intervention? A case report and review of literature

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Abstract

BACKGROUND

Hemangioma of the small intestine is a rare vascular malformation. Before the advent of capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE), preoperative diagnosis of this disease was extremely difficult.

CASE SUMMARY

In this study, we report a 24-year-old female with a large transmural small bowel cavernous hemangioma, which was diagnosed with CE and BAE preoperatively and removed successfully using minimally invasive surgery. Meanwhile, we perform a literature review of the studies about intestinal hemangiomas published after 2000. Literature review revealed that 91.9% of the lesions were diagnosed preoperatively by CE and/or BAE and 45.9% of them were treated endoscopically, which is a marked improvement compared to before 2000. Therefore, CE and BAE are useful modalities for the preoperative diagnosis of hemangiomas in the small intestine.

CONCLUSION

Endoscopic treatment of intestinal hemangioma is

generally prudent and might be suitable for multiple, relatively small lesions.

Key words: Hemangioma; Capsule endoscopy; Balloon-assisted enteroscopy; Endoscopic intervention; Surgery; Case report

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Core tip: Hemangioma of the small intestine is a rare disease and mostly presents as gastrointestinal bleeding. With the advent of capsule endoscopy and balloon-assisted enteroscopy, the preoperative diagnosis of this disease has been considerably improved. Surgical resection is the conventional treatment modality. With the improvement of endoscopic therapeutic interventions, less invasive procedures are becoming possible. However, potential risks of endoscopic treatment include bleeding and intestinal perforation. Since intestinal hemangiomas originate from the submucosal layer and some of them are transmural, endoscopic treatment might sometimes result in uncontrolled bleeding or perforation.

Hu PF, Chen H, Wang XH, Wang WJ, Su N, Shi B. Small intestinal hemangioma: Endoscopic or surgical intervention? A case report and review of literature. *World J Gastrointest Oncol* 2018; 10(12): 516-521
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INTRODUCTION

Hemangioma of the small intestine is a rare disease, accounting for 7%-10% of all benign tumors of the small intestine^[1,2]. It may be solitary or multiple, with the jejunum being the most common site of involvement^[3]. The main presenting symptoms include hemorrhage, abdominal pain, obstruction, intussusceptions, or rarely, perforation^[4,5]. It originates from the submucosal vascular plexuses and may extend into the muscular layer or beyond^[6]. Histologically, hemangiomas are congenital benign vascular lesions that can be classified as capillary, cavernous, or mixed-type according to the size of the vascular channels^[2]. With the advent of capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE), complete investigation of the small bowel is possible^[7]. The preoperative diagnosis of this disease has been considerably improved. Recent advances in endoscopic techniques have led to successful endoscopic intervention, but most large lesions have been treated surgically. Here, we present a case with solitary small bowel hemangioma, which was diagnosed preoperatively by CE and BAE and removed successfully using minimally invasive surgery.

CASE PRESENTATION

Chief complaints

A 24-year-old female suffered from recurrent melena and fatigue for 1 year.

History of present illness

Over the past year, the patient experienced repeated black stool, accompanied by fatigue, without hematemesis, hematochezia, abdominal pain or fever. The lowest level of hemoglobin was 42 g/L.

History of past illness

Past and family medical history was unremarkable.

Physical examination

Physical examination showed moderate anemia. Detailed dermatological evaluation did not show any cutaneous lesions.

Laboratory testing

Laboratory studies revealed moderated microcytic and hypochromic anemia (hemoglobin, 7.5 g/dL). Fecal occult blood test was positive.

Imaging examination

Gastroscopy and colonoscopy were normal. CE was performed, showing a prominent polypoid lesion in the ileum with no sign of active bleeding (Figure 1). Transanal double-balloon enteroscopy (DBE) revealed a reddish purple lesion in the ileum about 80 cm proximal to the ileocecal valve (Figure 2A). A titanium clip was used to mark the limit reached. Transoral DBE was performed to assess the remainder of small bowel, which revealed no additional lesions (Figure 2B).

MULTIDISCIPLINARY EXPERT CONSULTATION

Ping-Fang Hu, MD, Attending Doctor, Department of Gastroenterology

From the endoscopic appearance of the lesion, it was most likely a hemangioma. Considering that the lesion was large and diffuse, endoscopic interventions such as endoscopic mucosal resection (EMR) and endoscopic sclerotherapy might lead to uncontrolled bleeding or perforation. Therefore, laparoscopic surgery was deemed the best choice.

Bin Shi, MD, Professor, Department of Gastroenterology

The patient had repeated bleeding and a large amount of bleeding every time. Since the lesion was large and diffuse, surgery would be better for the patient.

Han Chen, MD, Attending Doctor, Department of Surgery

The patient suffered from recurrent melena in the past year. From the results of the CE and BAE, the cause

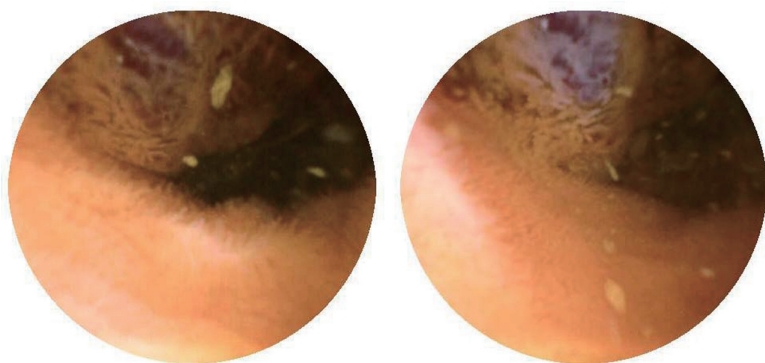


Figure 1 Capsule endoscopic appearance of the lesion. Capsule endoscopy showed a prominent polypoid lesion in the ileum.

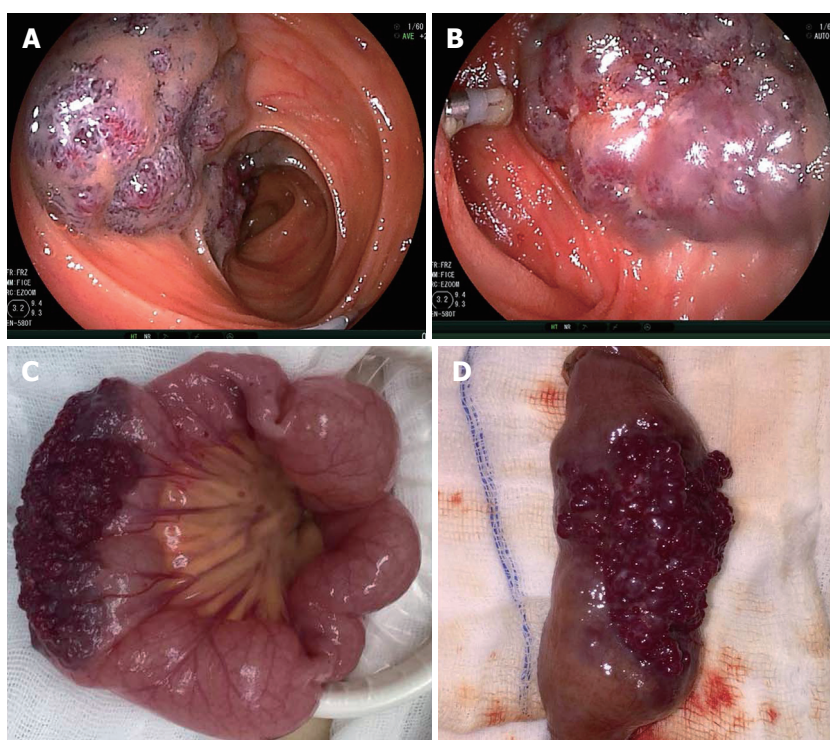


Figure 2 Endoscopic and gross appearance of the lesion. A: Transanal double-balloon enteroscopy revealed a reddish purple lesion in the ileum about 80 cm proximal to the ileocecal valve, and a titanium clip was used to mark the limit reached; B: Transoral double-balloon enteroscopy showed the same lesion and the marked titanium clip; C: Gross intraoperative appearance of the lesion; D: Gross appearance of the lesion after resection.

is likely the small intestinal hemangioma. The surgical indication was explicit.

Ning Su, MD, Attending Doctor, Department of Surgery

The diagnosis is relatively clear. Since biopsy might lead to uncontrolled bleeding, we could not verify the diagnosis preoperatively.

Wei-Jun Wang, Professor, Department of Surgery

Imaging examination including ultrasound and CT scan did not find any abnormalities. From the endoscopic appearance of the lesion, it was most likely a hemangioma. The patient was a young female with a good health status. We could consider resecting the

lesion laparoscopically.

