ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2017 December 15; 9(12): 457-501

Published by Baishideng Publishing Group Inc

WJGO World Journal of Gastrointestinal Oncology

A peer-reviewed, online, open-access journal of gastrointestinal oncology

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2016-2019

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World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 9 Number 12 December 15, 2017

World Journal of Gastrointestinal Oncology
Volume 9 Number 12 December 15, 2017

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
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World Journal of Gastrointestinal Oncology
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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
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E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
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7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
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Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
December 15, 2017

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

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2017 December 15; 9(12): 457-465

DOI: 10.4251/wjgo.v9.i12.457

ISSN 1948-5204 (online)

MINIREVIEWS

Neoadjuvant therapy for resectable pancreatic cancer

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Author contributions: Rahman SH participated in the concept, design and search of the scientific literature, extracted the data and wrote the manuscript including the tables; Urquhart R participated in the concept and design and participated in revising the manuscript; Molinari M formulated the research question, designed the literature search, supervised and co-authored the manuscript with Rahman SH.

Conflict-of-interest statement: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Manuscript source: Unsolicited manuscript

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Received: June 25, 2017
Peer-review started: June 27, 2017
First decision: August 7, 2017
Revised: August 24, 2017
Accepted: September 15, 2017
Article in press: September 15, 2017
Published online: December 15, 2017

Abstract

The use of neoadjuvant therapies has played a major role for borderline resectable and locally advanced pancreatic cancers (PCs). For this group of patients, preoperative chemotherapy or chemoradiation has increased the likelihood of surgery with negative resection margins and overall survival. On the other hand, for patients with resectable PC, the main rationale for neoadjuvant therapy is that the overall survival with current strategies is unsatisfactory. There is a consensus that we need new treatments to improve the overall survival and quality of life of patients with PC. However, without strong scientific evidence supporting the theoretical advantages of neoadjuvant therapies, these potential benefits might turn out not to be worth the risk of tumors progression while waiting for surgery. The focus of this paper is to provide the readers an overview of the most recent evidence on this subject.

Key words: Pancreatic adenocarcinoma; Neoadjuvant chemotherapy; Neoadjuvant chemoradiation therapy; Meta-analysis; Decision analysis; Borderline resectable; Locally advanced; Randomized controlled trial; Phase Ⅰ trial; Phase Ⅱ trial; Phase Ⅲ trial

Core tip: The use of neoadjuvant therapy for patients with resectable pancreatic cancer (PC) has been used by an increasing number of cancer centers around

the world. The main rationale of using neoadjuvant therapies in resectable PC is the hope that patients' likelihood of long-term overall survival will benefit from the chemo or chemoradiation therapy administered when their overall conditions allow them to tolerate the treatment. At this time, there is no phase Ⅲ trial to support the use of neoadjuvant therapies in resectable PC. Without strong scientific evidence supporting the theoretical advantages of neoadjuvant therapies, these potential benefits might turn out not to be worth the risk of tumors progression while waiting for surgery.

Rahman SH, Urquhart R, Molinari M. Neoadjuvant therapy for resectable pancreatic cancer. *World J Gastrointest Oncol* 2017; 9(12): 457-465 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/457.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.457

INTRODUCTION

The most common form of pancreatic cancers (PCs) originates from the ductal cells of the exocrine gland[1,2]. In the United States, it represents the fourth leading cause of cancer-related deaths with 44000 new cases per year[2,3]. The prognosis of patients with PC remains poor with only 5%-10% of patients alive after five years[4]. Their outcome is significantly improved if they undergo surgery; however, even in this case, 5-year survival is only 25%-40%[1,4]. PC is a difficult tumor to cure as it behaves as a systemic disease even in its early stages. Although surgery remains the only potential cure, it is still inadequate for most of the patients who will develop recurrent disease within five years. The use of multimodality therapy (surgery, chemotherapy and radiation therapy) provides the best chance for long-term survival[5], but the ideal sequence and duration of these treatments remain unknown due to the lack of scientific evidence.

Despite these limitations, there is a consensus that, because of the poor outcomes observed with old treatment modalities, new strategies are necessary[6]. Among them, the use of neoadjuvant chemotherapy has gained traction and, in recent years, an increasing number of oncologists and surgeons are recommending it[7,8].

For borderline resectable and locally advanced PC, there is evidence that neoadjuvant therapy increases the probability of negative resection margins and the number of patients who can undergo surgery[8,9]. On the other hand, for resectable PC, neoadjuvant chemotherapy or chemoradiation remains debatable because of the conflicting data on its effectiveness, and because there is no phase Ⅲ trial to support their use[10-12]. The focus of this publication is to provide an overview of the most recent evidence on this topic, appraise the potential benefits and disadvantages of neoadjuvant *vs* surgery first approach, and finally, to review the ongoing phase Ⅲ trials that might address some of the questions that are still unanswered.

RESECTABILITY

Surgery remains the only potential cure for patients with PC. Determining if the disease is resectable or not at the time of diagnosis is crucial, but often subjective to the interpretation of preoperative imaging tests. Resectability is usually determined using a combination of imaging tests and laparoscopic assessment of the peritoneal cavity to rule out small hepatic or peritoneal metastases that might be missed even with high-quality contrast enhanced computerized tomography (CT scans) or magnetic resonance imaging (MRI) studies[2,13]. There are several definitions of tumor resectability that are summarized in Table 1[13-16]. All criteria currently used to identify patients with resectable disease are based on the degree of contact between the tumor and blood vessels adjacent to the pancreas in the absence of distant disease.

TREATMENT STRATEGIES

Until recently, the most accepted treatment paradigm for resectable PC was surgery followed by postoperative systemic chemotherapy or chemoradiation. In recent years, the use of systemic pre-operative chemotherapy alone or in combination with radiation therapy has been offered to an increasing number of patients with the main intent of reducing the size of the tumor, increase the likelihood of negative resection margins, and test the effects of cytotoxic medications *in vivo*[9]. Most patients who are treated with neoadjuvant chemotherapy or chemoradiation receive oral or intravenous medications for the duration of three to six months before undergoing surgery[17].

ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT THERAPY

Neoadjuvant therapy has several theoretical benefits but also drawbacks (Table 2). It is usually well tolerated, does not increase the perioperative morbidity, reduces the interval between diagnosis and the initiation of systemic treatment[17] and has the potential benefit of facilitating radical resections by lessening the size of the tumors before surgery. Despite these advantages, postponing surgery for neoadjuvant treatment might give enough time for the tumor to progress and become unresectable[17,18].

RECENT STUDIES

Table 3 summarizes details of the latest phase Ⅰ and Ⅱ trials reporting the outcomes of patients treated with neoadjuvant chemotherapy or chemoradiation for radiologically resectable PC. In all these studies, tumor

Table 1 Operational definitions of resectability of pancreatic cancer

Classification of resectability of pancreatic cancer	Definition by AHPBA/SSO/SSAT	Definition by MD Anderson Cancer Centre
Resectable	The tumor does not abut or encase any of the following vascular structures: the superior mesenteric vein or portal vein, superior mesenteric artery or common hepatic artery or celiac trunk	The tumor abuts or encases the superior mesenteric vein or portal vein without occluding the lumen. Absence of abutment or encasement of the superior mesenteric artery, common hepatic artery or celiac trunk
Borderline resectable	Abutment, encasement or occlusion of the superior mesenteric vein or portal vein. Abutment of the superior mesenteric artery. Abutment or short segment encasement of the common hepatic artery. Absence or abutment or encasement of the celiac trunk	Tumor causing a short-segment occlusion of the superior mesenteric vein or portal vein. Presence of abutment of the superior mesenteric artery, abutment or encasement of a short segment of the common hepatic artery, absence of abutment or encasement of the celiac trunk
Locally advanced	Tumor located in the proximity of the superior mesenteric vein or portal vein and the superior mesenteric vein or portal vein are unable to be resected and reconstructed. Tumor encasing the superior mesenteric artery, or long-segment encasement of the common hepatic artery, or abutment of the celiac trunk	Tumor located in the proximity of the superior mesenteric vein or portal vein that are not reconstructible. Presence of tumor encasement of the superior mesenteric artery, long-segment encasement of the common hepatic artery and encasement of the celiac trunk

AHPBA: Americas Hepato-Pancreato-Biliary Association; SSO: Society of Surgical Oncology; SSAT: Society for Surgery of the Alimentary Tract.

Table 2 Summary of the benefits and drawbacks of neo-adjuvant and adjuvant therapies for the treatment of patients with resectable pancreatic cancer

Neo-adjuvant therapy		Adjuvant therapy	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
In comparison to the strategy of adjuvant chemotherapy or chemoradiation therapy where up to 50% of patients who undergo surgery cannot complete their therapy due to complications or decline of their function, neoadjuvant strategy has been shown to be well tolerated by the majority of patients and therefore a greater proportion receive systemic therapy	Neoadjuvant therapy requires the placement of biliary stents to decompress the biliary obstruction prior to surgery of patients with jaundice. The placement of biliary stents before surgery increases the risk of infections in the perioperative period	One of the advantages of surgery first approach is that patients have a short period of time between when they are diagnosed and when they undergo resections of their tumor. This might have some benefits on patients' and their families' anxiety	About 20%-50% of patients will not be able to complete their postoperative therapy due to surgical complications or overall decline of their performance status
The use of neo-adjuvant therapy might sterilize the presence of small metastatic disease and reduce the size of the primary tumor. Downsizing the primary tumor might increase the likelihood of negative resection margins	Pre-operative therapy delays surgery and increases the risk of progression of the disease to the point of becoming unresectable	Since patients undergo surgery as soon as possible after their diagnosis, their risk of tumor progression is smaller than patients who wait a longer time before being operated on	One of the risk of undergoing surgery first for pancreatic cancer is that, some patients will undergo a major operation without the benefit of being cured as they might already have micrometastases
Treating patients before surgery, gives physicians some time to identify the tumors with poor prognosis that do not respond to the therapy. The identification of those patients who are likely to experience early metastases is very important because prevents them to undergo unnecessary surgery	The use of neoadjuvant therapies might increase the risk of perioperative morbidity and mortality due to the side effects of chemotherapy or chemoradiation	Patients who undergo surgery first do not routinely need the placement of biliary stents to release their jaundice before undergoing resection	Patients who undergo surgery first have a higher risk of positive resection margins
One of the advantages of using chemotherapy or chemoradiation therapy before surgery is that the blood supply to the pancreatic tumor is not compromised by the ligation of vessels. Therefore, chemotherapy agents can be delivered to the pancreatic tumor in higher concentrations			

response was evaluated differently as some investigators reported radiographic or clinical response before surgical exploration and others the histopathological response observed in the surgical specimen.

Gillen *et al*[17] published the first systematic meta-analysis on the effects of preoperative therapy in PC. The authors reviewed 515 studies, but only 111 trials were included with a total of 4394 patients. Among these studies, 15 were a phase I, 13 were a phase Ⅰ/Ⅱ, 28 were phase Ⅱ, 14 were cohort studies, and 41 were case series. Most the studies were prospective (No. 78). Chemotherapy was used as neoadjuvant therapy in

Table 3 Phase Ⅰ and Phase Ⅱ studies assessing the outcomes of patients with resectable pancreatic cancer treated with neoadjuvant therapies