FINAL DIAGNOSIS

Small bowel bleeding and small intestinal hemangioma.

TREATMENT

The patient was sent to laparoscopy, and a 5 cm × 3 cm × 3 cm purple-colored, raspberry-like lesion was found spreading diffusely along the serosal surface of the ileum (Figure 2C). The lesion was completely resected (Figure 2D). Hematoxylin-eosin staining (Figure 3A) and CD31 immunohistochemistry (Figure 3B) indicated

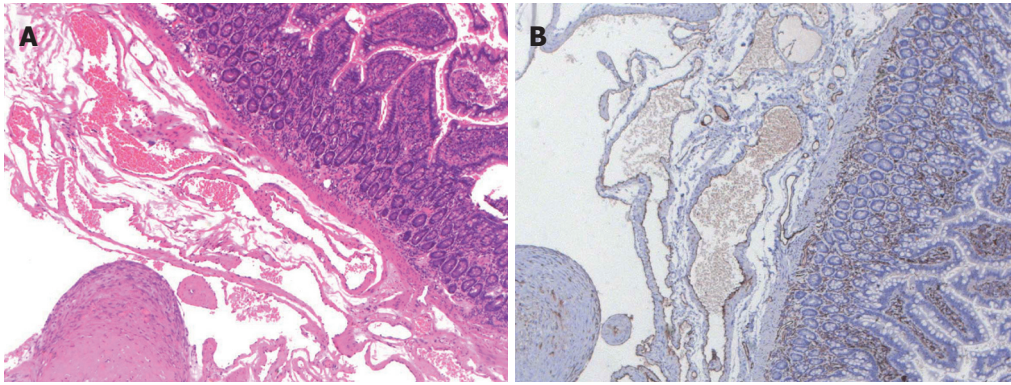


Figure 3 Histopathological examination of the lesion. A: Hematoxylin-eosin staining showed a blood-filled sinus-like space in the whole layer of the ileum ($\times 50$); B: Immunohistochemistry indicated the cells lined with the vascular spaces were CD31-positive ($\times 50$).

a transmural cavernous hemangioma.

OUTCOME AND FOLLOW-UP

The patient recovered quickly and had no further episodes of bleeding since the operation. The hemoglobin value increased to normal (12.4 g/dL) and was stable.

DISCUSSION

Hemangioma accounts for only 0.05% of all gastrointestinal (GI) neoplasms. They mostly present with occult GI bleeding and iron deficiency anemia. Because of its rarity, it is not considered a common cause of GI bleeding. Previously, the preoperative diagnosis of this disease was difficult, and almost all cases were diagnosed during or after the operation^[1]. With the introduction of CE and BAE over the past decades, the small intestine has now become an area that can be targeted^[8]. We searched the PubMed database for studies about intestinal hemangiomas published after 2000 utilizing the following search terms: "hemangioma", "vascular malformation", "small intestine" and "small bowel". A manual search was also performed using the references of eligible articles. The language was limited to English. A total of 37 cases (16 women, 21 men, mean age 39 years) were retrieved and reviewed (Table 1). The most common manifestation included GI bleeding and anemia. A total of 75.7% (28/37) of the cases were single, and the common location of the small intestine was the jejunum (60.9%). Thirty-four of the 37 lesions (91.9%) were diagnosed before operation by CE and/or BAE. Of these cases, 11 were detected with CE alone, and 22 were diagnosed with both CE and BAE. Compared with the cases reported before 2000, a markedly increased proportion of cases were preoperatively diagnosed^[1]. As in our case, CE was used to initially examine the GI tract, which was based on the algorithms for the diagnosis and treatment of obscure GI bleeding^[7]. Both transanal DBE and transoral DBE were then performed to complete total enteroscopy, which was useful to localize the lesion and rule out

other lesions.

Surgical resection, which is relatively more invasive, is the conventional treatment modality for intestinal hemangiomas. With the improvement of endoscopic therapeutic interventions, less invasive procedures are becoming more widely employed. Of the 37 cases of intestinal hemangiomas published after 2000 (Table 1), 17 cases (45.9%) were treated endoscopically. Among them, 3 cases were removed by EMR, one case was treated by argon plasma coagulation, and 13 cases were subjected to sclerotherapy. Most of these lesions were multiple (14/17, 82.4%), and the lesions were relatively small. As suggested by the guideline on the management of small bowel bleeding, the patient should be managed with endoscopic therapy if a source of bleeding is found. Surgical treatment is generally regarded as a last resort^[7]. Compared with surgery, endoscopic treatments including sclerotherapy and EMR are less invasive. However, they increase the potential risks of GI bleeding and intestinal perforation. Since intestinal hemangiomas originate from the submucosal layer, endoscopic treatment such as EMR is dangerous because of the risk of perforation. Endoscopic treatment might lead to perforation because some intestinal hemangiomas were transmural, as in our case. Considering that the hemangioma was large in the current case, uncontrolled bleeding would probably occur after endoscopic intervention. After discussion with a multidisciplinary team, which included gastroenterologists, endoscopists and surgeons, we decided to remove the lesion by laparoscopy. It turned out that a laparoscopic approach was likely the best choice for our case, as the lesion was relatively large and most importantly, transmural. Thus, endoscopic treatment of intestinal hemangioma should be prudent. It is likely suitable for multiple, relatively small lesions.

In conclusion, we present a case of small bowel hemangioma that was preoperatively diagnosed by CE and BAE and treated by laparoscopy. We believe it is important for both the endoscopist and surgeons to recognize this somewhat unusual lesion. It is recommended that careful consideration of the indications for

Table 1 Summary of hemangioma of small intestine reported after 2000

Ref.	Country	Case	Sex/age	Complaint	Diagnosis	Location	Single/multiple	Treatment	Pathology
Easler <i>et al</i> ^[9]	United States	1	M/71	Anemia, melena	BAE	Jejunum	Single	EMR	Cavernous
Ng <i>et al</i> ^[10]	China	1	F/20	Anemia	Small bowel enema	Terminal ileum	Multiple	APC	-
Wardi <i>et al</i> ^[11]	Israel	1	M/77	Anemia, melena	CE	Ileum	Single	Laparoscopy	Capillary
Ersoy <i>et al</i> ^[6]	Turkey	1	F/50	Melena, hematemesis	CE + BAE	Proximal jejunum	Single	Laparoscopy	Cavernous
Fernandes <i>et al</i> ^[12]	Portugal	1	F/56	Hematochezia, syncope	CE	Ileum	Single	Laparoscopy	Cavernous
Law ^[13]	China	1	F/31	Melena	CE + BAE	Jejunum	Single	Laparoscopy	Cavernous
Ning <i>et al</i> ^[4]	China	1	M/10	Melena	BAE	Jejunum/ileum	Multiple	Polidocanol injection	-
Elias <i>et al</i> ^[15]	United States	1	M/30	Anemia	CE + BAE	Jejunum	Multiple	Surgery	Cavernous
Shibuya <i>et al</i> ^[16]	Japan	1	M/74	Melena	CE + BAE	jejunum	Single	EMR	Capillary
Willert <i>et al</i> ^[6]	Australia	1	M/19	Anemia	CE + BAE	Jejunum/ileum	Multiple	EMR	Cavernous
Igawa <i>et al</i> ^[17]	Japan	12	6M/6F	Gastrointestinal bleeding	CE + BAE	Jejunum/ileum	7 single/5 multiple	Polidocanol injection	-
Takase <i>et al</i> ^[18]	Japan	2	F-62/M-52	Melena	CE + BAE	Jejunum/ileum	Single	Laparoscopy	Cavernous/capillary
Akazawa <i>et al</i> ^[19]	Japan	1	F/56	Melena	CE + BAE	Jejunum	Single	Laparoscopy	Cavernous
Chen <i>et al</i> ^[20]	United States	1	M/23	Fatigue	CE	Ileum	Single	Laparoscopy	Cavernous
Dhumane <i>et al</i> ^[21]	France	1	M/60	Anemia	CE + BAE	Jejunum	Single	Laparoscopy	Cavernous
Bae <i>et al</i> ^[22]	South Korea	1	M/13	Dizziness, fatigue	CE	Jejunum	Single	Laparoscopy	Cavernous
Huber <i>et al</i> ^[23]	Germany	1	M/23	Weakness, dizziness	CE + BAE	Jejunum	Single	Laparoscopy	Cavernous
Quentin <i>et al</i> ^[5]	France	1	F/32	Hematochezia	CE	Jejunum	Single	Laparoscopy	Cavernous
Khurana <i>et al</i> ^[24]	United States	1	M/62	Melena	BAE	Jejunum	Single	Surgery	Cavernous
Pera <i>et al</i> ^[25]	Spain	1	M/16	Fatigue	CE	Jejunum	Single	Laparoscopy	-
Pinho <i>et al</i> ^[26]	Portugal	1	F/9	Melena, anemia	CE	Ileum	Single	Surgery	Cavernous
Magnano <i>et al</i> ^[27]	Italy	1	M/13	Fatigue, malaise	CE	Ileum	Single	Laparoscopy	Cavernous
Kuo <i>et al</i> ^[28]	China	1	F/20	Abdominal pain	-	Jejunum	Single	Laparoscopy	Cavernous
Guardiola <i>et al</i> ^[29]	Spain	1	M/19	Anemia	CE	Ileum	Single	Laparoscopy	Cavernous
Purdy-Payne <i>et al</i> ^[30]	United States	1	F/20	Abdominal pain	-	Terminal ileum	Single	Laparoscopy	Cavernous

CE: Capsule endoscopy; BAE: Balloon assisted enteroscopy; EMR: Endoscopic mucosal resection; APC: Argon plasma coagulation.

endoscopic treatment. As in our case, hemangiomas may sometimes involve the entire wall of the intestine. Endoscopic intervention may lead to uncontrolled bleeding or perforation. For the large and diffuse lesions, a laparoscopic excision might be a better approach.

EXPERIENCES AND LESSONS

Hemangioma of the small intestine is a rare disease, which mostly presented as occult GI bleeding and iron deficiency anemia. With the advent of CE and BAE, the diagnosis of lesions in the small intestine has been considerably improved. Endoscopic treatment of intestinal hemangioma should be prudent, and it might be suitable for multiple and relatively small lesions.

REFERENCES

1 Ramanujam PS, Venkatesh KS, Bettinger L, Hayashi JT, Rothman MC, Fietz MJ. Hemangioma of the small intestine: case report and literature review. *Am J Gastroenterol* 1995; **90**: 2063-2064 [PMID: 7485031]
2 Kumar N, Adam SZ, Goodhartz LA, Hoff FL, Lo AA, Miller FH. Beyond hepatic hemangiomas: the diverse appearances of gastrointestinal and genitourinary hemangiomas. *Abdom Imaging* 2015; **40**: 3313-3329 [PMID:

- 26239397 DOI: 10.1007/s00261-015-0515-8]
- 3 **Quentin V**, Lermite E, Lebigot J, Marannes MZ, Arnaud JP, Boyer J. Small bowel cavernous hemangioma: wireless capsule endoscopy diagnosis of a surgical case. *Gastrointest Endosc* 2007; **65**: 550-552 [PMID: 17321267 DOI: 10.1016/j.gie.2006.12.024]
 - 4 **Rao AB**, Pence J, Mirkin DL. Diffuse infantile hemangiomatosis of the ileum presenting with multiple perforations: a case report and review of the literature. *J Pediatr Surg* 2010; **45**: 1890-1892 [PMID: 20850639 DOI: 10.1016/j.jpedsurg.2010.05.019]
 - 5 **Ruiz AR Jr**, Ginsberg AL. Giant mesenteric hemangioma with small intestinal involvement: an unusual cause of recurrent gastrointestinal bleed and review of gastrointestinal hemangiomas. *Dig Dis Sci* 1999; **44**: 2545-2551 [PMID: 10630511 DOI: 10.1023/A:1026659710815]
 - 6 **Ersay O**, Akin E, Demirezer A, Koseoglu H, Balci S, Kiyak G. Cavernous haemangioma of small intestine mimicking gastrointestinal stromal tumour. *Arab J Gastroenterol* 2013; **14**: 139-140 [PMID: 24206746 DOI: 10.1016/j.ajg.2013.08.008]
 - 7 **Gerson LB**, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding. *Am J Gastroenterol* 2015; **110**: 1265-1287; quiz 1288 [PMID: 26303132 DOI: 10.1038/ajg.2015.246]
 - 8 **Willert RP**, Chong AK. Multiple cavernous hemangiomas with iron deficiency anemia successfully treated with double-balloon enteroscopy. *Gastrointest Endosc* 2008; **67**: 765-767 [PMID: 18155208 DOI: 10.1016/j.gie.2007.07.044]
 - 9 **Easler JJ**, Papachristou GI. A case of obscure gastrointestinal bleeding. *Gastroenterology* 2012; **142**: 700, 1044 [PMID: 22370215 DOI: 10.1053/j.gastro.2011.09.009]
 - 10 **Ng EK**, Cheung FK, Chiu PW. Blue rubber bleb nevus syndrome: treatment of multiple gastrointestinal hemangiomas with argon plasma coagulator. *Dig Endosc* 2009; **21**: 40-42 [PMID: 19691801 DOI: 10.1111/j.1443-1661.2008.00817.x]
 - 11 **Wardi J**, Shahmurov M, Czerniak A, Avni Y. Clinical challenges and images in GI. Capillary hemangioma of small intestine. *Gastroenterology* 2007; **132**: 1656, 2084 [PMID: 17484862 DOI: 10.1053/j.gastro.2007.03.081]
 - 12 **Fernandes D**, Dionisio I, Neves S, Duarte P. Cavernous hemangioma of small bowel: a rare cause of digestive hemorrhage. *Rev Esp Enferm Dig* 2014; **106**: 214-215 [PMID: 25007019]
 - 13 **Law WL**. Cavernous hemangioma: uncommon cause of obscure gastrointestinal bleeding. *J Am Coll Surg* 2007; **205**: 511 [PMID: 17765169 DOI: 10.1016/j.jamcollsurg.2006.10.035]
 - 14 **Ning S**, Zhang Y, Zu Z, Mao X, Mao G. Enteroscopic sclerotherapy in blue rubber bleb nevus syndrome. *Pak J Med Sci* 2015; **31**: 226-228 [PMID: 25878650 DOI: 10.12669/pjms.311.5858]
 - 15 **Elias G**, Toubia N. Hemangioma of the small intestine presenting with recurrent overt, obscure gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2010; **8**: A18, A18.e1 [PMID: 19362610 DOI: 10.1016/j.cgh.2009.03.036]
 - 16 **Shibuya T**, Osada T, Mitomi H, Takeda T, Nomura O, Nakayama H, Hidaka Y, Mori H, Beppu K, Sakamoto N, Nagahara A, Otaka M, Ogihara T, Yao T, Watanabe S. Jejunal capillary hemangioma treated by using double-balloon endoscopy (with video). *Gastrointest Endosc* 2010; **72**: 660-661 [PMID: 20546731 DOI: 10.1016/j.gie.2009.12.051]
 - 17 **Igawa A**, Oka S, Tanaka S, Kuniyama S, Nakano M, Chayama K. Polidocanol injection therapy for small-bowel hemangioma by using double-balloon endoscopy. *Gastrointest Endosc* 2016; **84**: 163-167 [PMID: 26907744 DOI: 10.1016/j.gie.2016.02.021]
 - 18 **Takase N**, Fukui K, Tani T, Nishimura T, Tanaka T, Harada N, Ueno K, Takamatsu M, Nishizawa A, Okamura A, Kaneda K. Preoperative detection and localization of small bowel hemangioma: Two case reports. *World J Gastroenterol* 2017; **23**: 3752-3757 [PMID: 28611528 DOI: 10.3748/wjg.v23.i20.3752]
 - 19 **Akazawa Y**, Hiramatsu K, Nosaka T, Saito Y, Ozaki Y, Takahashi K, Naito T, Ofuji K, Matsuda H, Ohtani M, Nemoto T, Suto H, Yamaguchi A, Imamura Y, Nakamoto Y. Preoperative diagnosis of cavernous hemangioma presenting with melena using wireless capsule endoscopy of the small intestine. *Endosc Int Open* 2016; **4**: E249-E251 [PMID: 27004239 DOI: 10.1055/s-0041-111321]
 - 20 **Chen CH**, Jones J, McGowan P. Profound iron deficiency anemia caused by a small-intestinal cavernous hemangioma. *Gastrointest Endosc* 2009; **69**: 1392-1393; discussion 1393 [PMID: 19481664 DOI: 10.1016/j.gie.2009.01.049]
 - 21 **Dhumane P**, Mutter D, D'Agostino J, Mavrogenis G, Leroy J, Marescaux J. Small bowel exploration and resection using single-port surgery: a safe and feasible approach. *Colorectal Dis* 2013; **15**: 109-114 [PMID: 22672499 DOI: 10.1111/j.1463-1318.2012.03118.x]
 - 22 **Bae SJ**, Hwang G, Kang HS, Song HJ, Chang WY, Maeng YH, Kang KS. Single Cavernous Hemangioma of the Small Bowel Diagnosed by Using Capsule Endoscopy in a Child with Chronic Iron-Deficiency Anemia. *Clin Endosc* 2015; **48**: 340-344 [PMID: 26240811 DOI: 10.5946/ce.2015.48.4.340]
 - 23 **Huber A**, Abdel Samie A, Kychenko D, Theilmann L. A rare cause of recurrent iron-deficiency anemia: cavernous hemangioma of the small intestine. *J Gastrointest Liver Dis* 2012; **21**: 343 [PMID: 23256111]
 - 24 **Khurana V**, Dala R, Barkin JS. Small bowel cavernous hemangioma. *Gastrointest Endosc* 2004; **60**: 96 [PMID: 15229433 DOI: 10.1016/S0016-5107(04)01292-1]
 - 25 **Pera M**, Márquez L, Dedeu JM, Sánchez J, García M, Ramón JM, Puigvehí M. Solitary cavernous hemangioma of the small intestine as the cause of long-standing iron deficiency anemia. *J Gastrointest Surg* 2012; **16**: 2288-2290 [PMID: 22875598 DOI: 10.1007/s11605-012-1991-6]
 - 26 **Pinho R**, Rodrigues A, Proença L, Silva AP, Fernandes S, Leite S, Amaral I, de Sousa P, Fraga J. Solitary hemangioma of the small bowel disclosed by wireless capsule endoscopy. *Gastroenterol Clin Biol* 2008; **32**: 15-18 [PMID: 18405648 DOI: 10.1016/j.gcb.2007.11.004]
 - 27 **Magnano A**, Privitera A, Calogero G, Nanfity L, Basile G, Sanfilippo G. Solitary hemangioma of the small intestine: an unusual cause of bleeding diagnosed at capsule endoscopy. *J Pediatr Surg* 2005; **40**: e25-e27 [PMID: 16226971 DOI: 10.1016/j.jpedsurg.2005.06.014]
 - 28 **Kuo LW**, Chuang HW, Chen YC. Small bowel cavernous hemangioma complicated with intussusception: report of an extremely rare case and review of literature. *Indian J Surg* 2015; **77**: 123-124 [PMID: 25972669 DOI: 10.1007/s12262-014-1194-3]
 - 29 **Guardiola A**, Navajas J, Valle J, López-Pardo R, Rodríguez-Merlino R, Lombera Mdel M, Alcántara M. Small bowel giant cavernous hemangioma diagnosed by capsule endoscopy. *Rev Esp Enferm Dig* 2012; **104**: 277-278 [PMID: 22662783 DOI: 10.4321/S1130-01082012000500011]
 - 30 **Purdy-Payne EK**, Miner JF, Foles B, Tran TA. The "Endothelialized Muscularis Mucosae": A Case Report Describing a Large Cavernous Hemangioma at the Terminal Ileum and a New Histologic Clue for Preoperative Diagnosis from Endoscopic Biopsy. *Case Rep Gastrointest Med* 2015; **2015**: 454836 [PMID: 26442160 DOI: 10.1155/2015/454836]