Author (yr)/ journal/trial/ institution	No. of patients	Clinical stage/ duration of neoadjuvant therapy	Study design	Chemotherapy/ chemoradiation	Radiological response	Resection rate (%)	Negative resection margins (%)	Median overall survival (mo)
Hoffman (1998)/*J Clin Oncol*/ECOG	53	Resectable PC/2.8 mo	Phase Ⅱ, prospective study, November 1991 to September 1993	5-FU (1000 mg/m^2) per day + Mitomycin C (10 mg/m^2) + RT (50 Gy)	Partial response 8%; Stable disease 78%; Progression 16%	45	67	15 with surgery; without surgery 8; 10.9 for the entire cohort
PistersPister (2002)/*J Clin Oncol*/MD Anderson Cancer Centre	35	Resectable PC/1.8 mo	Phase Ⅱ, prospective study, timeframe not specified	Paclitaxel (60 mg/m^2) weekly, RT (30 Gy)	Partial response 4%; Stable disease 23%; Progression 20%	57	68	12 for the entire cohort; 19 with surgery; 10 without surgery
Joensuu (2004)/ *Int J Radiat Oncol Biol Phys*/Helsinki University	28	Resectable PC/3.5 mo	Phase Ⅰ-Ⅱ prospective study, November 1999 to December 2001	Gemcitabine (20 mg/m^2 *vs* 50 mg/m^2 *vs* 100 mg/m^2) twice a week + RT (50 GY)	NA	71	NA	13.6 for the entire cohort
Talamonti (2006)/ *Ann Surg Oncol*/ Northwestern University	20	Resectable PC/3.8 mo	Phase Ⅱ prospective, multi-institutional study, April 2002 to October 2003	Gemcitabine (1000 mg/m^2 weekly) + RT (36 Gy)	Partial response 15%; Stable disease 80%; Progression 5%	85	94	26 mo with surgery
Palmer (2007)/ *Ann Surg Oncol*/ University of Birmingham	24	Resectable PC/4 mo	Phase Ⅱ, prospective study, November 1999 to May 2003	Gemcitabine (1000 mg/m^2 weekly)	Partial Response 0%; Stable Disease 29%; Progression 4%; Unable to measure 4%	38	75	28.4 with surgery; 9.9 for the entire cohort
Palmer (2007)/ *Ann Surg Oncol*/ University of Birmingham	26	Resectable PC/4 mo	Phase Ⅱ, prospective study, November 1999 to May 2003	Gemcitabine (1000 mg/m^2 weekly) + Cisplatin (25 mg/m^2)	Partial Response 0%; Stable Disease 66%; Progression 21%; Unable to measure 4%	70	75	28.4 with surgery; 9.9 for the entire cohort
Le Scodan (2009)/ *Ann Oncol*/SFRO-FFCD	41	Resectable PC/3 mo	Phase Ⅱ, prospective study, January 1998 to March 2003	RT (50 Gy) + 5-FU (300 mg/m^2 daily) + Cisplatin (20 mg/m^2)	Partial response 10%; Stable Disease 65%; Progression 25%	63	81	11.7 with surgery; 9.4 for the entire cohort
Heinrich (2008)/*Ann Surg*/University Hospital of Zurich	28	Resectable PC/2 mo	Phase Ⅱ, prospective study, August 2001 to April 2007	Gemcitabine (1000 mg/m^2 twice weekly) + Cisplatin (50 mg/m^2)	Partial response 4%; Stable Disease 61%; Progression 13%	89	80	19.1 mo with surgery
Evans (2008)/*J Clin Oncol*/MD Anderson Cancer Centre	80	Resectable PC/3 mo	Phase Ⅱ, prospective study, July 1998 to October 2001	Gemcitabine (400 mg/m^2 weekly) + RT (30 Gy)	NA	85	82	34 mo with surgery; 22.7 mo for the entire cohort; 7 mo without surgery
Varadhachari (2008)/*J Clin Oncol*/MD Anderson Cancer Centre	90	Resectable PC/4.3 mo	Phase Ⅱ, prospective study, October 2002 to February 2006	Gemcitabine (750 mg/m^2 weekly) + Cisplatin (30 mg/m^2) every 2 wk + RT (30 Gy)	NA	58	96	31.0 mo with surgery; 17.4 mo for the entire cohort; 10.5 mo without surgery
Turrini (2009)/ *Oncology* /University Mediterranean	34	Resectable PC/2.1 mo	Phase Ⅱ, prospective study, May 2003 to July 2005	Docetazel (30 mg/m^2) weekly + RT (45 GY)	Partial response 9%; Stable disease 59%; Progression 32%	68	100	32 mo with surgery; 15.5 mo for entire cohort; 11 mo without surgery

Landry (2010)/*J Surg Oncol*/Emory University/Multicenter ECOG	21	Resectable PC/3 mo	Phase Ⅱ, prospective two-arm study, October 2013 to June 2015	Arm A: Gemcitabine (500 mg/m^2) weekly + RT (50 Gy) Arm B: Gemcitabine (175 mg/m^2) + Cisplatin (20 mg/m^2) + 5-FU (600 mg/m^2) + RT (50 Gy)	Arm A: Partial response 10%, Arm B: Partial response 18.2%	NA	NA	Arm A: Entire cohort 19.4 mo. Arm B: entire cohort 13.4 mo. 26.3 mo with surgery
Wo (2014)/*Radiother Oncol*/Multicentric	10	Resectable PC	Phase Ⅰ, prospective study	Capecitabine (1650 mg/m^2) over 10 d + RT (30 Gy)	NA	80	NA	NA
Shinoto (2013)/*Cancer*/Japan	26	Resetable PC	Phase Ⅰ, prospective study, April 2003 to December 2010	RT (30 Gy)	Partial response 3.8%; Stable disease 96.1%	81	90	18.6 mo for entire cohort; NA for patients who underwent surgery
O'Reilly (2014)/*Ann Surg*/Memorial Sloan Kettering Cancer Centre	38	Resectable PC	Phase Ⅱ, prospective study, July 2007 to December 2011	Gemcitabine (1000 mg/m^2) + Oxaliplatin (80 mg/m^2) every 2 wk	Partial response 10.5%; Stable disease 73.7%; Progression 7.9%; NA 7.9%	77	74	27.2 mo for the enire cohort; 22 mo progression free survival with surgery
Golcher (2015)/*Strahlenther Onkol*/Germany	66 (33 patients allocated to surgery + 33 patients allocated to chemoradiation followed by surgery)	Resectable PC	Phase Ⅱ, prospective randomized trial with two arms: Primary surgery *vs* preoperative chemoradiation followed by surgery. June 2003 to December 2009	Gemcitabine (300 mg/m^2) + Cisplatin (30 mg /m^2) + RT (50.4 Gy) (Preoperative for patients enrolled in Arm A)	NA	Preoperative chemoradiation: 69% Surgery first: 57%	Arm A (preoperative chemoradition): 48. Arm B (surgery first): 51	Arm A (preoperative chemoradiation): 18.9 mo. Arm B (surgery first): 25.0 mo
Van Buren (2013)/*Ann Surg Oncol*/Multicenter/United States	59	Resectable PC	Phase Ⅱ, prospective study, February 2007 to February 2011	Gemcitabine (1500 mg/m^2) ever 2 wk + Bevacizumab (10 mg/kg) + RT (30 Gy)	Partial response 8.4%; Stable disease 73.7%; Progression 7.9%	74	88	19.7 mo with surgery; 16.8 mo for the entire cohort

NA: Not available.

107 (96%) and radiotherapy in 104 (94%) with doses ranging from 24 to 63 Gy. In 13 trials, patients received intraoperative radiation therapy with doses between 10 and 30 Gy.

Six studies stated that the RECIST criteria were used to assess the preoperative radiological response to neoadjuvant therapy. The criteria used to evaluate tumor response were clearly stated in 44 studies, while in 61 studies the criteria used were not adequately reported. Pooled results of patients with resectable cancers at the time of diagnosis showed a complete response in 3.6%, partial response in 30.6%, progression in 20.9% and stable disease in 42.1%. Resections were performed in 73.6% (95%CI: 65.9%-80.6%) of patients. Perioperative morbidity occurred in 26.7% (95%CI: 20.7%-33.3%) and mortality in 3.9% (95%CI: 2.2%-6.0%) which were comparable to the outcomes of patients undergoing surgery first. Negative resection margins (R0) were observed in 82.1% of patients (95%CI: 73.1%-89.6%) with a median survival of 23.3 mo (range 12-54). Analysis of trials with monotherapy *vs* poly-chemotherapy revealed higher rates of complete or partial response when multiple chemotherapy agents were used. Higher response rates, however, did not translate into higher resection rates.

One year later, Assifi *et al*[19], published a second systematic review and meta-analysis of only phase Ⅱ neoadjuvant therapy trials. Out of 397 studies published from 1993 to 2010, 14 trials were included with a total of 536 patients. All studies were prospective, with 12 out of 14 (86%) being a single arm. Patients who had resectable tumors were 402 (75% of the sample). Gemcitabine was used in 8 trials, while the remaining 6 used 5-FU. Radiotherapy was given in 12 of 14 studies

(85%) with doses ranging between 30 and 50.4 Gy. In patients with resectable disease at diagnosis, complete radiological response was observed in 0.8% (95%CI: 0.0%-2.6%), partial response in 9.5% (95%CI: 2.9%-19.4%), stable disease in 73.9% (95%CI: 63.2%-83.3%) and progression in 17.0% (95%CI: 11.9%-22.7%). After neoadjuvant therapy, the resection rate was 65.8% (95%CI: 55.4%-75.6%) and negative resection margins were observed in 85.1% (95%CI: 76.8%-91.9%). Median survival was 23.0 mo (range 11.7-34.0). The most significant finding of these two meta-analyses was that even if safe, neoadjuvant therapy did not seem to add any substantial survival advantage[18].

Due to the heterogeneity of these studies, no conclusion can be drawn regarding the overall impact on survival and what are the most effective chemotherapy agents or the best combination of chemotherapy agents for resectable PC.

More recently, D'Angelo *et al*[20] completed another systematic review of randomized controlled trials on adjuvant and neoadjuvant therapies for resectable PC. Fifteen studies were included covering a period of 30 years (1985 to 2015). Their analysis suggested that despite all the best efforts, the question whether neoadjuvant therapy provides a better overall survival than adjuvant therapy remains unanswered.

DECISION ANALYSES

VanHouten *et al*[21] used a decision analysis model to assess what is the best treatment strategy for resectable PC. A survival advantage of 7 mo was found in patients who underwent neoadjuvant therapy in comparison to surgery first (27.2 mo *vs* 19.9 mo).

Another Markov decision analysis by de Geus *et al*[22] supported the use of neoadjuvant chemotherapy that provided longer overall survival (32 mo *vs* 27 mo) and quality-adjusted life expectancy (25 mo *vs* 21 mo) in comparison to surgery followed by adjuvant chemotherapy. Sensitivity analysis of the model showed that if the probability of surgical resection after neoadjuvant therapy was lower than 57%, upfront surgery was the best treatment option.

Another group led by Sharma *et al*[23] compared the efficacy of neoadjuvant-based chemotherapy with adjuvant treatment with an intention-to-treat analysis using a two-arms Markov model. In the neoadjuvant group, patients were treated with an average of 3 mo of neoadjuvant therapy followed by surgery. After surgery, patients who received preoperative chemotherapy did not receive any adjuvant treatment. On the other hand, patients who underwent surgery first, underwent chemotherapy after they recovered from their operations. In this model, the median overall survival was longer for the neoadjuvant cohort (22 mo) in comparison to the adjuvant group (20 mo), and the cumulative quality-adjusted survival for patients who underwent the neoadjuvant strategy was 19.8 mo compared to 18.4 mo for patients who had adjuvant therapy. One-way sensitivity analysis showed that surgery first provided higher quality-adjusted survival rates if more than 44% of patients treated with neoadjuvant therapy experienced progression of their disease and failed to undergo surgical resection.

All these models provided evidence that neoadjuvant therapies have better overall survival and quality of life in comparison to surgery first, although the differences were clinically quite small.

PERSISTENT CONTROVERSY

For borderline or locally advanced PC, the use of neoadjuvant therapy makes sense, and it is desirable for both patients and physicians. For patients' perspective, neoadjuvant treatments might decrease the tumor burden and give them the chance of becoming resectable. Similarly, for the surgeons' perspective, any reduction of the tumor size is welcome as it facilitates the technical aspect of the resection around critical vascular structures such as the superior mesenteric-portal vein junction or superior mesenteric artery.

However, this is not the case for resectable PC. Neoadjuvant therapy does not facilitate surgery, as the tumor is resectable at the time of diagnosis. Preoperative therapy might increase the rate of negative margins; however, this needs to be proven in randomized controlled trials, as the current evidence is not sufficient. Furthermore, for patients' perspective, there is a considerable risk of missing out the only opportunity of being cured with surgery as the tumor might progress to become unresectable while neoadjuvant therapies are delivered.

Because the current evidence is inadequate, there are no unequivocal criteria able to assist health-care providers to select the strategy with the best long-term survival for resectable PC. Physicians are left to decide whether to use neoadjuvant therapy and whether to use of one or multiple pre-operative chemotherapeutic agents or chemoradiation is worth the risk of toxicities and the possibility of disease progression. In theory, neoadjuvant treatments would be unanimously recommended for patients at high risk of positive resection margins, as their surgery would not be curative. The selection of these patients is not easy. To overcome this concerns, Bao *et al*[24] developed a predictive module to maximize the probability of identifying patients with true resectable tumors by using commonly available preoperative imaging modalities. With this model, the authors could classify patients with low-risk and high-risk for non-curative resections and concluded that until better evidence is available, patients who are unlikely to have R0 margins should be treated with neoadjuvant therapy.