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Experience in the diagnosis and treatment of mesenteric lymphangioma in adults: A case report and review of literature

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Abstract

BACKGROUND

Mesenteric lymphangioma (ML) in adults is a very rare disease. We report six hospitalized adult patients with ML in our hospital between January 2013 and July 2018 to investigate the characteristics and prognosis of ML in adults.

CASE SUMMARY

The male-to-female ratio was 3:3, and the median age at diagnosis was 55.2 years. Clinical manifestations varied; however, most were acute cases (5/6). No history of trauma was reported. None (0/6) of the patients were accurately diagnosed with ML in the emergency and outpatient departments. Mesenteric cysts were identified in four patients (66.7%) by abdominal ultrasound and in five patients (83.3%) by computed tomography. ML was postoperatively confirmed by pathology. Most MLs (4/6) were associated with infection of other systems. ML was located in the mesentery of the small intestine ($n = 4$), ileum ($n = 1$) and rectum ($n = 1$). Cyst fluid was clear ($n = 4$), chylous ($n = 1$) and bloody ($n = 1$). Surgical procedures included complete tumor removal and partial intestinal excision ($n = 6$). Recurrence and adhesive intestinal obstruction were not observed during the 3-12 mo follow-up period.

CONCLUSION

ML in adults is a rare benign acquired disease that can be cured by surgical treatment. Infection may be a cause of ML.

Key words: Mesenteric lymphangioma; Mesenteric cyst; Adults; Acute abdominal pain; Case report

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Core tip: Mesenteric lymphangioma (ML) is a rare congenital lymphangioma that predominantly affects children. We reported six cases of adult patients with ML and reviewed the literature. The report is helpful in comprehensively understanding the characteristics and prognosis of ML in adults and arousing the clinician's attention to this disease.

Chen J, Du L, Wang DR. Experience in the diagnosis and treatment of mesenteric lymphangioma in adults: A case report and review of literature. *World J Gastrointest Oncol* 2018; 10(12): 522-527

URL: <https://www.wjgnet.com/1948-5204/full/v10/i12/522.htm>
DOI: <https://dx.doi.org/10.4251/wjgo.v10.i12.522>

INTRODUCTION

Mesenteric lymphangioma (ML) is a rare congenital lymphangioma of uncertain etiology that predominantly occurs in children. ML lacks specific clinical signs and symptoms, and patients are often admitted to the hospital due to complications, such as abdominal pain, abdominal distension, intestinal obstruction and other acute abdominal manifestations. In adults, it is often found coincidentally during auxiliary examinations or even exploratory abdominal laparotomy, leading to passive surgery or surgical preparation, sometimes missing the best surgical opportunity due to delayed diagnosis. Cases and misdiagnosed cases have been reported in previous studies^[1-3]. However, these studies mainly focused on imaging. Here, we retrospectively analyzed six adults with ML confirmed by pathological examination and admitted between January 2013 and July 2018. Our findings may improve our understanding of this disease and provide more clinical references for early and correct treatment.

CASE PRESENTATION**Chief complaints**

Case 1: A 45-year-old man with abdominal pain for 16 h.

Case 2: A 59-year-old man with severe abdominal pain, no defecation and exhaustion for 3 d.

Case 3: A 62-year-old man with abdominal pain, nausea and fever for 3 h.

Case 4: A 71-year-old woman with abdominal pain, fever, diarrhea, and gastrointestinal bleeding for 1 wk.

Case 5: A 42-year-old woman with abdominal distension for 2 years that had recurred for 1 d.

Case 6: A 52-year-old woman with mild abdominal pain and distension, nausea and fever for more than 1 d.

History of present illness

None of the patients had a significant history of trauma. Most MLs (4/6) were associated with infection of other systems. Case 1: cholecystitis; Case 2: no other systemic co-infection was found; Case 3: cholangitis; Case 4: urinary tract infection; Case 5: no other systemic co-infection was found; Case 6: Gastrointestinal tract infection, acute gastritis and colitis.

History of past illness

The history of symptoms ranged from 3 h to 2 yr. Case 3 had a medical history of cholangiolithiasis and endoscopic retrograde cholangiopancreatography, Case 5 had an untreated abdominal cyst 2 years previously and diabetes for more than 5 years and was admitted to our hospital due to acute abdominal distension. All other cases were admitted to the emergency department for acute abdominal pain without history of other chronic diseases.

Physical examination

Case 2: middle and upper abdominal tenderness and rebound tenderness, no muscle guarding; bowel sound was high pitched tinkling. Case 4: periumbilical tenderness, no rebound tenderness and muscle guarding, a palpable mass of about 10 cm in diameter was detected when abdominal pain occurred, but disappeared when abdominal pain was relieved. All other cases showed tenderness in different parts of the abdomen, no rebound tenderness and muscle guarding, and bowel sounds were normal.

Laboratory testing

Tumor markers were normal in all cases, and laboratory tests indicated increased white blood cell to different degrees. In addition, Case 2 and 3 showed a slight increase in alanine aminotransferase and γ -glutamyl transpeptidase. Case 4 and Case 6 indicated fecal occult blood (+), and fecal bacteria cultures were negative.

Imaging examination

All patients underwent abdominal ultrasound and abdominal computed tomography/magnetic resonance imaging (commonly known as CT/MRI) examination after admission (Figures 1 and 2), and some patients

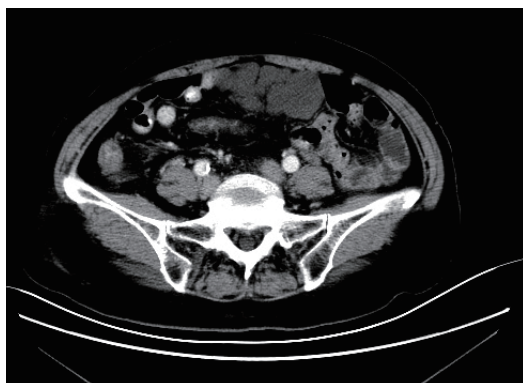


Figure 1 Abdominal computed tomography scan reveals lumpy low-density shadows around the upper middle intestine, 86 mm × 42 mm in size, and no enhancement was observed (Case 4).

had abdominal X-ray examination. In one patient with acute intussusception and one patient with diarrhea, abdominal X-rays showed fluid and an incomplete intestinal obstruction. In other patients with acute abdominal pain, abdominal X-ray showed no obvious abnormalities. Five patients were found to have an intraperitoneal cystic or solid cystic mass by CT/MRI. Abdominal ultrasonography failed to detect an abdominal cyst in Case 3 and Case 4. Preoperative ultrasound and CT failed to detect an abdominal cyst in Case 3.