FUTURE DIRECTIONS

D'Angelo *et al*[20] pointed out that the current literature is biased because the likelihood that radiologically

Table 4 List of ongoing phase Ⅱ and phase Ⅲ trials comparing neoadjuvant therapies *vs* adjuvant strategies for resectable pancreatic adenocarcinoma

Study	Design	No. of patients needed	Therapy	Primary outcome
NEOPAC (NCT01314027)	Phase Ⅲ Enrollment 2009-2014	350	Neoadjuvant gemcitabineoxaliplatin + adjuvant gemcitabine *vs* Adjuvant gemcitabine	Progression free survival
NEOPAC (NCT01521702)	Phase Ⅲ Initiated in 2011	310	Preoperative FOLFIRINOX, followed by adjuvant gemcitabine after surgery *vs* adjuvant gemcitabine after resection	Five-year progression free survival
NCT01900327	Phase Ⅲ	410	Neoadjuvant gemcitabine-based chemoradiation therapy followed by adjuvant gemcitabine *vs* adjuvant gemcitabine	Three-year overall survival
NCT01771146	Phase Ⅱ	100	Neoadjuvant FOLFIRINOX	Progression free survival
NEONAX (NCT02047513)	Randomized phase Ⅱ	166	Neoadjuvant gemcitabine + nab-paclitaxel followed by adjuvant gemcitabine + nab-paclitaxel *vs* adjuvant gemcitabine + nab-paclitaxel	Disease-free survival at 18 mo
NCT01150630	Randomized phase Ⅱ/Ⅲ	370	Adjuvant PEXG *vs* adjuvant gemcitabine *vs* neoadjuvant PEXG - followed by surgery and then adjuvant PEXG	One year event-free survival
ACOSOG-Z5041 (NCT00733746)	Phase Ⅱ	123	Neoadjuvant gemcitabine + erlotinib (completed; results pending)	Two-year overall survival
NCT00727441	Phase Ⅱ	87	Neoadjuvant GVAX +/- IV or oral cyclophosphamide followed by adjuvant gemcitabine + CRT	Safety, feasibility, and immune response
NCT02178709	Phase Ⅱ	48	Neoadjuvant FOLFIRINOX	Pathologic complete response
GEMCAD1003 (NCT01389440)	Phase Ⅱ	24	Neoadjuvant gemcitabine + erlotinib	R0 resection rate
NCT02562716	Phase Ⅱ Enrollment 2015-2019	112	Neoadjuvant and adjuvant mFOLFIRINOX *vs* neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine	Overall survival
NCT02243007	Randomized phase Ⅱ	112	Neoadjuvant FOLFIRINOX *vs* gemcitabine + nab-paclitaxel	18-mo overall survival
NCT02030860	Pilot	15	Neoadjuvant gemcitabine + nab-paclitaxel ± paricalcitol	Number of adverse events
NCT02305186	Randomized phase Ⅰb/Ⅱ	56	Neoadjuvant capecitabine-based CRT ± pembrolizumab (MK-3745)	Safety and immune response

CRT: Chemoradiation therapy; GVAX: Granulocyte-macrophage colony-stimulating factor gene-transfected tumor cell vaccine; PEXG: Cisplatin, epirubicin, capecitabine, gemcitabine; R0: Margin-negative surgical resection.

resectable PCs is indeed unresectable at the time of surgery is only about 40%[25]. Therefore, the only way to find out if there is any benefit from neoadjuvant therapy is to complete an intention to treat randomized controlled trial where one arm entails surgery followed by adjuvant therapy (current standard of care) and the second arm involves neoadjuvant therapy followed by surgery followed by adjuvant therapy (experimental group).

Recent chemotherapy regimens, such as FOLFI RINOX [folinic acid (leucovorin)/5-FU/Irinotecan/ Oxaliplatin], have already demonstrated promising results in a small group of patients with borderline resectable tumors[26,27]. Given these findings, several ongoing prospective studies are examining the role of FOLFIRINOX in a neoadjuvant setting for resectable disease (Table 4). Other studies include NEOPAC, NEONAX, NCT01660711, and NCT02172976. NEOPAC (Adjuvant *vs* Neoadjuvant Plus Adjuvant Chemotherapy in Resectable Pancreatic Cancer) will compare neo-adjuvant gemcitabine and oxaliplatin plus adjuvant gemcitabine *vs* adjuvant gemcitabine alone. NEONAX, (Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer) will assess the effects of neoadjuvant plus adjuvant Nab-Paclitaxel plus gemcitabine *vs* adjuvant only Nab-Paclitaxel plus gemcitabine. Other ongoing trials are a single-arm nonrandomized trial evaluating preoperative and postoperative FOLFIRINOX in patients with resectable disease (NCT01660711) and the multi-center German randomized trial investigating adjuvant gemcitabine compared with neoadjuvant and adjuvant FOLFIRINOX (NCT02172976).

CONCLUSION

Based on the current literature, there is still insufficient evidence to fully support the use of neoadjuvant therapy for all patients with radiologically resectable PC. Randomized controlled trials are urgently needed to address many of the questions that are still un-answered. Until then, clinicians need to weigh the pros and cons of the two treatment strategies and guide their patients. Ideally, patients should be educated on the advantages, and detrimental effects associated with each of the two possible therapies and their preferences should be elicited. Since each patient is unique, proposing neoadjuvant therapy with one-size-fits-all approach should be discouraged, and patients should become active participants and share with their

physicians the responsibility of selecting the treatment strategy that fits best with their goals and values.

ACKNOWLEDGMENTS

The authors would like to acknowledge: Stefanie Condon-Oldreive founder and director of Craig's Cause Pancreatic Cancer Society (www.craigscause.ca) for the research scholarship that supported Dr. Sheikh Hasibur Raman while working on this project. The authors thank Melissa Connell for her administrative support and technical and language editing that helped improving the quality of the manuscript and the quality of the audio file.

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P- Reviewer: Kim SM, Munoz M, Nakai Y, Sun XT **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2017 December 15; 9(12): 466-474

DOI: 10.4251/wjgo.v9.i12.466

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study

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Author contributions: Scheer R and Klaase JM designed the research; Scheer R and Zoidze S performed the research; Baidoshvili A supervised the histological scoring and took final decisions in case of discrepancy in scores between Scheer R and Zoidze S; Elferink MAG collected data from the population-based The Netherlands Cancer Registy and analyzed the data; Berkel AEM, Klaase JM and van Diest PJ supervised and interpreted the results; Scheer R and Zoidze S wrote the paper; all authors critically reviewed and accepted the final version of the manuscript.

Institutional review board statement: The requirement for informed consent and ethical approval was waived because of the retrospective study design. The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at j.klaase@mst.nl. Participants' informed consent was not obtained, but the presented data are anonymized and risk of identification is low.

Manuscript source: Invited manuscript

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Received: June 22, 2017
Peer-review started: July 14, 2017
First decision: August 7, 2017
Revised: September 17, 2017
Accepted: October 15, 2017
Article in press: October 15, 2017
Published online: December 15, 2017

Abstract

AIM

To evaluate the prognostic value of the tumor-stroma ratio (TSR) in rectal cancer.

METHODS

TSR was determined on hematoxylin and eosin stained histological sections of 154 patients treated for rectal adenocarcinoma without prior neoadjuvant treatment in the period 1996-2006 by two observers to assess

reproducibility. Patients were categorized into three categories: TSR-high [carcinoma percentage (CP) ⩾ 70%], TSR-intermediate (CP 40%, 50% and 60%) and TSR-low (CP ⩽ 30%). The relation between categorized TSR and survival was analyzed using Cox proportional hazards model.

RESULTS

Thirty-six (23.4%) patients were scored as TSR-low, 70 (45.4%) as TSR-intermediate and 48 (31.2%) as TSR-high. TSR had a good interobserver agreement (κ = 0.724, concordance 82.5%). Overall survival (OS) and disease free survival (DFS) were significantly better for patients with a high TSR (P = 0.01 and P = 0.02, respectively). A similar association existed for disease specific survival (P = 0.06). In multivariate analysis, patients without lymph node metastasis and an intermediate TSR had a higher risk of dying from rectal cancer (HR = 5.27, 95%CI: 1.54-18.10), compared to lymph node metastasis negative patients with a high TSR. This group also had a worse DFS (HR = 6.41, 95%CI: 1.84-22.28). An identical association was seen for OS. These relations were not seen in lymph node metastasis positive patients.

CONCLUSION

The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases.

Key words: Rectal cancer; Adenocarcinoma; Prognosis; Recurrence; Pathology; Tumor-stroma ratio

Core tip: The tumor-stroma ratio (TSR) can be determined accurately on routine histopathological sections by different observers. The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases. It could therefore be useful in decision making regarding adjuvant treatment in individual patients.

Scheer R, Baidoshvili A, Zoidze S, Elferink MAG, Berkel AEM, Klaase JM, van Diest PJ. Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study. *World J Gastrointest Oncol* 2017; 9(12): 466-474 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/466.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.466

INTRODUCTION

Colorectal cancer (CRC) is a common form of cancer in both men and women. More than 15000 new patients with a colorectal carcinoma were diagnosed in The Netherlands in 2016[1]. The common form to stage this type of cancer is the TNM staging system of the Union Internationale Contre le Cancer/American Joint Cancer Committee (UICC/AJCC)[2]. This system is also used in decision making about the appliance of (neo)adjuvant (chemo)radiotherapy. Although the TNM staging system is still regarded as the most important prognostic factor[3], it seems insufficiently able to predict the prognosis of the individual patient. This applies in particular to patients with stage II rectal cancer[4]. A part of the patients is overtreated and consequently exposed to a higher risk on therapy related complications, indicating a need for additional prognostic factors.

More recently, some studies have focused on the tumor-host interaction in relation to metastatic invasion. This interaction is enacted in an environment including cancer cells, the stromal tissue, consisting of different cell types like fibroblasts, myofibroblasts, endothelial cells and immune cells, and the extracellular matrix[5]. Mesker *et al*[6] showed that a high tumor-stroma ratio (TSR), the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor, is an indicator of a better outcome of disease in colon cancer. This is more outspoken for right sided tumors[6]. Similar results were seen in breast cancer, oral squamous cell carcinoma and prostate cancer[7-9]. A high TSR is possibly related to both a longer disease free and overall survival (OS) according to a study on a small number of rectal cancer patients[10]. In this respect, it is meaningful to explore the relevance of the TSR in a larger cohort of patients with rectal adenocarcinoma.

MATERIALS AND METHODS

Patients

Patients with rectal adenocarcinomas under the peritoneal reflection were identified out of all patients, who underwent surgery for left sided colorectal malignancies at our hospital between 1996 and 2006, by analyzing the histopathological reports. Only patients treated with curative intent were included, *i.e.*, patients without known distant metastases at surgery and radically resected tumors (M0, R0 resections). Patients who received neoadjuvant therapy, with malignancies in the past, other than radically excised basal cell carcinoma of the skin, and cases where no tumor was found in the resected specimen, despite preoperative adenocarcinoma in the biopsy of a suspected abnormality, were excluded. Other exclusion criteria were the presence of synchronous colorectal tumors, Lynch syndrome, familial adenomatous polyposis, and inflammatory bowel diseases. Patients who died within thirty days after surgery, with incomplete follow-up or unavailable histopathological material were also excluded (Figure 1).

Data concerning local recurrences, distant metastases, death, and cause of death were collected from the patient records and by consultation of general practitioners. Furthermore, dates of death were retrieved from the population-based Netherlands Cancer Registry. All data were handled in a coded anonymous

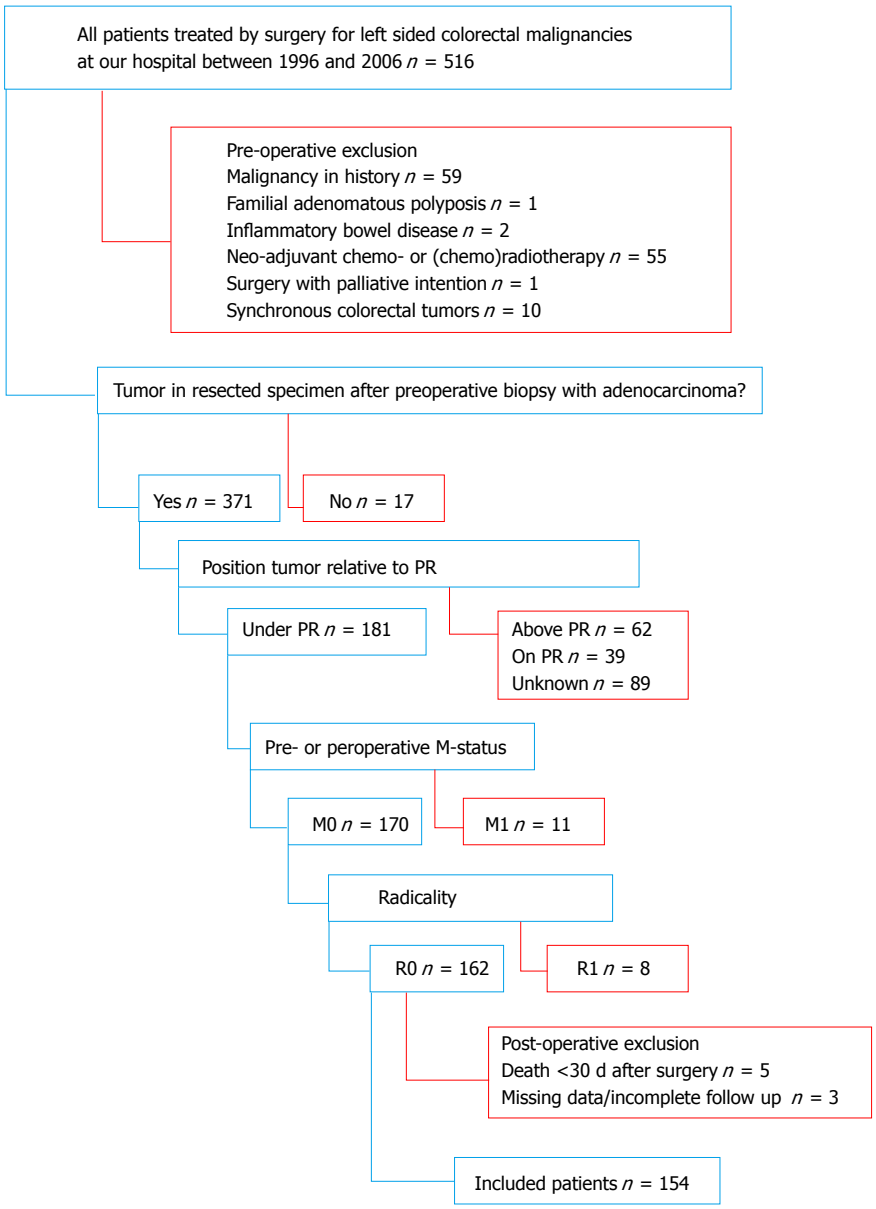

Figure 1 Flowchart of exclusion criteria applied to the dataset of all patients. PR: Peritoneal reflection.

fashion according to the Code for proper secondary use of human tissue from the Dutch Federation of Medical Scientific Societies and with respect to the Helsinki Declaration.

TSR assessment

TSR was determined on hematoxylin and eosin (H and E) stained histological sections. The section with the most invasive part of the tumor was identified to semiquantitatively assess the carcinoma percentage (CP) in 10% steps. The CP is a derivative of the TSR and is complementary to the percentage of stroma and other components, like mucus. For example, a CP of 20% corresponds to a stroma percentage of 80%, which coincides with a low TSR. The section was viewed with a 5 × objective (50 times magnification). The CPs were determined on all image fields of the entire section with tumor cells in all sides of it (North-East-South-West). Areas with the lowest CP were given more weight in rating the mean CP of the total assessed area, as is common practice in routine pathology in determining tumor differentiation. All sections were assessed separately by two observers (René Scheer and Shorena Zoidze) to allow assessment of reproducibility.

The absolute CPs were categorized for a good clinical reproducibility and clarity reasons into three categories, finally. TSR-low including the CP-values $\leqslant$ 30%, TSR-intermediate including the CP-values 40%, 50% and 60%, and TSR-high including the CP-values $\geqslant$ 70% (Figure 2). In the results only the categorized TSR are shown for clarity.

In case of a difference of 10% in determined CPs, which lead to a different TSR category, the lowest CP was used for the determination of the final TSR. The sections were reviewed by a third observer (AB) in case of > 10% difference in determined CPs leading

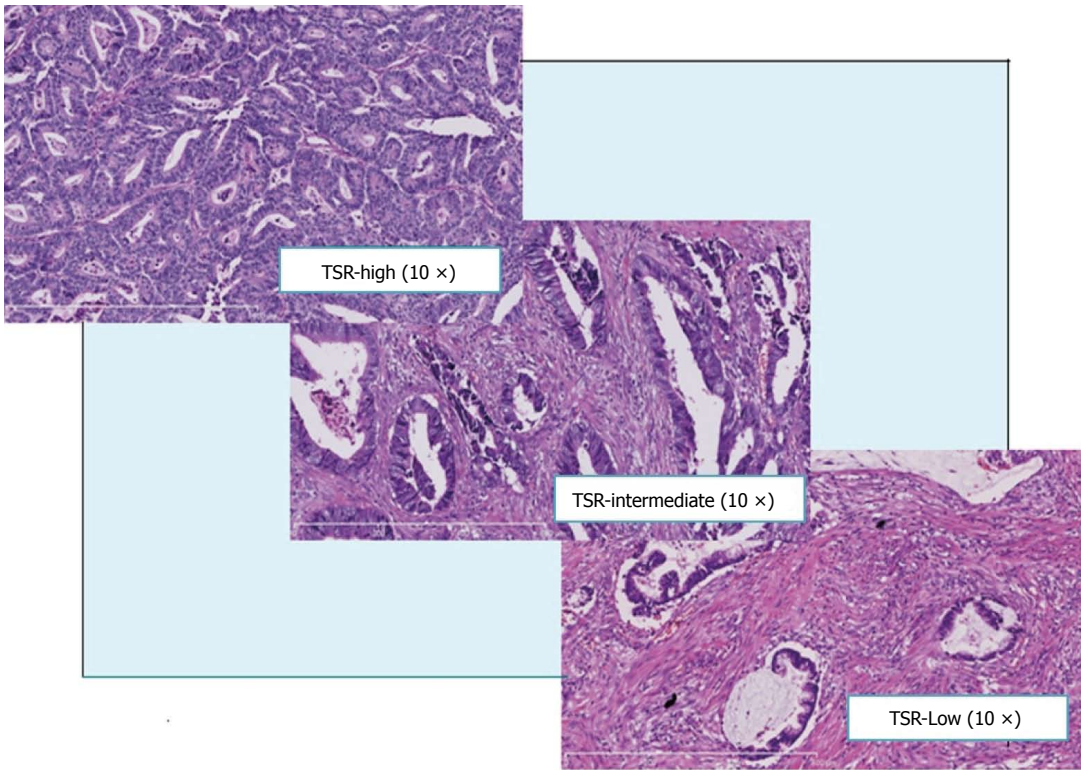

Figure 2 Examples of different categories of the tumor-stroma ratio. H and E stained 2 μm paraffin sections of primary rectal adenocarcinoma. TSR-high (carcinoma percentage ⩾ 70%), TSR-intermediate (carcinoma percentage 40%, 50% and 60%), and TSR-low (carcinoma percentage ⩽ 30%). TSR: Tumor-stroma ratio.

to different TSR categories. This third opinion was considered as decisive.

Statistical analysis

Data were analyzed using SPSS, version 19.0 (SPSS Inc., Chicago, IL, United States) and Stata, version 12.0 (StataCorp LP, College Station, Texas, United States). The statistical methods of this study were reviewed by Elferink MA, from the Netherlands Comprehensive Cancer Organization.

Patient characteristics were compared using Pearson χ^2 tests and one-way ANOVA. Interobserver reproducibility for the absolute and categorized CPs was analyzed by using Cohen's Kappa (κ) coefficient. A κ-value of 0.0 or less was considered to represent poor agreement, 0.01-0.20 slight agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 sufficient to good, and 0.81-1.00 near-perfect agreement[11]. Survival analyses based on categorized CPs included comparison of OS, disease free survival (DFS), and disease specific survival (DSS) by Kaplan-Meier survival analysis and log-rank statistics. Follow-up time in OS analyses was defined as the period between the date of primary surgery and the date of death from any cause, or the date of last follow-up. The DSS was restricted to death from rectal cancer only. Follow-up time in DFS analyses was defined as the time from the date of primary surgery until the date of a local recurrence or distant metastasis (irrespective of site). In DFS analyses, cases were censored in case of a second primary tumor (colorectal or other types) or death. The date of last follow-up was used as endpoint to calculate follow-up time, if none of these events occurred.

The relation between categorized TSR and survival (OS, DFS, and DSS) was analyzed, and adjusted for confounders (age, gender, grading, pathological T- and N-stage, and adjuvant treatment), using Cox proportional hazards model. Probability values < 0.05 (2-sided) were considered statistically significant.

RESULTS

Patient characteristics

A total of 154 patients met the inclusion criteria for this study. Three types of resections were used: Abdominoperineal resection in 67 (43.5%), low anterior resection in 63 (40.9%), and Hartmann resection, a modulated low anterior resection without construction of an anastomosis, in 24 patients (15.6%). The median follow-up of all patients was 5.3 years. Out of the analyzed samples, 36 (23.4%) were scored as TSR-low, 70 (45.4%) as TSR-intermediate, and 48 (31.2%) as TSR-high. There were more lymph node metastasis positive patients with a low TSR in comparison with patients with a higher TSR (P = 0.029), who consequently received adjuvant treatment. Radiotherapy was the most common form of adjuvant therapy. Detailed patient characteristics are shown by categorized TSR in Table 1.

Table 1 Patient characteristics by categorized tumor-stroma ratio

	TSR-low (*n* = 36)		TSR-intermediate (*n* = 70)		TSR-high (*n* = 48)		*P*-value[1]
	n	%	*n*	%	*n*	%	
Gender							NS
Male	24	66.7	44	62.9	32	66.7	
Female	12	33.3	26	37.1	16	33.3	
Age (yr)	M 68.0 (range 49.0-82.0)	SD 8.0	M 67.3 (range 40.0-87.0)	SD 10.3	M 65.7 (range 43.0-91.0)	SD 10.3	NS[2]
Treatment							NS
APR	19	52.6	31	44.3	17	35.4	
LAR	11	30.6	28	40.0	24	50.0	
Hartmann	6	16.7	11	15.7	7	14.6	
T-status							NS
pT1	1	2.8	1	1.4	4	8.3	
pT2	9	25.0	23	32.9	18	37.5	
pT3	24	66.7	43	61.4	25	52.1	
pT4	2	5.6	3	4.3	1	2.1	
N-status							0.029
pN0	16	44.4	44	62.9	34	70.8	
N1	15	41.7	13	18.6	11	22.9	
N2	5	13.9	13	18.6	3	6.3	
Stage							NS
I	7	19.4	21	30.0	17	35.4	
II	9	25.0	23	32.9	17	35.4	
III	20	55.6	26	37.1	14	29.2	
Grading							NS
Well	0	0	1	1.4	3	6.3	
Moderate	31	86.1	58	82.9	40	83.3	
Poor	5	13.9	11	15.7	5	10.4	
Adjuvant treatment	19	52.8	21	30.0	11	22.9	0.012[3]
Radiotherapy	17		18		9		
Chemoradiotherapy	1		3		2		
Chemotherapy	1		-		-		

[1]Pearson χ^2 test; [2]One-Way ANOVA; [3]*P*-value for adjuvant treatment in general. Significant *P*-values are shown bold. *n*: Number of patients; %: Percentage; Age defined as period from birth until date of primary surgery; LAR: Low anterior resection; APR: Abdominoperineal resection; pT: Pathological tumor status; pN: Pathological nodal status; Stage according to UICC/AJCC TNM staging system, 5th edition; TSR: Tumor-stroma ratio; UICC/AJCC: Union Internationale Contre le Cancer/American Joint Cancer Committee.

Interobserver reproducibility

A third opinion about a final TSR in case of interobserver disagreement about CPs with > 10% difference in determined CPs leading to different TSR categories was needed in 12 patients (7.8%). Mainly strong heterogeneity of the tumor complicated the determination of the CP for the total section. CPs were scored in a range between 10 and 90 percent. Lower CPs were found in mucinous adenocarcinomas.

Cohen's Kappa (κ) coefficient for interobserver agreement of the absolute CP showed a moderate agreement (κ = 0.522, concordance 59.1%). By categorizing the CP into three categories TSR (TSR-low, TSR-intermediate, and TSR-high) the κ-value improved and showed a good agreement (κ = 0.724, concordance 82.5%).

Prognostic impact on outcome

The 5-year survival rate for OS was 64.6% in the TSR-high population, *vs* 50.0% and 55.6% in the TSR-intermediate and TSR-low population, respectively. For the DFS, the 5-year survival rates for TSR-high, TSR-intermediate, and TSR-low were 77.2%, 51.8%, and 55.2%, respectively. The OS and DFS were significant different between the three TSR categories (*P* = 0.01 and *P* = 0.02, respectively). The 5-year survival rates for DSS were 81.6% for TSR-high, 60.3% for TSR-intermediate, and 63.9% for TSR-low. Although a higher DSS for the TSR-high population was thereby seen, the differences between the three TSR categories were just not significant (*P* = 0.06). The Kaplan-Meier survival curves are shown in Figure 3.