FINAL DIAGNOSIS

All cysts were examined by pathology after operation, and all were ML (Figure 3).

TREATMENT

Case 6 of a suspected rectal tumor and Case 5 of an intra-abdominal benign cyst chose elective surgery, and the remaining four patients underwent emergency surgery within 48 h of hospital admission. Intraoperative ML was identified in the jejunum in four cases, the ileum in one case, and the rectum in one case. Four cases had clear cystic fluid, one case had chylous fluid and one case had bloody fluid. Tumor invasion was noted in the bile duct in one case, the duodenum in one case, the transverse colon in one case, and the rectum in one case. All six cases underwent complete removal of the tumor and partial intestinal excision, ranging from 6 to 50 cm.

OUTCOME AND FOLLOW-UP

Six patients were included in this study. Patient information and clinical manifestations are shown in Table 1. Of the six patients, three were male and three were female, aged 42–71 years, with an average age of 55.2 years. The clinical manifestations of ML included acute abdominal pain, acute intestinal obstruction (vomiting, abdominal distension, no defecation

and exhaustion), fever, diarrhea, and gastrointestinal bleeding. The initial diagnoses included: one case of acute intussusception, three cases of abdominal tumors (mesenteric lipoma, duodenal and rectum tumor), one case of acute cholangitis, and one case of acute hemorrhagic enteritis. All six patients were diagnosed with ML by pathology following surgery. The accuracy of initial diagnosis was zero (0/6). The diagnostic accuracy of ultrasound for mesenteric cyst was 66.7% (4/6). The diagnostic accuracy of CT/MRI for mesenteric cyst was 83.3% (5/6).

All of the patients had good postoperative recovery, the abdominal mass disappeared, appetite, defecation and urine output became normal. All patients were followed up for 3 mo by abdominal CT, and no recurrence or adhesive intestinal obstruction occurred. Five cases (83.3%) were followed for up to one year, and no recurrences were observed.

DISCUSSION

Lymphangiomas are uncommon congenital malformations of the lymphatic system. They can occur at any site in the body, but are most commonly found in the neck and head area as well as the abdominal wall, but rarely in the mesentery^[4]. It is reported that the incidence of ML is approximately 5%, and the male-female ratio is about 1.5–3:1^[5,6]. In addition, ML has been described in less than 1% of all lymphangiomas^[1,7,8].

The exact etiology of ML is unknown. It is likely to be a developmental anomaly of the lymphatic system, as 65% of MLs are present at birth and 90% of all patients are diagnosed before the age of 2^[7]. However, they can also develop due to an inflammatory process, lymphatic obstruction, surgery, radiation and abdominal trauma^[9,10]. ML is rarely seen in adults. Therefore, it is not clear what the incidence of ML is in adults. Only a few case reports of ML in adults are available in the published literature^[11]. In adults, lymphangiomas primarily occur on the body surface or in the abdominal cavity, and the incidence of ML is 1/100000^[2], mostly in the small intestine, followed by the omentum majus, mesentery and retroperitoneum. ML is a benign lesion, with a relatively asymptomatic onset, slow growth and a long disease course.

Most MLs are initially asymptomatic, and are therefore usually discovered incidentally. However, when the tumor is large, it can compress the surrounding viscera or block the intestine, producing corresponding symptoms. The clinical symptoms of ML vary depending on location. ML can manifest as abdominal pain, abdominal distension, diarrhea, hematochezia, constipation, hypoproteinemia, intussusception, and decreased physical quality^[12]. Due to the lack of specific clinical signs and symptoms, ML is easily missed and misdiagnosed. Abdominal ultrasonography or CT can be used to identify an early abdominal cystic mass, especially in patients with recurrent abdominal pain, abdominal distension, and stubborn constipation. Emer-

Table 1 Information and clinical manifestations in the six patients

Cases	1	2	3	4	5	6
Gender	M	M	M	F	F	F
Age, yr	45	59	62	71	42	52
Abdominal pain	+	+	+	+	-	+
Nausea	-	-	+	-	-	+
Vomiting	-	+	-	-	-	-
Diarrhea	-	-	-	+	-	-
GI bleeding	-	-	-	+	-	-
Fever	-	-	+	+	-	+
Concurrent infection	Cholecystitis	UK	Cholangitis	Urinary tract	UK	GI tract
Abdominal distension	-	-	+	+	+	+
Intestinal obstruction	-	+	-	-	-	-
Medical history	-	-	Cholangiolithiasis, ERCP	-	Diabetes	-
Trauma	-	-	-	-	-	-

UK: Unknown; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal tract.

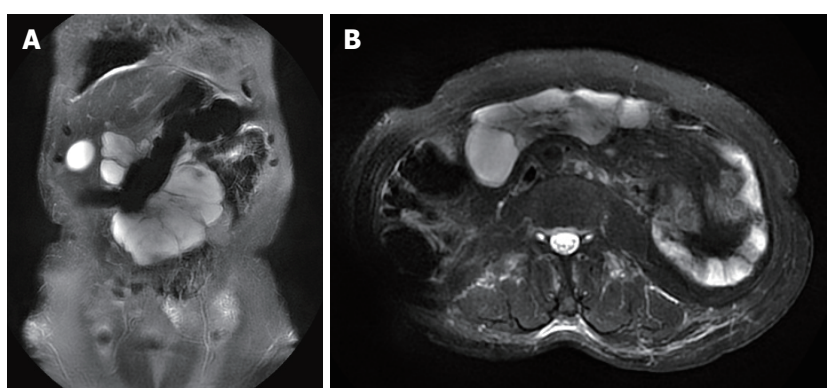


Figure 2 Abdominal magnetic resonance imaging shows cystic long T1 and long T2 signal masses in the anterior wall of the middle abdomen, 110 mm × 40 mm in size. No abnormal enhancement was observed (Case 4). A: Coronal position; B: Axial position.

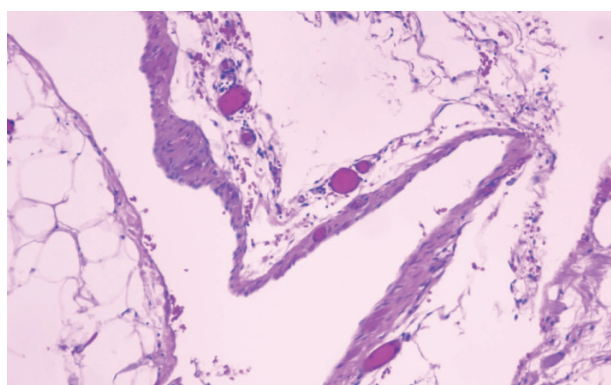


Figure 3 Histopathology shows that the cyst wall was composed of fibrous adipose tissue and a few lymphatic endothelial proliferations. Case 4, hematoxylin and eosin, 100 ×.

gency doctors should be vigilant, and early abdominal ultrasound or CT examination should be carried out to detect this disease as soon as possible.

Ultrasonography is of high diagnostic value in detecting the location, size, division of the cyst, cyst fluid, cyst wall and its relation to surrounding tissues^[13]. In small cysts, abdominal CT is more sensitive and helps to differentiate from other related abdominal

pelvic cysts, such as greater omentum cysts, intestinal repetitive malformations, ovarian cysts, common bile duct cysts, and kidney cysts. CT is useful for further understanding the relationship between the cyst and the surrounding tissues and organs, especially large blood vessels and the bowel, which ultimately aids treatment decisions and surgical approaches in these patients^[14]. MRI is more sensitive in patients with intracavitary hemorrhage. In the case of intrathecal hemorrhage, the imaging may show solid cystic signs^[15,16].

Pathological examination is the gold standard for the diagnosis of ML, and it provides strong evidence for postoperative identification of other types of cysts. Microscopy shows dilated lymphatics, and the thin wall lining epithelial cells in the lymphatic cavity gap and a small amount of smooth muscle tissue can be seen. During infection, the infiltration of lymphocytes, plasma cells, eosinophils and other inflammatory cells are also visible. MLs are classified as simple, cavernous and cystic. The simple type of ML is primarily situated superficially in the skin and is composed of small thin-walled lymphatic vessels. The cavernous type has dilated lymphatic vessels and has connections with normal adjacent lymphatics. Cystic lymphangioma is composed of large macroscopic lymphatic spaces surrounded

by collagen and smooth muscle and does not have connections with adjacent normal lymphatics (CD34 and CD31 positive)^[17].