After adjusting for known prognostic factors (age, grading, and the use of adjuvant therapy), an intermediate TSR in lymph node metastasis negative patients showed a trend to a lower OS rate (HR = 2.04, 95%CI: 0.99-4.21) in comparison with a high TSR. There were no statistical differences between the TSR categories in OS among lymph node metastasis positive patients (Table 2). A statistically significant worse DFS was seen among the lymph node metastasis negative patients with an intermediate TSR (HR = 6.41, 95%CI: 1.84-22.28) compared to patients with a high TSR. Among lymph node metastasis positive patients, no statistically significant differences were seen between TSR categories for DFS (Table 3). Lymph node meta-

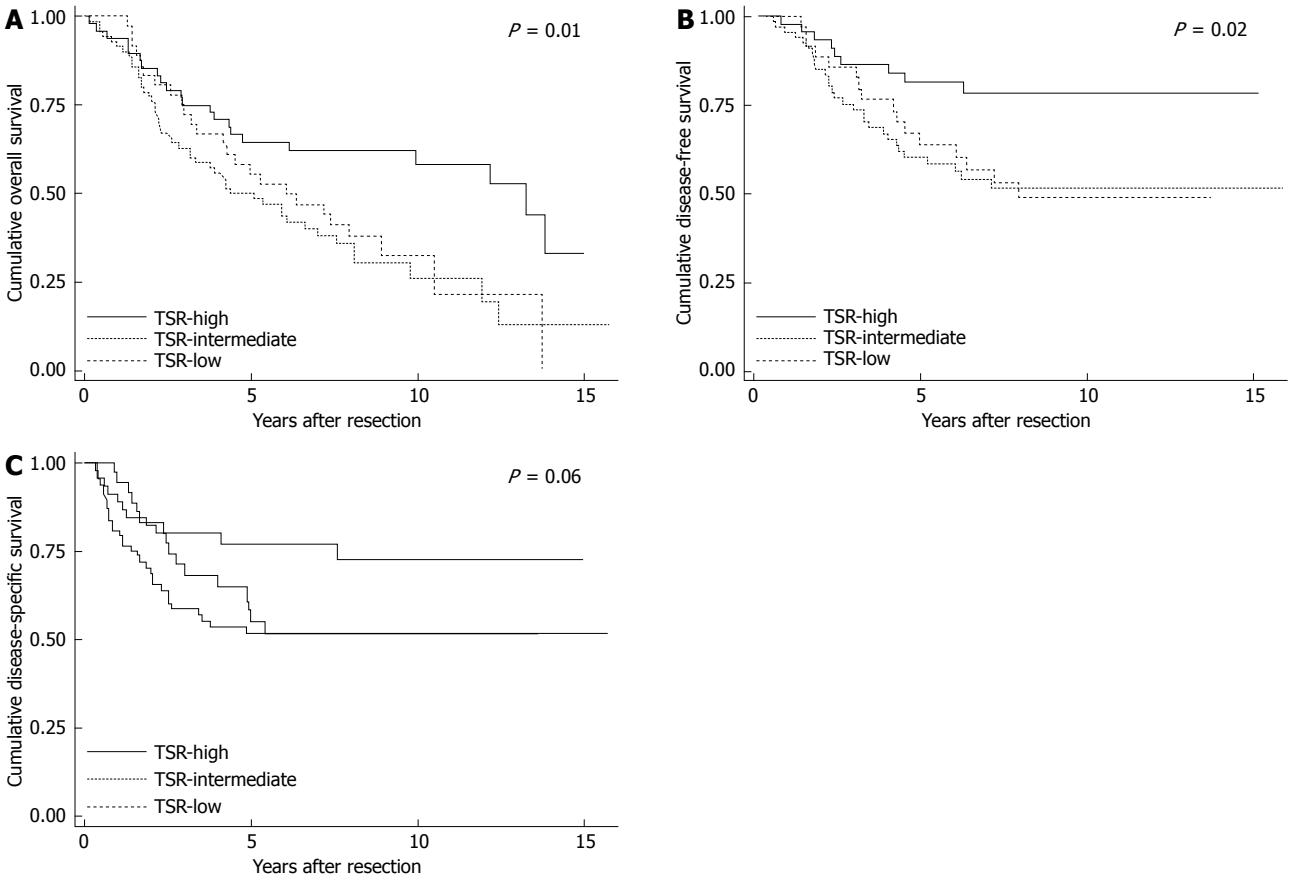

Figure 3 Kaplan-Meier survival curves of overall survival, disease free survival and disease specific survival by categorized tumor-stroma ratio. A: Overall survival; B: Disease free survival; C: Disease specific survival. *P*-values of Log-rank statistics. TSR-high (carcinoma percentage ⩾ 70%), TSR-intermediate (carcinoma percentage 40%, 50% and 60%), and TSR-low (carcinoma percentage ⩽ 30%). TSR: Tumor-stroma ratio.

stasis negative patients with an intermediate TSR had a higher risk of dying from rectal cancer (HR 5.27, 95%CI: 1.54-18.10) in comparison with patients with a high TSR. These differences were not seen in lymph node metastasis positive patients (Table 4).

DISCUSSION

This study, analyzing data of 154 patients with rectal adenocarcinoma diagnosed in the period 1996-2006, showed that the TSR is a prognostic factor for patients without lymph node metastasis. In such cases, a high TSR had a longer local recurrence and distant metastasis free period, and a lower risk of death from rectal adenocarcinoma. Besides, a high TSR was associated with a lower risk of death from any cause. The determination of the TSR may therefore contribute to stratify patients for prognosis. Determination of the TSR turned out to be feasible and reproducible among observers on routinely made sections of rectal cancers. The TSR therefore has the potential to contribute to decision making regarding the individual treatment policy in rectal cancer.

The relation between the prognosis and the TSR may be explained pathophysiologically. A dual effect of the tumor stroma in the tumor-host interaction has been described. The tumor stroma is able to exert inhibitory effects on the malignant cells at first. With ongoing tumor growth, the tumor can exploit its stroma, for example by changing its composition (*e.g.*, vasculature), to promote tumor growth and metastasis. A process called stromagenesis, which occurs parallel with tumor progression. Stromagenesis is characterized by bidirectional communication between the tumor and its stroma. The interactional pathways are multiple and complex[12-14]. Despite this complexity it is justifiable to conclude that the stromal tissue is not a passive component surrounding the tumor. A sufficient amount of stroma contributes to a more aggressive phenotype of tumor, as is shown in this study as well.

Indeed, the poor prognosis for lymph node negative patients with an intermediate TSR is remarkable. The survival rates for death from all causes, death from rectal cancer, and the occurrence of local recurrences and distant metastasis are the lowest for this group of patients. This may be explained by a favorable balance between the tumor and its stroma. In this way, the tumor may be able to exploit the surrounding tumor stroma very efficiently. The concept of a balance between pro- and antitumor factors had been hypothesized earlier. For example, there is a relation between the degree of the peritumoral inflammatory

Table 2 Cox multivariate analysis for overall survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1	Ref.	1	Ref.
> 70 yr	3.32[a]	1.75-6.28	2.26[a]	1.10-4.65
Grading				
Poor	1	Ref.	1	Ref.
Moderate	1.03	0.43-2.49	0.52	0.25-1.10
Well	0.36	0.04-2.99	0.56	0.06-5.31
Adjuvant treatment				
No	1	Ref.	1	Ref.
Yes	0.47	0.06-3.50	0.66	0.27-1.60
TSR				
TSR-high	1	Ref.	1	Ref.
TSR-intermediate	2.04	0.99-4.21	1.19	0.50-2.84
TSR-low	1.43	0.57-3.60	1.04	0.40-2.69

[a]$P < 0.05$. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; TSR: Tumor-stroma ratio.

Table 3 Cox multivariate analysis for disease free survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1.00	Ref.	1.00	Ref.
> 70 yr	0.36	0.13-1.01	0.89	0.36-2.22
pT-status				
T1	1.00	Ref.	1.00	Ref.
T2	0.11	0.01-1.21	0.66	0.10-4.44
T3	0.85	0.09-7.58	1.51	0.31-7.30
T4	1.61	0.07-39.27	[1]	
Grading				
Poor	1.00	Ref.	1.00	Ref.
Moderate	1.43	0.29-6.99	0.58	0.25-1.35
Well	[1]		[1]	
Adjuvant treatment				
No	1.00	Ref.	1.00	Ref.
Yes	0.2	0.01-2.57	1.04	0.32-3.41
TSR				
TSR-high	1.00	Ref.	1.00	Ref.
TSR-intermediate	6.41[a]	1.84-22.28	1.31	0.49-3.51
TSR-low	3.7	0.84-16.42	0.93	0.31-2.74

[a]$P < 0.05$; [1]Too small numbers to analyze. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; pT: Pathological tumor status; TSR: Tumor-stroma ratio.

reaction and its ability to destroy invading colorectal malignant cells[15]. Lymph node metastasis can be seen as an expression of a developed tumor that has exploited its environment successfully. When lymph node metastasis has occurred, the effect of the tumor micro-environment may be negligible. This statement may explain why we did not find differences in survival in lymph node metastasis positive patients survival based on the TSR.

The effect of a high TSR on survival demonstrated in this study is in line with other studies on the prognostic impact of the TSR in colorectal carcinomas (CRCs) and

Table 4 Cox multivariate analysis for disease specific survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1.00	Ref.	1.00	Ref.
> 70 yr	0.47	0.16-1.40	1.19	0.53-2.67
pT-status				
T1	1.00	Ref.	1.00	Ref.
T2	0.12	0.01-1.29	0.48	0.06-3.50
T3	0.69	0.08-6.25	1.29	0.27-6.07
T4	0.46	0.02-8.70	[1]	
Grading				
Poor	1.00	Ref.	1.00	Ref.
Moderate	1.03	0.20-5.30	0.46	0.21-1.04
Well	[1]		[1]	
Adjuvant treatment				
No	1.00	Ref.	1.00	Ref.
Yes	0.2	0.01-2.57	1.04	0.32-3.41
TSR				
TSR-high	1.00	Ref.	1.00	Ref.
TSR-intermediate	5.27[a]	1.54-18.1	1.60	0.54-4.70
TSR-low	3.48	0.78-15.55	1.22	0.41-3.66

[a]$P < 0.05$; [1]Too small numbers to analyze. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; pT: Pathological tumor status; TSR: Tumor-stroma ratio.

other malignancies[6-10,16]. The present study is however the first that has identified a subgroup of patients with rectal cancer, namely lymph node metastasis negative patients with an intermediate TSR, whereby the TSR is a strong prognostic factor.

The interobserver agreement for absolute scores was moderate. The correlation coefficient improved to good, when grouping as TSR-low, TSR-intermediate, and TSR-high. The categorization into these categories was performed with the aim of generating enhanced prognostic information based on the TSR, which had been executed earlier in a previous study on the TSR in oesophageal adenocarcinomas[17]. Other studies concerning the TSR used an arbitrary cut-off value of 50%. No differences in the given survival rates were found at this and other cut-off values in our population (Appendix 1). The rate of agreement of the present study is slightly lower compared to these studies[7,8], which may be attributed to the determination of absolute CPs before the categorization and the addition of an extra CP-category.

This study has some shortcomings to be noted. Neo-adjuvant radiotherapy for rectal malignancies was applied more frequently at our hospital relatively late in the study period and consequentially patients received adjuvant therapy frequently. Neoadjuvant treated patients were excluded, while in most cases a neoadjuvant (chemo)radiotherapy regimen is given nowadays. Though, it remains valuable to investigate tissue based prognostic factors in non-pretreated patients. There is a tendency to treat elderly, for whom there is an increasing incidence of rectal cancer, without neoadjuvant radiotherapy due to postoperative

wound complications in The Netherlands. According to the Dutch Surgical Colorectal Audit, no neoadjuvant therapy was used in 26% of cT2 patients aged > 75 years with rectal carcinoma in comparison with 14% in younger patients[18]. Furthermore, there is still a debate about adjuvant chemotherapy for rectal cancer. Future research about the balance between the oncological benefit, *i.e.*, relative risk reduction of 50% in local recurrences and the side effects, *i.e.*, relative risk increase of 50% in acute treatment-relate toxicity, and long-term anorectal and sexual dysfunction[19-21] of neoadjuvant radiotherapy will help to determine the position of pretreatment dependent tissue-based markers like the TSR in predicting an individual prognosis.

It would be of interest to analyze the TSR and its prognostic value in biopsy specimens of well described areas of a rectal tumor. Prognostic information could then be provided before the use of neoadjuvant therapy. The visual estimation of the TSR could be made more accurate by the use of tumor or stroma specific stainings. Besides, it would be desirable to develop a more objective instrument to determine the TSR than the visual estimation in this study. This could be provided by the use of tumor specific staining and the development of computer software in the growing field of digital pathology.

Determination of the TSR has the potential to identify patients without lymph node metastasis with a good and a poor clinical outcome and can thereby help in decision making on (neo)adjuvant treatment policy in individual cases. Determination of the TSR in routine sections is feasible and can be done with a good concordance by different observers.

COMMENTS

Background

Colorectal cancer is one of the most common form of cancer in both men and women. The TNM staging system, the most common system to stage colorectal tumors, is used to discriminate between patients with a better and a poor prognosis, but it seems insufficiently able to predict the prognosis of the individual patient. Additional prognostic factors are desirable, because a part of the patients is overtreated and consequently exposed to a higher risk on therapy related complications. The tumor-stroma ratio (TSR), the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor, has proven to be of prognostic value in several malignancies.

Research frontiers

A previous study, on a small number of rectal cancer patients, showed that a high TSR is possibly related to both a longer disease free and overall survival. In this respect, it is meaningful to explore the relevance of the TSR in a larger cohort of patients with rectal adenocarcinoma, as the authors did.

Innovations and breakthroughs

This paper showed that the TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases. The effect of a high TSR on survival demonstrated in this study is in line with other studies on the prognostic impact of the TSR in colorectal carcinomas and other malignancies. The present study is however the first that has identified a subgroup of patients with rectal cancer, namely lymph node metastasis negative patients with an intermediate TSR, whereby the TSR is a strong prognostic factor.

Applications

The determination of the TSR may contribute to stratify patients for prognosis and has the potential to contribute to decision making regarding the individual treatment policy in rectal cancer.

Terminology

The TSR is the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor. The carcinoma percentage (CP) is a derivative of the TSR and is complementary to the percentage of stroma and other components, like mucus. TSR-low including the CP-values $\leqslant$ 30%, TSR-intermediate including the CP-values 40%, 50% and 60%, and TSR-high including the CP-values $\geqslant$ 70%.

Peer-review

The study is well designed and clearly presented and the topic of high interest for oncologists that should decide after surgery what patients will benefit more from an adjuvant treatment.

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P- Reviewer: Cecchin E, Fogli L, Velenik V **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2017 December 15; 9(12): 475-491

DOI: 10.4251/wjgo.v9.i12.475

ISSN 1948-5204 (online)

META-ANALYSIS

Laparoscopic *vs* open complete mesocolic excision with central vascular ligation for colon cancer: A systematic review and meta-analysis

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Author contributions: Negoi I and Negoi RI acquisition of data; Negoi I analysis of data; Negoi I and Hostiuc S interpretation of data; Negoi I drafting the article; Hostiuc S and Negoi RI revising the article; Negoi I, Hostiuc S, Negoi RI and Beuran M final approval; Beuran M conception and design of the study, critical revision; all authors had equally contributed to this scientific paper.

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

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: May 29, 2017
Peer-review started: June 5, 2017
First decision: July 3, 2017
Revised: July 8, 2017
Accepted: September 4, 2017
Article in press: September 4, 2017
Published online: December 15, 2017

Abstract

AIM

To compare the effectiveness of laparoscopic complete mesocolic excision (CME) with central vascular ligation (L-CME) with its open (O-CME) counterpart.

METHODS

We conducted an electronic search of the PubMed/MEDLINE, Excerpta Medica Database, Web of Science Core Collection, Cochrane Center Register of Controlled Trails, Cochrane Database of Systematic Reviews, SciELO, and Korean Journal databases from their inception until May 2017. We considered randomized controlled trials (RCTs) and controlled clinical trials (CCTs) that included patients with colonic cancer comparing L-CME and O-CME. Primary outcomes included the quality of the resected specimen (lymph nodes retrieved, complete mesocolic plane excision, tumor to arterial high tie, resected mesocolon surface). Secondary outcomes included the three-year and five-year overall and disease-free survival rates, recurrence of the disease, surgical data, and postoperative morbidity and mortality. Two authors of the review screened the methodological quality of the eligible trials and independently extracted data from individual

studies.

RESULTS

A total of one RCT and eleven CCTs (four from Europe and seven from Asia) met the inclusion criteria for the current meta-analysis. These studies involved 1619 patients in L-CME and 1477 patients in O-CME. The L-CME was associated with the same quality of the resected specimen, with no differences regarding the retrieved lymphnodes (MD = -1.06, 95%CI: -3.65 to 1.53, P = 0.42), and tumor to high tie distance (MD = 14.26 cm, 95%CI: -4.30 to 32.82, P = 0.13); the surface of the resected mesocolon was higher in the L-CME group (MD = 11.75 cm^2, 95%CI: 9.50 to 13.99, P < 0.001). The L-CME was associated with a lower rate of blood transfusions (OR = 0.45, 95%CI: 0.27 to 0.75, P = 0.002), faster recovery of gastrointestinal function, and less postoperative overall complication rate. The L-CME approach was associated with a statistical significant better three-year overall (OR = 2.02, 95%CI: 1.31 to 3.12, P = 0.001, I^2 = 28%) and disease-free (OR = 1.45, 95% CI: 1.00 to 2.10, P = 0.05, I^2 = 0%) survival.

CONCLUSION

The laparoscopic approach offers the same quality of the resected specimen as the open approach in complete mesocolic excision with central vascular ligation for colon cancer. The laparoscopic complete mesocolic excision with central vascular ligation is superior in all perioperative results and at least non-inferior in long-term oncological outcomes.

Key words: Colon cancer; Complete mesocolic excision; D3 lymphadenectomy; Central vascular ligation

Core tip: The laparoscopic complete mesocolic excision with central vascular ligation was associated with the same quality of the resected specimen, with no differences regarding the retrieved lymphnodes, and tumor to high tie distance; the surface of the resected mesocolon was higher in the laparoscopic group. Laparoscopy was associated with a lower rate of blood transfusions, faster recovery of gastrointestinal function, and less postoperative overall complication rate. The laparoscopic approach was associated with a statistical significant better three-year overall and disease-free survival.

Negoi I, Hostiuc S, Negoi RI, Beuran M. Laparoscopic *vs* open complete mesocolic excision with central vascular ligation for colon cancer: A systematic review and meta-analysis. *World J Gastrointest Oncol* 2017; 9(12): 475-491 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/475.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.475

INTRODUCTION

Complete mesocolic excision (CME) with central vascular ligation (CVL) represents an extension to the colonic cancer of the already standardized resection for rectal cancer. It adheres to the same guiding principle that sharp surgical dissection, following embryological planes, with central vascular ligation, should improve oncological outcomes[1].

Hohenberger *et al*[2] (2007) published the technical details of a new concept termed CME and central ligation for colonic cancer. During CME with CVL for right-sided tumors, the ileocolic and right colic vessels should be ligated at their origin from the superior mesenteric artery. Transverse colon tumors require transection of the middle colic artery at its origin. Left-sided tumors require transection of the inferior mesenteric artery (IMA) at its origin from the aorta[3]. Using CME and CVL, Hohenberger *et al*[4] reported a reduction of the local five-year recurrence rate from 6.5% to 3.6% and an increase in the cancer-related five-year survival rate from 82.1% to 89.1%. This specimen-oriented technique is associated with the removal of more tissue compared with standard surgery, a wider distance from the tumor to the high vascular tie (131 mm *vs* 90 mm, P < 0.0001), a longer length of large bowel (314 mm *vs* 206 mm, P < 0.0001), a wider area of removed mesentery (19657 mm^2 *vs* 11829 mm^2, P < 0.0001) and a greater lymph node yield (30 *vs* 18, P < 0.0001)[5]. These differences may partially explain the higher reported survival rates with CME and CVL.

One should note the similarities between D3 lymphadenectomies, recommended as a standard of care for stage Ⅱ and Ⅲ colon cancer in Eastern countries, and Western CME[3,6]. The Japanese nomenclature includes D1 as pericolic (close to the bowel wall), D2 as intermediate (along the feeding artery), and D3 as main (at the origin of the feeding artery) lymph nodes. For right-sided tumors, a D3 lymphadenectomy requires the transection of the feeding arteries next to their origin from the superior mesenteric artery. In left-sided cancers, a D3 lymphadenectomy requires transection of the IMA close to its aortic origin[7].

Current evidence is consistent with a faster postoperative recovery for laparoscopic colectomies compared with the open approach; the former is not associated with any negative impact regarding local recurrence and survival rates. Therefore, according to the latest National Comprehensive Cancer Network guidelines, the laparoscopic approach is preferred given access to a surgeon with experience in advanced minimally invasive procedures[8].

The objective of this systematic review and meta-analysis is to summarize the current evidence regarding laparoscopic CME (L-CME) and to compare its effectiveness with its open (O-CME) counterpart.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[9].

Electronic search, study selection, data extraction, and quality assessment was performed independently by two reviewers.

Data sources and search strategy

We conducted an electronic search to identify all published randomized controlled trials (RCTs) and controlled clinical trials (CCTs) using the following databases: United States National Library of Medicine - National Institutes of Health PubMed/MEDLINE, EMBASE, Web of Science Core Collection, Cochrane Center Register of Controlled Trails (CENTRAL), Cochrane Database of Systematic Reviews, SciELO, and Korean Journal databases from their inception until May 2017. We did not use any language restrictions. The most recent search in PubMed was performed in May 2017.

We constructed the search strategy using various combinations of terms related to CME or D3 lymphadenectomy using an open or laparoscopic approach to colon cancer. We used in different combinations the following key words: colon, cancer, complete mesocolic excision, central vascular ligation, D3 lymphadenectomy, minimally invasive, laparoscopy, open, surgery, colectomy and resection. These words were identified as truncated words in the title, abstract, or in the medical subject headings (MeSH). We additionally used electronic and manual cross-referencing to find other relevant sources. The search strategy used in PubMed/Medline was: [colon (MeSH Terms)] OR colonic (Title/Abstract) OR lower intestinal (Title/Abstract) OR large bowel (Title/Abstract) AND cancer (MeSH Terms) OR neoplasia (Title/Abstract) OR neoplasm (Title/Abstract) OR tumor (Title/Abstract) AND laparoscopy(MeSH Terms) OR minimally invasive (Title/Abstract) OR laparoscopic (Title/Abstract) AND complete mesocolic excision (Title/Abstract) OR central vascular ligation (Title/Abstract) OR D3 lymphadenectomy (Title/Abstract).

Trial selection

Study eligibility criteria: We considered RCTs and CCTs comparing open with laparoscopic CME or D3 lymphadenectomy as eligible for inclusion if they included patients with colonic cancer.

Outcome measures

Primary outcome: Quality of the resected specimen (lymph nodes retrieved, complete mesocolic plane excision, tumor to arterial high tie, resected mesocolon surface).

Secondary outcomes: Three-year and five-year overall and disease-free survival rates, recurrence of the disease, surgical data (operation time, length of the abdominal incision, conversion rate), intraoperative complications, blood loss, postoperative complications (anastomotic leakage, wound infections, overall complications), length of hospital stay, thirty-day mortality, immunologic response, quality of life, and cost.

Data extraction

Two authors[10] (Negoi and Hostiuc) assessed the methodological quality of the eligible trials and independently extracted data from individual studies using a data-extraction form. We extracted the following data: Year of publication, source, title, first author, contact address, criteria for patient inclusion and exclusion, sample size, baseline characteristics, and patient characteristics including mean age, sex ratio, location of the tumor, number of patients assigned to each treatment group, and details of the intervention regimens. We registered the following outcomes: One-, three- and five-year overall and disease-free survival rates, number of removed lymph nodes, length of the resected colon, resection of the mesocolic plane, operation time, length of hospital stay, number and frequency of postoperative complications, and quality of life.

Assessment of risk of bias

To assess the risk of bias, we used the Cochrane Collaboration tool for RCTs. This tool grades the random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases[11]. To evaluate the non-randomized trials, we used the methodological index of non-randomized studies (MINORS)[12]. We scored all of the 12 methodological items for non-randomized comparative studies as follows: 0 - not reported; 1 - reported but inadequate; or 2 - reported and adequate. The global ideal score for comparative (non-comparative) studies was 24.

Statistical analysis

For statistical analysis, we used Review Manager Software 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark)[11] provided by the Cochrane Collaboration and OpenMetaAnalyst[13] with metaphor package[14] as statitstical softwares. We selected the mean difference (MD) as an effect measure for continuous data and the odds ratio (OR) for dichotomous data; we also reported the 95%CI. In cases of continuous data presented as median and range, we estimated the mean and standard deviation according to the methods described by Hozo *et al*[15]. We used Chi-square and I^2 statistics to assess the studies' heterogeneity and explain the total variation observed between the studies that be generated by the differences between the trials rather than the sampling error (chance). An I^2 value $\leqslant$ 25% indicates less heterogeneity, an I^2 value > 25% but $\leqslant$ 75% indicates a moderate heterogeneity, and I^2 values > 75% indicate higher heterogeneity[16]. We explored the reasons behind the statistical heterogeneity using sensitivity analyses and the exclusion of specific studies. We used fixed-effect model analysis for outcomes with low heterogeneity. If we found clinical heterogeneity between included studies due to differences with respect to eligibility criteria (study population), the type of surgical technique, and lacking or differing definitions of outcomes, we performed meta-analysis by applying a random-