ML needs to be differentiated from peritoneal abscess, hematoma, malignant tumor center liquefaction necrosis, malignant tumor cystic adenoma and some solid masses derived from mesenchymal tissue such as sarcomas. Simple abdominal ultrasonography may be difficult to distinguish, and abdominal CT/MRI can provide more information. However, the diagnosis of ML primarily depends on pathological diagnosis. When necessary, ultrasound-guided diagnostic puncture can further differentiate between cyst, abscess and hematoma. Ultrasound-guided needle aspiration cytology can identify whether the mass is benign or malignant, providing a basis for differential diagnosis.

To treat ML, most doctors recommend radical surgical excision, as ML can grow very large and invade adjacent structures, develop complications and the risk of sarcoma transformation upon irradiation^[9]. After excision of a mass that involves the whole mesentery, internal herniation is likely to occur due to the presence of skeletonized vessels. A biological collagen implant can be used to repair the mesenteric defect after excision of a large ML, and monitoring for recurrence during follow-up is necessary^[18]. However, opinions differ about the course of treatment.

A previous study^[19] showed that for asymptomatic or mild lymphangioma patients, conservative treatment and close follow-up are recommended. In a case report, colorectal lymphangioma spontaneously disappeared. We suggest that if the ML is relatively large, it is possible to infiltrate the surrounding organs and cause tissue ischemic necrosis, causing potentially life-threatening complications, such as traumatic rupture, anemia secondary to intraabdominal or intra-cavitary bleeding, intestinal gangrene secondary to volvulus and intermittent intestinal obstruction^[2,16]. It is better to remove it as soon as possible.

In the present study, the ratio of men to women was 3:3, with no significant gender difference. The rate of accurate initial diagnosis was zero. This indicated that clinicians lack awareness of ML in adults, and the average age at diagnosis in these patients was 55.2 years. All of these patients had received routine physical examination in the past few years, but no abdominal cysts were found. Five of these six cases had no previous history of abdominal cysts, but all patients had acute onset, mainly presenting with acute abdominal pain, incomplete intestinal obstruction, and mucinous bloody diarrhea. The remaining patient was found to have abdominal cysts two years previously, which were untreated. Acute abdominal distension was not treated with anti-inflammatory therapy and was diagnosed and cured after surgery.

Following symptom onset, the abdominal cysts were not identified by abdominal color Doppler ultrasound or CT. However, the diagnosis of abdominal cysts was

confirmed during laparotomy. It is speculated that adult ML may be an acquired disease and that infection may be a risk factor. Of these six cases, two had biliary tract infection, one had urinary tract infection, one had digestive tract infection, and two patients had no obvious infection. The pathogenesis of ML may include the formation of secondary cysts caused by lymphatic obstruction due to infection. Moreover, we found that the detection rate of abdominal cysts by ultrasound was lower than that of abdominal CT (66.7% vs 88.3%). This may have been due to the following possibilities: (1) due to the rarity of ML in adults, ultrasound clinicians lacked awareness of ML, resulting in misdiagnosis; (2) misdiagnosed cystic lesions such as ascites or dilated bowel may be caused by intestinal obstruction; and (3) ML may be an acquired disease.

As clinicians are accustomed to prescribing abdominal ultrasound first and then CT, an abdominal cyst may not yet have formed when ultrasonography is performed. Pathological examination is the gold standard in the diagnosis of ML. An accurate and thorough surgical technique is an effective method of treating ML. No recurrence was found during the follow-up period of 3-12 mo in the six patients included in this study. However, timely surgery is essential. In a patient with mucinous diarrhea, infiltration of the transverse colon was found during surgery, leading to transverse colonic ischemic necrosis, and partial transverse colectomy was performed.

In summary, ML in adults is an extremely rare benign, potentially acquired disease distinct from ML in children, which is due to congenital lymphatic dysplasia. Infection may be involved in the pathogenesis of ML in adults. However, the exact etiology should be confirmed in a large sample study. In some cases, ML can be fatal, as it may cause tissue ischemic necrosis due to infiltration of surrounding viscera, compression of the intestine or peritoneal vessels, resulting in serious complications. Timely and effective radical surgery is necessary, which requires increased awareness of the disease in clinicians to avoid misdiagnosis and missed diagnosis.

EXPERIENCES AND LESSONS

Although ML occurs more frequently in children, it also occurs in adults, but the exact etiology in adults requires further study. Although ML is benign, it can also lead to serious and fatal consequences. Timely and effective radical surgery can cure this disease. Clinicians should raise awareness of ML in adults.

REFERENCES

- 1 **Suthiwartnarueput W**, Kiatipunsodsai S, Kwankua A, Chaumrattanakul U. Lymphangioma of the small bowel mesentery: a case report and review of the literature. *World J Gastroenterol* 2012; **18**: 6328-6332 [PMID: 23180956 DOI: 10.3748/wjg.v18.i43.6328]
- 2 **Losanoff JE**, Kjossev KT. Mesenteric cystic lymphangioma: unusual cause of intra-abdominal catastrophe in an adult. *Int J*

- Clin Pract* 2005; **59**: 986-987 [PMID: 16033626 DOI: 10.1111/j.1368-5031.2005.00554.x]
- 3 **Chen CW**, Hsu SD, Lin CH, Cheng MF, Yu JC. Cystic lymphangioma of the jejunal mesentery in an adult: a case report. *World J Gastroenterol* 2005; **11**: 5084-5086 [PMID: 16124074 DOI: 10.3748/wjg.v11.i32.5084]
 - 4 **Okazaki T**, Iwatani S, Yanai T, Kobayashi H, Kato Y, Marusaka T, Lane GJ, Yamataka A. Treatment of lymphangioma in children: our experience of 128 cases. *J Pediatr Surg* 2007; **42**: 386-389 [PMID: 17270554 DOI: 10.1016/j.jpedsurg.2006.10.012]
 - 5 **Fernández Ibieta M**, Rojas Ticona J, Martínez Castaño I, Reyes Ríos P, Villamil V, Giron Vallejo O, Méndez Aguirre N, Sánchez Morote J, Aranda García MJ, Guirao Piñera MJ, Zambudio Carmona G, Ruiz Pruneda R, Ruiz Jiménez JI. [Mesenteric cysts in children]. *An Pediatr (Barc)* 2015; **82**: e48-e51 [PMID: 24635977 DOI: 10.1016/j.anpedi.2013.11.025]
 - 6 **Huis M**, Balijs M, Lez C, Szerda F, Stulhofer M. Mesenteric cysts. *Acta Med Croatica* 2002; **56**: 119-124 [PMID: 12630343]
 - 7 **Geraci G**, Sciumè C, Pisello F, Volsi FL, Facella T, Tinaglia D, Amone E, Modica G. Mesenteric cyst lymphangioma; a case report and literature review. *Ann Ital Chir* 2006; **77**: 521-527; discussion 528 [PMID: 17343238]
 - 8 **Rajiah P**, Sinha R, Cuevas C, Dubinsky TJ, Bush WH Jr, Kolokythas O. Imaging of uncommon retroperitoneal masses. *Radiographics* 2011; **31**: 949-976 [PMID: 21768233 DOI: 10.1148/rg.314095132]
 - 9 **Losanoff JE**, Richman BW, El-Sherif A, Rider KD, Jones JW. Mesenteric cystic lymphangioma. *J Am Coll Surg* 2003; **196**: 598-603 [PMID: 12691938 DOI: 10.1016/S1072-7515(02)01755-6]
 - 10 **Iwabuchi A**, Otaka M, Okuyama A, Jin M, Otani S, Itoh S, Sasahara H, Odashima M, Kotanagi H, Satoh M, Masuda H, Masamune O. Disseminated intra-abdominal cystic lymphangiomatosis with severe intestinal bleeding. A case report. *J Clin Gastroenterol* 1997; **25**: 383-386 [PMID: 9412929 DOI: 10.1097/00004836-199707000-00022]
 - 11 **Wani I**. Mesenteric lymphangioma in adult: a case series with a review of the literature. *Dig Dis Sci* 2009; **54**: 2758-2762 [PMID: 19142726 DOI: 10.1007/s10620-008-0674-3]
 - 12 **Kim TO**, Lee JH, Kim GH, Heo J, Kang DH, Song GA, Cho M. Adult intussusception caused by cystic lymphangioma of the colon: a rare case report. *World J Gastroenterol* 2006; **12**: 2130-2132 [PMID: 16610070 DOI: 10.3748/wjg.v12.i13.2130]
 - 13 **Zhu LX**, Guan BY, Yu XL, He XH, Fang Q. Ultrasonographic characteristics of abdominal cystic lymphangioma in Children. *Nanchang Daxue Xuebao (Yixueban)* 2014; **54**: 59-61
 - 14 **Mao XN**, Lu ZM, Liao W, Wen F, Guo QY. CT findings of intra-abdominal lymphangioma in children. *Zhongguo Linchuang Yixue Yingxiang Zazhi* 2013; **24**: 485-488
 - 15 **Pampal A**, Yagmurlu A. Successful laparoscopic removal of mesenteric and omental cysts in toddlers: 3 cases with a literature review. *J Pediatr Surg* 2012; **47**: e5-e8 [PMID: 22901942 DOI: 10.1016/j.jpedsurg.2012.03.080]
 - 16 **Kim SH**, Kim HY, Lee C, Min HS, Jung SE. Clinical features of mesenteric lymphatic malformation in children. *J Pediatr Surg* 2016; **51**: 582-587 [PMID: 27106580 DOI: 10.1016/j.jpedsurg.2015.11.021]
 - 17 **Enzinger FM**, Weiss SW. Tumors of the lymph vessels. In: Enzinger FM, Weiss SW, eds. *Soft Tissue Tumors*. St. Louis, MO: Mosby Publishers, 1994: 679-700
 - 18 **Kim SH**, Yoon KC, Lee W, Kim HY, Jung SE. Result of using a biologic collagen implant (Permacol) for mesenteric defect repair after excision of a huge mesenteric lymphangioma in a child. *Ann Surg Treat Res* 2015; **89**: 330-333 [PMID: 26665129 DOI: 10.4174/astr.2015.89.6.330]
 - 19 **Lee JM**, Chung WC, Lee KM, Paik CN, Kim YJ, Lee BI, Cho YS, Choi HJ. Spontaneous resolution of multiple lymphangiomatosis of the colon: a case report. *World J Gastroenterol* 2011; **17**: 1515-1518 [PMID: 21472113 DOI: 10.3748/wjg.v17.i11.1515]