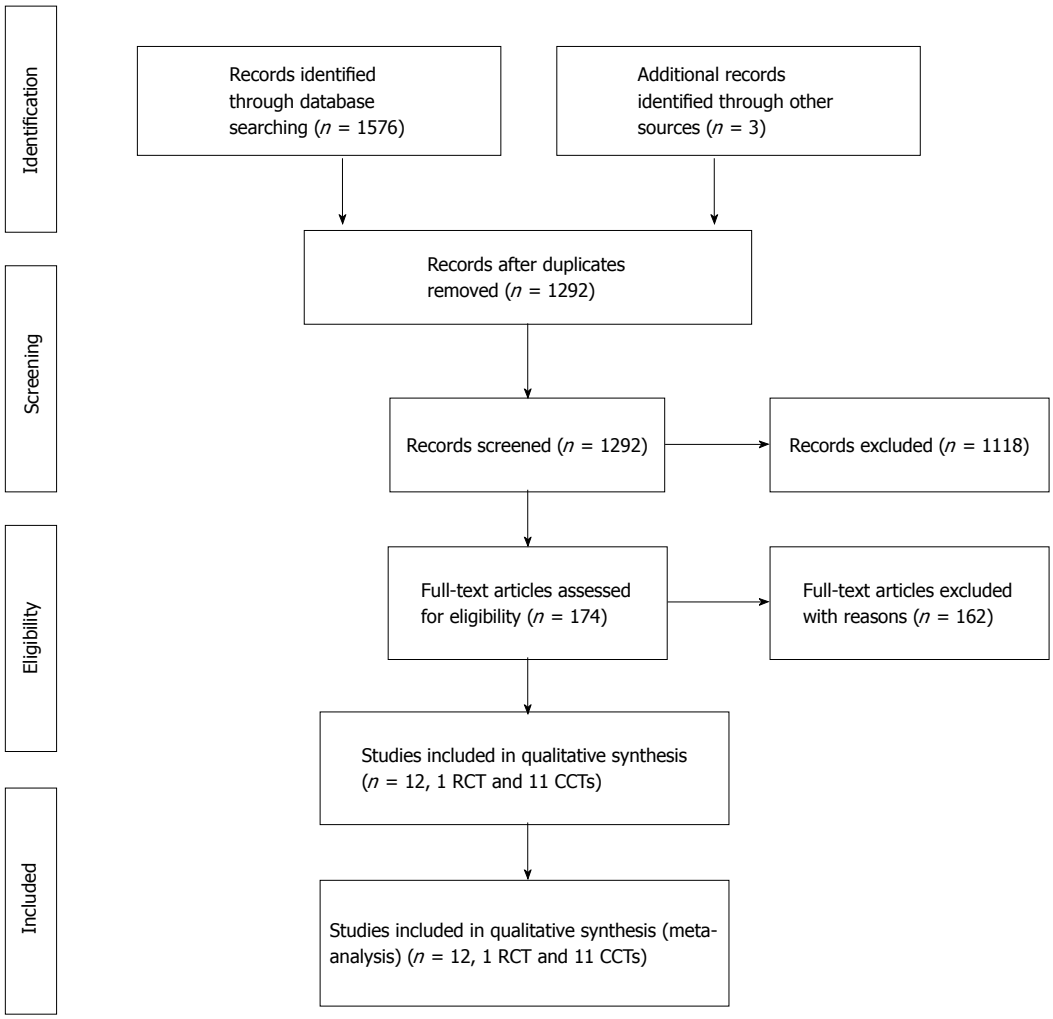

Figure 1 Flow diagram of the systematic literature search and study selection according to prisma statement. RCT: Randomized control trial; CCT: Controlled clinical trial.

effect model (the DerSimonian-Laird method)[17]. We used Begg's funnel plot and Egger's test for assessing publication bias[18]. The statistical significance was defined as $P < 0.1$ in Egger's test and $P < 0.05$ for the other statistical tests. To correct possible publication bias, we performed trim and fill analysis[19]. The statistical methods of this study were reviewed by Sorin Hostiuc from the Department of Legal Medicine and Bioethics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

RESULTS

Description of studies

Results of the search: The initial electronic and manual literature searches revealed 174 full-text articles. A total of one RCT (from Japan)[20,21] and eleven CCTs (four from Europe and seven from Asia)[22-32] met the inclusion criteria for the qualitative and quantitative (meta-analysis) synthesis; these studies involved 1619 patients in L-CME and 1477 patients in O-CME. Eleven studies were published in English and one in Chinese. The reasons for exclusion in each stage of the process are shown in Figure 1.

Included studies: The characteristics of the included studies are summarized in Table 1. All of the studies were published between 2012 and 2016, the RCT being published in 2014. The sample size of the studies ranged from 23 to 533 patients. The CME or D3 lymphadenectomy was defined as dissection along the Told's fascia space and a high (apical or central) ligation of the feeding vessel. Colonic mobilization was conducted using a medial-to-lateral or a lateral-to-medial approach according to the surgeon's preference. For right-sided tumors, the vascular pedicles were divided at their origin together with removal of the draining lymph nodes along the border of the superior mesenteric vein. For left-sided tumors, removal of the central lymph nodes from the origin of the inferior mesenteric artery was performed with high ligation or with preservation of the left colic artery. In the JCOG 0404 study, the accredited surgeons had completed more than 30 laparoscopic and 30 open colorectal resections[20]. In all of the other studies, the procedures were performed or supervised by colorectal surgeons. Conversion to laparotomy was defined as the extension of the abdominal incision more than eight cm or as the inability to complete the dissection fully laparoscopically. The reported rate

Table 1 Characteristics of the included studies

Ref.	Country of origin	Study type	Study period	Female (number, L/O)	Mean age (yr, L/O)	Intervention (L-CME) right/ transverse/left location of the tumor	Control (O-CME) right/transverse/ left location of the tumor	Adjuvant chemotherapy
Kim *et al*[23], 2016	South Korea	Case control, unicentre, prospective database	2008-2013	62/44	69/67	116/0/0	99/0/0	L-CME = 68 pts (58.62%), O-CME = 78 pts (78.78%), recommended to all stage Ⅱ and Ⅲ
Storli *et al*[22], 2016	Norway	Prospective non RT, unicentre	2007-2014	22/13	73/23	0/33/0	0/23/0	L-CME = 8 (61.5%), O-CME = 5 (62.5%), all stage Ⅲ below 75 yr
Huang *et al*[24], 2015	China	Case control, unicentre	2012-2013	20/21	56/55	53/0/0	49/0/0	NR
Yamamoto *et al*[20], 2014	Japan	RCT, multicentre	2004-2009	248/215	64/64	144/0/389	156/0/368	NR, recommended for all stage Ⅲ
Munkedal *et al*[25], 2014	Denmark	Prospective nonRT, unicentre	2008-2011	30/38	69.1/72.9	30/0/53	41/0/38	NR
Bae *et al*[27], 2014	South Korea	Case control, unicentre	2006-2008	40/38	64/65	73/12/0	76/9/0	All stage Ⅲ and Ⅱ with poor prognosis
Han *et al*[26], 2014	China	Case control, unicentre	2003-2010	94/67	67/65	177/0/0	147/0/0	NR, recommended for high risk stage Ⅱ and stage Ⅲ
Zhao *et al*[28], 2014	China	Case control, multicentre	2000-2009	53/44	61.3/64.5	89/30/0	65/36/0	NR, recommended for high risk stage Ⅱ and stage Ⅲ
Cong *et al*[29], 2014	China	Case control, unicentre	2008-2011	53/45	61.5/62.3	96/0/0	82/0/0	NR
Storli *et al*[30], 2013	Norway	Prospective nonRT, unicentre	2007-2010	49/60	71.9/73.1	50/18/60 2 pts - multiple	35/44/42	All stage Ⅲ below 75 yr
Gouvas *et al*[31], 2012	Greece	Prospective nonRT, multicentric	2006-2010	19/17	62.1/66.3	7/9/33	9/9/23	NR
Sun *et al*[32], 2012	China	Case control, unicentre	2000-2008	58/45	60.1/61.9	49/7/91	43/9/74	NR, according to stage

L-CME: Laparoscopic complete mesocolic excision; O-CME: Open complete mesocolic excision; RT: Randomized control trial; Non RT: Non randomized control trial; L/O: Laparoscopy/open groups; NR: Not reported.

of conversion to laparotomy was between 2.82% and 7.6%[20,22-32]. Transverse colon cancers were excluded from the JCOG 0404 study[20]. Storli *et al*[30] performed 9 (7.3%) transverse colectomies in the open approach but none in the laparoscopic group. In a second paper, Storli *et al*[22] published their experience regarding CME only in transverse colon cancer. Gouvas *et al*[31] managed all of the transverse colon cancers using an extended right hemicolectomy. Munkedal *et al*[25] excluded all cancers in the transverse colon or flexures from their analysis. Bae *et al*[26], Han *et al*[27], and Zhao *et al*[28] managed all cases by a right or extended right hemicolectomy. All studies exhibited remarkable similar exclusion criteria: Stage Ⅳ disease and emergency surgery. All of the studies described the technique of laparoscopic CME. Perioperative care was not described in most trials.

The patient demographics and baseline clinical data were similar between the treatment groups; the L-CME group exhibited a mean age of 69.91 years, and the O-CME group exhibited a mean age of 65.41 years. Women comprised 46.20% and 41.23% of the L-CME and O-CME patients, respectively. None of the studies were blinded, and all of the studies were powered to demonstrate the non-inferiority of the laparoscopic approach.

Excluded studies: We excluded all studies in which the surgical technique did not comply with CME or D3 lymphadenectomy principles[33-42]. We also excluded studies based on the hand-assisted laparoscopic technique[43,44]. Due to the probability of overlapping patients, we have excluded first report of Kim *et al*[45] which includes only T4 patients.

Risk of bias in the included studies

The risk of bias in the one Japanese RCT was low in all domains[20]. Although blinding of patients and medical personnel was not performed in either trial, the endpoints were considered to be objective, particularly when they were supported by photos. The prospective and

Table 2 Quality assessment of included non-randomized controlled trials

Quality evaluation criteria	Kim *et al*[23], 2016	Storli *et al*[22], 2016	Storli *et al*[30], 2016	Huang *et al*[24], 2015	Munkedal *et al*[25], 2014	Bae *et al*[27], 2014	Han *et al*[26], 2014	Zhao *et al*[28], 2014	Cong *et al*[29], 2014	Gouvas *et al*[31], 2012	Sun *et al*[32], 2012
Clear stated aim	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2	2	2	1	2	2
Prospective data collection	2	2	2	0	2	0	0	0	0	2	0
Endpoints appropriate to the study aim	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of study end-point	2	2	2	2	2	2	2	1	1	2	1
Appropriate follow-up period	2	2	2	1	2	2	2	2	2	2	2
Loss to follow-up less than 5%	1	2	2	1	2	2	2	1	1	2	1
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0
Adequate group control	2	2	2	2	2	2	2	2	0	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence	2	2	2	2	2	2	2	2	2	2	2
Adequate statistical analysis	2	2	2	2	2	2	2	2	2	2	1
Total	21	22	22	18	22	20	20	18	15	22	17

0: Non-reported; 1: Reported but inadequate; 2: Reported and adequate.

retrospective non-randomized studies had good MINORS scores, although the risk of selection, performance, and detection bias was high (Table 2). As expected, the prospective observational studies[22-23,25,30,31] had a higher methodological quality comparing with the retrospective studies[24,26-29].

Effects of intervention

Overall survival: Three-year overall survival was reported by four studies, including 1010 patients (Table 3). The laparoscopic approach was associated with a statistical significant better three-year overall survival, with an OR of 2.02 (95%CI: 1.31 to 3.12, $P = 0.001$, $I^2 = 28\%$). The five-year overall survival was reported by three studies, with a high heterogeneity between them ($I^2 = 63\%$). The combined data revealed no statistical significant differences between the L-CME and O-CME (OR = 0.77, $P = 0.38$, 95%CI: 0.44 to 1.37) (Figure 2). Meta-regression of studies on three-year overall survival according to the number of included patients revealed a trend, although not statistical significant (omnibus $P = 0.127$), for decreasing of the size of the effect with increasing the number of patients (Figure 3A). The subgroup analysis of studies that include or not only right sided colon cancers, reveled statistical significant results irrespective of that ($P = 0.003$ and $P = 0.018$, respectively) (Figure 3B). On the other hand, the cumulative meta-analysis showed a progressively increasing of the size effect while experience is accumulating (Figure 3C).

Disease-free survival

Three studies, with a total of 686 patients, reported the three-year DFS with a low heterogeneity between them ($I^2 = 0\%$). However, to adjust for possible methodological differences we used the random-effects model, which revealed that the laparoscopic approach is associated with a statistical significant better three-year DFS (OR = 1.45, 95%CI: 1.00 to 2.10, $P = 0.05$) (Figure 4). Meta-regression of studies on three-year overall survival according to the number of the included patients revealed a trend, although not statistical significant (Omnibus $P = 0.718$), for decreasing of the size of the effect with increasing the number of patients (Figure 5).

Local and distant recurrences

The local recurrence rate was presented by five studies, including 1233 patients. In the fixed-effect meta-analysis there were no statistical significant differences between L-CME and O-CME (OR = 0.67, 95%CI: 0.38 to 1.17, $P = 0.16$, $I^2 = 0\%$) (Figure 6).

The distant recurrence rate was presented by four studies, with a moderate heterogeneity between them ($I^2 = 40\%$). In the random-effects meta-analysis there were no statistical significant differences between the two groups (OR = 0.98, 95%CI: 0.61 to 1.58, $P = 0.94$). Using Egger's test, no publication bias was found for local ($t = 0.22$, $P = 0.42$) or distant recurrences ($t = 0.38$, $P = 0.36$).

The port size metastasis rate was reported by two studies including 494 patients, with a low heterogeneity between them ($I^2 = 0\%$). In the fixed-effect analysis model there was no difference regarding the port size metastasis rate between laparoscopic and open CME (OR = 1.52, 95%CI: 0.20 to 11.42, $P = 0.69$).

Quality of the resected specimen

Standardized evaluation of the resected specimen and grading its quality are objective measures that predict recurrence rate and survival. These data are correlated with the accuracy of the surgical technique.