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Considering FOLFOXIRI plus bevacizumab for metastatic colorectal cancer with left-sided tumors

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Abstract

A recent subgroup analysis of the TRIBE trial suggested that FOLFOXIRI plus bevacizumab may be a preferred option for the first-line treatment of only right-sided metastatic colorectal cancer (mCRC), regardless of RAS or *BRAF* status. Our subanalysis of a phase II trial of the FOLFOXIRI triplet regimen plus bevacizumab in patients with mCRC who had RAS mutant tumors showed that tumor shrinkage was better and the duration of treatment was longer in patients with left-sided tumors than in those with right-sided tumors, leading to a higher rate of conversion to surgery in mCRC patients with left-sided tumors. The early and deep responses to the triplet-regimen in patients with left-sided tumors might facilitate conversion treatment resulting in favorable survival. Our data suggest that the FOLFOXIRI plus bevacizumab might be a promising treatment for left-sided mCRC involving RAS mutant tumors.

Key words: Tumor sidedness; FOLFOXIRI; Bevacizumab; Colorectal cancer; RAS mutation

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Core tip: FOLFOXIRI plus bevacizumab regimen might be a preferred option for the first-line treatment of only right-sided metastatic colorectal cancer (mCRC) regardless of RAS or *BRAF* status. However, subanalysis of a phase II trial of the triplet plus bevacizumab in patients with RAS mutant mCRC demonstrated that more patients with left-sided tumors achieved good tumor shrinkage and long duration of treatment than did patients with right-sided tumors, leading to higher rate of conversion to surgery in mCRC patients with left-sided tumors. Our data suggest that FOLFOXIRI plus bevacizumab may be a promising treatment for left-sided mCRC associated with RAS mutant tumors.

Sunakawa Y, Satake H, Ichikawa W. Considering FOLFOXIRI plus bevacizumab for metastatic colorectal cancer with left-sided tumors. *World J Gastrointest Oncol* 2018; 10(12): 528-531
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TO THE EDITOR

A randomized study, the TRIBE trial, has demonstrated that FOLFOXIRI plus bevacizumab is more beneficial than FOLFIRI plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (mCRC). In addition, a number of clinical studies, including the STEAM and CHARTA trials, have shown similar clinical benefits of treatment with FOLFOXIRI plus bevacizumab^[1-3]. Therefore, the triplet-regimen is considered one of the standard first-line treatments for mCRC in the National Comprehensive Cancer Network and European Society for Medical Oncology consensus guidelines^[4,5]. Recently, a subgroup analysis of the TRIBE trial was performed to investigate the effect of upfront tumor sidedness on therapeutic effectiveness and whether this potentially heterogeneous effect differed according to RAS and *BRAF* mutational status in mCRC. The results indicated that patients who harbored right-sided tumors achieved an evident survival benefit from the triplet-regimen as backbone chemotherapy regardless of RAS and *BRAF* status. Namely, FOLFOXIRI plus bevacizumab can be considered to be a preferred treatment option in a first-line setting for only right-sided mCRC^[6].

The location of the primary tumor has an impact on clinical behavior and has prognostic value in mCRC. A recent meta-analysis suggested that tumor sidedness is a predictive marker of the response to anti-epidermal growth factor receptor (EGFR) therapy in patients with RAS wild-type mCRC. Patients with left-sided tumors were shown to derive a greater benefit from chemotherapy plus an anti-EGFR antibody than from chemotherapy plus bevacizumab, whereas right-sided tumors were associated with trends toward

detrimental effects of anti-EGFR therapy^[7]. Therefore, anti-EGFR therapy with cetuximab or panitumumab is recommended for only RAS wild-type and left-sided tumors. A subanalysis of the TRIBE trial according to tumor sidedness showed no higher survival benefit from a triplet-regimen as compared with a doublet-regimen in patients with RAS wild-type mCRC who had left-sided tumors, suggesting that a doublet-regimen plus an anti-EGFR antibody is the preferred treatment for patients with left-sided RAS wild-type tumors. On the other hand, in patients with RAS mutant tumors, which do no benefit from anti-EGFR antibodies, the question remains whether intensification of the triplet regimen plus bevacizumab should be limited to patients who have mCRC with right-sided tumors.

In the subgroup analysis of the TRIBE trial, the objective response rate (ORR) of the triplet-arm was 65.0% for left-side tumors and 62.5% for right-side tumors in patients with RAS mutant tumors. The median progression-free survival (PFS) was 12.5 mo for patients with left-side tumors and 11.0 mo for those with right-side tumors. The efficacy of intensive chemotherapy with bevacizumab did not appear to differ significantly between tumor sidedness in patients with RAS mutant mCRC. Moreover, in patients who had left-sided tumors with RAS mutation, the ORR and PFS were slightly but not significantly higher in the triplet-arm than in the doublet-arm.

We have conducted a phase II trial of first-line FOLFOXIRI plus bevacizumab for mCRC with RAS mutant tumors. The ORR was the primary endpoint, and the secondary endpoints included PFS, early tumor shrinkage (ETS), and depth of response (DpR). The ORR and ETS rates in enrolled patients were 75.8% and 73.8%, respectively. According to primary tumor side, the ORR and ETS were both much better in patients with left-sided tumors than in patients with right-sided tumors (82.2% vs 58.8%, 77.3% vs 64.7%, respectively)^[8]. Here, we performed an exploratory analysis of DpR using spider-plots in each tumor side. Interestingly, the spider-plots demonstrated that tumor shrinkage was better and the duration of treatment was longer in the patients with left-sided tumors than in those with right-sided tumors (Figure 1). One (6%) of 17 patients could undergo conversion surgery in the right-sided group, while 11 (28%) of 40 patients could receive conversion surgery in the left-sided group. The early and deep responses to the triplet regimen in the left-sided group may facilitate conversion treatment associated with favorable survival.

We showed an analysis of the evaluated radiographic responses to FOLFOXIRI plus bevacizumab for mCRC according to each tumor side using spider plots. Cremolini *et al.*^[9] has reported the association of ETS and DpR with clinical outcomes of triplet plus bevacizumab treatment using the TRIBE data; however, the results according to tumor sidedness have not been reported yet. Our phase II trial was a prospective

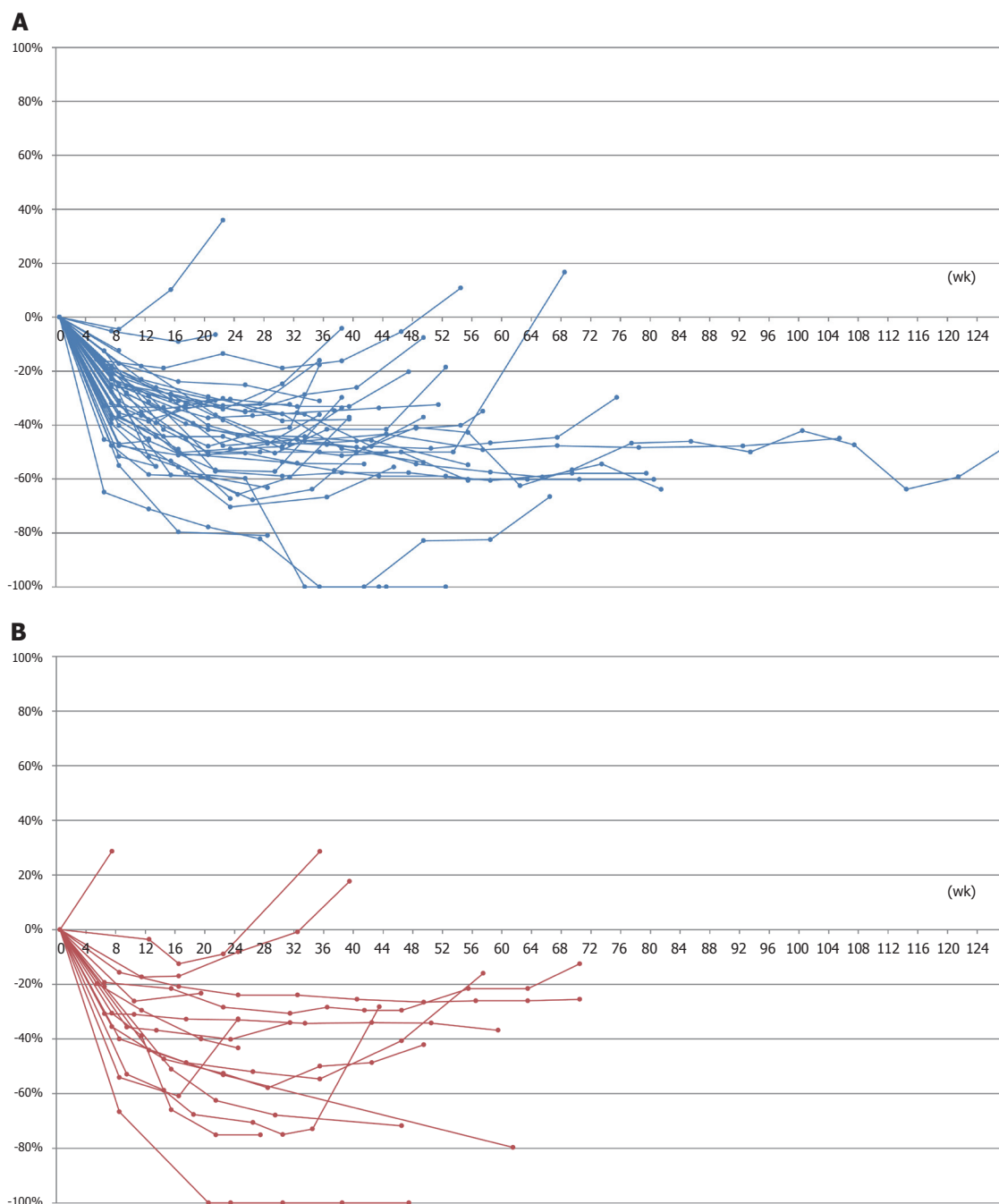


Figure 1 Spider plots of the response to 1st-line FOLFOXIRI plus bevacizumab in patients with RAS mutation (JACCRO CC-11). A: Spider plots of tumor burden changes in patients with left-sided tumors ($n = 44$); B: Spider plots of tumor burden changes in patients with right-sided tumors ($n = 17$).

study designed to evaluate the efficacy of FOLFOXIRI plus bevacizumab in molecular-selected patients with RAS mutation. Moreover, tumor response as a primary endpoint was evaluated prospectively by an external review board. Our findings for RAS mutant mCRC would be more reliable than the findings of the sub-analysis of the TRIBE trial. FOLFOXIRI plus bevacizumab was not beneficial in left-sided tumors in the TRIBE trial, while FOLFOXIRI plus bevacizumab appeared to be better compared to FOLFOX plus bevacizumab in left-sided tumors in other 2 trials^[2,3]. Types of backbone chemotherapy may affect the results of sub-analyses

by tumor sidedness. Although a recent study reported that FOLFOXIRI plus bevacizumab may be regarded as a preferred option for only right-sided mCRC^[6], our data suggest that the triplet-regimen may be a promising treatment for left-sided mCRC with RAS mutant tumors.

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REFERENCES

- 1 **Loupakis F**, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; **371**: 1609-1618 [PMID: 25337750 DOI: 10.1056/NEJMoa1403108]
- 2 **Hurwitz H**, Tan BR, Reeves JA, Xiong HQ, Somer BG, Lenz H-J, Hochster HS, Scappaticci F, Palma JF, Mancao C, Lee JJ, Nicholas A, Sommer N, Bendell JC. Updated efficacy, safety, and biomarker analyses of STEAM, a randomized, open-label, phase II trial of sequential (s) and concurrent (c) FOLFOXIRI-bevacizumab (BV) vs FOLFOX-BV for first-line (1L) treatment (tx) of patients with metastatic colorectal cancer (mCRC). *J Clin Oncol* 2017; **35**: 657 [DOI: 10.1200/JCO.2017.35.4_suppl.657]
- 3 **Schmoll HJ**, Meinert FM, Cygon F, Garlipp B, Junghans C, Leithäuser M, Vogel A, Schaefer M, Kaiser U, Hoeffkes H-G, Florschütz A, Rüssel J, Kanzler S, Edelmann T, Forstbauer H, Goehler T, Hannig C, Hildebrandt B, Steighardt J, Stein A. "CHARTA": FOLFOX/Bevacizumab vs FOLFOXIRI/Bevacizumab in advanced colorectal cancer—Final results, prognostic and potentially predictive factors from the randomized Phase II trial of the AIO. *J Clin Oncol* 2017; **35**: 3533 [DOI: 10.1200/JCO.2017.35.15_suppl.3533]
- 4 **Van Cutsem E**, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Rieke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanen A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386-1422 [PMID: 27380959 DOI: 10.1093/annonc/mdw235]
- 5 **Yoshino T**, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, Kim TW, Ismail F, Tan IB, Yeh KH, Grothey A, Zhang S, Ahn JB, Mastura MY, Chong D, Chen LT, Kopetz S, Eguchi-Nakajima T, Ebi H, Ohtsu A, Cervantes A, Muro K, Tabernero J, Minami H, Ciardiello F, Douillard JY. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. *Ann Oncol* 2018; **29**: 44-70 [PMID: 29155929 DOI: 10.1093/annonc/mdx738]
- 6 **Cremolini C**, Antoniotti C, Lonardi S, Bergamo F, Cortesi E, Tomasello G, Moretto R, Ronzoni M, Racca P, Loupakis F, Zaniboni A, Tonini G, Buonadonna A, Marmorino F, Allegrini G, Granetto C, Masi G, Zagonel V, Sensi E, Fontanini G, Boni L, Falcone A. Primary Tumor Sidedness and Benefit from FOLFOXIRI plus Bevacizumab as Initial Therapy for Metastatic Colorectal Cancer. *Ann Oncol* 2018 [PMID: 29897402 DOI: 10.1093/annonc/mdy140]
- 7 **Arnold D**, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, Heinemann V, Van Cutsem E, Pignon JP, Tabernero J, Cervantes A, Ciardiello F. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; **28**: 1713-1729 [PMID: 28407110 DOI: 10.1093/annonc/mdx175]
- 8 **Satake H**, Sunakawa Y, Miyamoto Y, Nakamura M, Nakayama H, Shiozawa M, Makiyama A, Kobayashi K, Kubota Y, Mori M, Kotaka M, Takagane A, Gotoh M, Takeuchi M, Fujii M, Ichikawa W, Sekikawa T. A phase II trial of 1st-line modified-FOLFOXIRI plus bevacizumab treatment for metastatic colorectal cancer harboring RAS mutation: JACCRO CC-11. *Oncotarget* 2018; **9**: 18811-18820 [PMID: 29721163 DOI: 10.18632/oncotarget.24702]
- 9 **Cremolini C**, Loupakis F, Antoniotti C, Lonardi S, Masi G, Salvatore L, Cortesi E, Tomasello G, Spadi R, Zaniboni A, Tonini G, Barone C, Vitello S, Longarini R, Bonetti A, D'Amico M, Di Donato S, Granetto C, Boni L, Falcone A. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol* 2015; **26**: 1188-1194 [PMID: 25712456 DOI: 10.1093/annonc/mdv112]

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