Lymphnodes retrieved

Ten studies reported the number of retrieved lymph nodes for 1376 L-CME patients and 1271 O-CME pa-

Table 3 Results of meta-analysis comparing laparoscopic with open complete mesocolic excision for colon cancer

Outcome or subgroups	No. of Studies	Participants	Statistical method (95%CI)	Effect estimate (95%CI)	*P* value	Heterogeneity *P*, I2 (%)
Survival and recurrences						
Overall survival	6	1777	OR (M-H, random)	1.32 (0.83, 2.10)	0.24	0.002, 70
Three-year	4	1010	OR (M-H, random)	2.02 (1.31, 3.12)	0.001	0.24, 28
Five-year	3	767	OR (M-H, random)	0.77 (0.44, 1.37)	0.38	0.07, 63
Disease free survival	4	856	OR (M-H, random)	1.15 (0.70, 1.87)	0.58	0.09, 54
Three-year	3	686	OR (M-H, random)	1.45 (1.00, 2.10)	0.05	0.89, 0
Five-year	1	170	OR (M-H, random)	0.50 (0.24, 1.05)	0.07	NA
Local recurrences	5	1233	OR (M-H, fixed)	0.67 (0.38, 1.17)	0.16	0.60, 0
One-year	2	466	OR (M-H, fixed)	0.52 (0.20, 1.35)	0.18	0.30, 7
Five-year	3	767	OR (M-H, fixed)	0.77 (0.38, 1.54)	0.46	0.52, 0
Distant recurrences	4	1018	OR (M-H, random)	0.98 (0.61, 1.58)	0.94	0.17, 40
Three-year	1	251	OR (M-H, random)	1.28 (0.54, 3.03)	0.58	NA
Five-year	3	767	OR (M-H, random)	0.90 (0.48, 1.69)	0.75	0.10, 57
Port site metastasis	2	494	OR (M-H, fixed)	1.52 (0.20, 11.42)	0.69	0.55, 0
Quality of the resected specimen						
Lymphnodes retrieved	10	2647	MD (IV, random)	-1.06 (-3.65, 1.53)	0.42	< 0.001, 92
RCTs	1	1057	MD (IV, random)	1.00 (-0.34, 2.34)	0.14	NA
NRCTs	9	1590	MD (IV, random)	-1.32 (-4.42, 1.78)	0.40	< 0.001, 92
Lymphnodes retrieved	10	2647	MD (IV, random)	-1.06 (-3.65, 1.53)	0.42	< 0.001, 92
< 100 patients	4	478	MD (IV, random)	-3.18 (-8.69, 2.33)	0.26	< 0.001, 85
> 100 patients	6	2169	MD (IV, random)	0.29 (-1.64, 2.21)	0.77	< 0.001, 83
Lymphnodes retrieved	10	2647	MD (IV, random)	-1.06 (-3.65, 1.53)	0.42	< 0.001, 92
Europe	4	559	MD (IV, random)	-3.33 (-8.31, 1.64)	0.19	< 0.001, 90
Asia	6	2088	MD (IV, random)	0.56 (-1.33, 2.46)	0.56	< 0.001, 77
Tumor to arterial high tie (mm)	2	252	MD (IV, random)	14.26 (-4.30, 32.82)	0.13	< 0.001, 92
Resected mesocolon surface (cm^2)	2	252	MD (IV, fixed)	11.75 (9.50, 13.99)	< 0.001	0.55, 0
Complete mesocolic plane excision	1	90	OR (M-H, fixed)	0.77 (0.20, 2.96)	0.71	NA
Operative data						
Duration of surgery	7	2266	MD (IV, random)	26.26 (5.06, 47.46)	0.02	< 0.001, 94
Incision length (cm)	2	1159	MD (IV, random)	-14.01 (-14.35, -13.66)	< 0.001	0.89, 0
Blood loss (mL)	5	1868	MD (IV, random)	-52.11 (-78.57, -25.65)	< 0.001	< 0.001, 89
Transfusion requirement	2	1272	OR (M-H, random)	0.45 (0.27, 0.75)	0.002	0.54, 0
Intraoperative morbidity	1	1057	OR (M-H, fixed)	2.12 (0.95, 4.72)	0.07	NA
Postoperative course						
Time to first flatus (d)	4	1771	MD (IV, random)	-0.90 (-1.46, -0.34)	0.002	< 0.001, 97
Time to liquid diet (d)	5	1031	MD (IV, random)	-1.84 (-2.93, -0.74)	0.001	< 0.001, 98
Short-term morbidity and mortality						
Thirty-day overall morbidity	7	2144	OR (M-H, fixed)	0.57 (0.46, 0.71)	< 0.001	0.76, 0
RCTs	1	1057	OR (M-H, fixed)	0.66 (0.49, 0.89)	0.006	NA
NRCTs	6	1087	OR (M-H, fixed)	0.49 (0.36, 0.68)	< 0.001	0.89, 0
Wound complications	8	2322	OR (M-H, fixed)	0.43 (0.30, 0.61)	< 0.001	0.80, 0
Postoperative bleeding	4	1662	OR (M-H, fixed)	1.20 (0.46, 3.12)	0.71	0.75, 0
Pneumonia	5	867	OR (M-H, random)	0.61 (0.20, 1.84)	0.38	0.21, 32
Anastomotic leakage	8	2471	OR (M-H, fixed)	0.82 (0.54, 1.25)	0.36	0.77, 0
Need for reoperation	2	1113	OR (M-H, fixed)	0.59 (0.28, 1.23)	0.16	0.79, 0
Thirty-day mortality	6	2237	OR (M-H, fixed)	0.42 (0.16, 1.12)	0.07	0.98, 0
Hospital stay (d)	9	2573	MD (IV, random)	-4.07 (-5.87, -2.28)	< 0.001	< 0.001, 91

M-H: Mantel-haenszel analysis method; IV: Inverse variance analysis method; RCT: Randomized control trial; NRCs: Non-randomized control trials; MD: Mean difference; OR: Odds ratio; NA: Not applicable.

tients. There was a high heterogeneity between the studies (I^2 = 92%). In the random-effects model, we found no statistically significant mean difference between L-CME and O-CME (MD = -1.06, 95%CI: -3.65 to 1.53, *P* = 0.42) (Figure 7). In order to address the observed heterogeneity, we performed subgroup analysis according to the number of included patients (less or more than 100 patients in each group) and the geographical location of the study (Europe and Asia). The subgroup analysis revealed a high heterogeneity between studies with less than (I^2 = 85%) or more (I^2 = 83%) than 100 patients into laparoscopy or open group. The results remained with no statistical significance into the two subgroups. Studies coming from Europe showed a high heterogeneity (I^2 = 90%) and with no differences regarding the number of retrieved lymphnodes (*P* = 0.19). Studies published in Asia had also a high heterogeneity (I^2 = 77%), and no statistical significant difference between L-CME and O-CME (*P* = 0.56). Meta-regression of retrieved lymphnodes according to the number of patients revealed that the equivalence between laparoscopic and open approach is stronger with the increased experience in laparoscopic approach (number of the included patients - omnibus *P*

Study or subgroup	Laparoscopy Events	Total	Open Events	Total	Weight	Odds ratio M-H, random, 95%CI
3-year						
Han 2014	148	177	114	147	16.2%	1.48 [0.85, 2.57]
Kim 2016	110	116	79	99	11.1%	4.64 [1.78, 12.09]
Storli 2013	113	128	99	123	14.3%	1.83 [0.91, 3.67]
Zhao 2014	109	119	85	101	12.5%	2.05 [0.89, 4.75]
Subtotal (95%CI)		540		470	54.1%	2.02 [1.31, 3.12]
Total events	480		377			
Heterogeneity: Tau^2 = 0.06; χ^2 = 4.17, df = 3 (P = 0.24); I^2 = 28%						
Test for overall effect: Z = 3.19 (P = 0.001)						
5-year						
Bae 2014	66	85	77	85	11.9%	0.36 [0.15, 0.88]
Han 2014	124	177	98	147	17.4%	1.17 [0.73, 1.87]
Sun 2012	102	147	93	126	16.6%	0.80 [0.47, 1.37]
Subtotal (95%CI)		409		358	45.9%	0.77 [0.44, 1.37]
Total events	292		268			
Heterogeneity: Tau^2 = 0.16; χ^2 = 5.37, df = 2 (P = 0.07); I^2 = 63%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95%CI)		949		828	100.0%	1.32 [0.83, 2.10]
Total events	772		645			
Heterogeneity: Tau^2 = 0.26; χ^2 = 20.27, df = 6 (P = 0.002); I^2 = 70%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: χ^2 = 6.93, df = 1 (P = 0.008); I^2 = 85.6%						

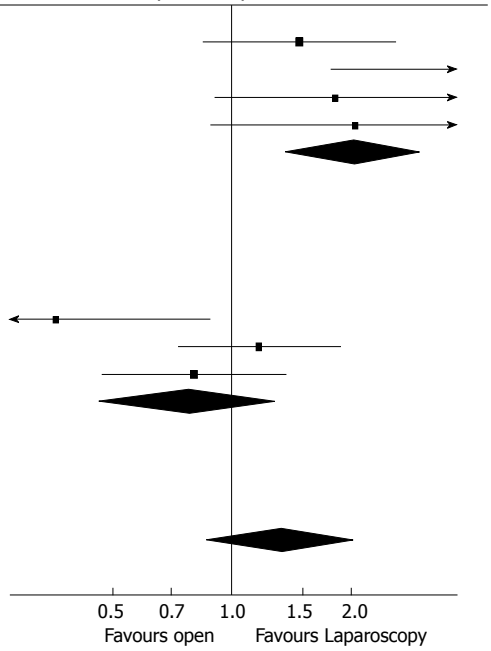

Figure 2 Meta-analysis of studies on overall survival of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

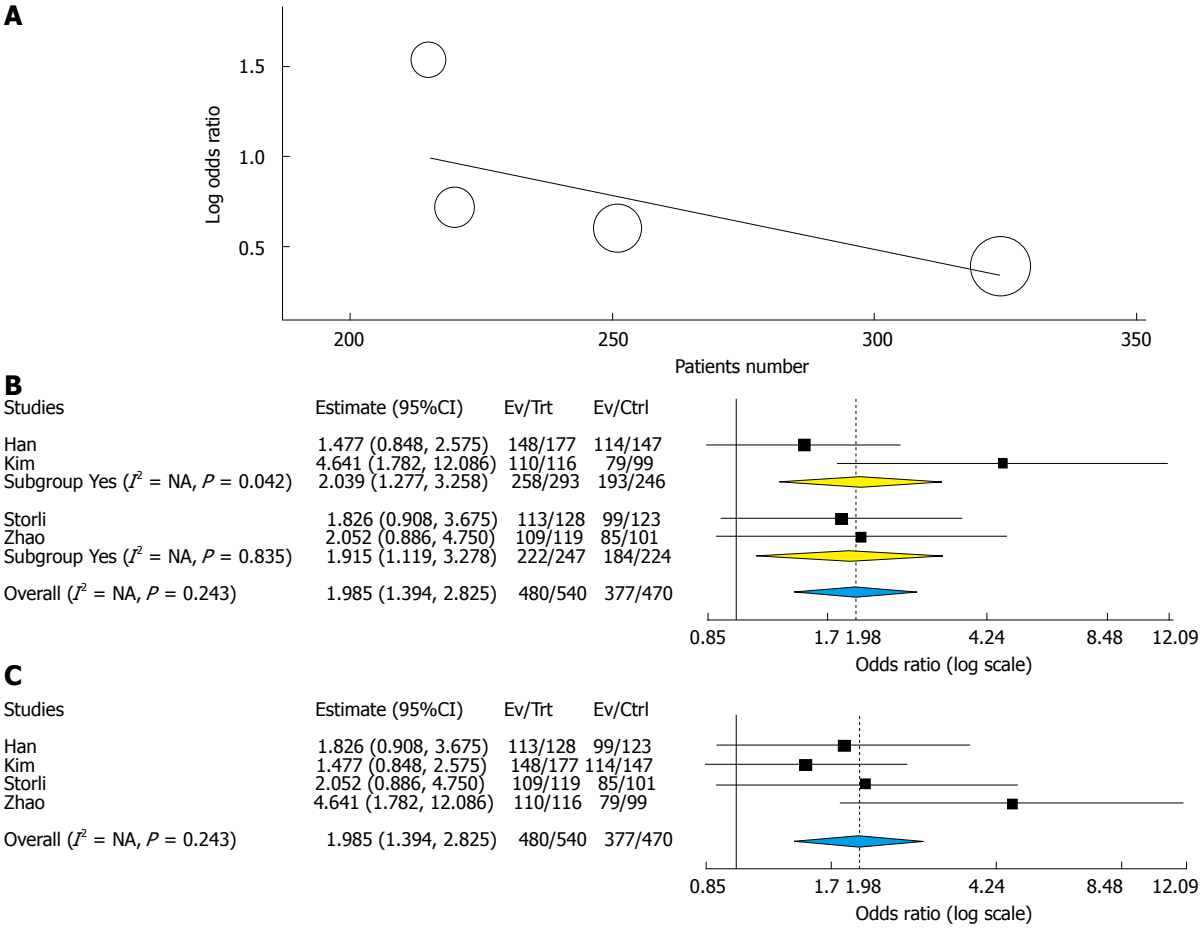

Figure 3 Results of statistical analysis. A: Meta-regression on three-year overall survival according with the number of included patients in each study, of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer; B: Subgroup meta-analysis according with the selection of patients with only right colon cancers (Yes group) or all-localizations colon cancer (No group); C: Cumulative meta-analysis according to the year of publishing for each study.

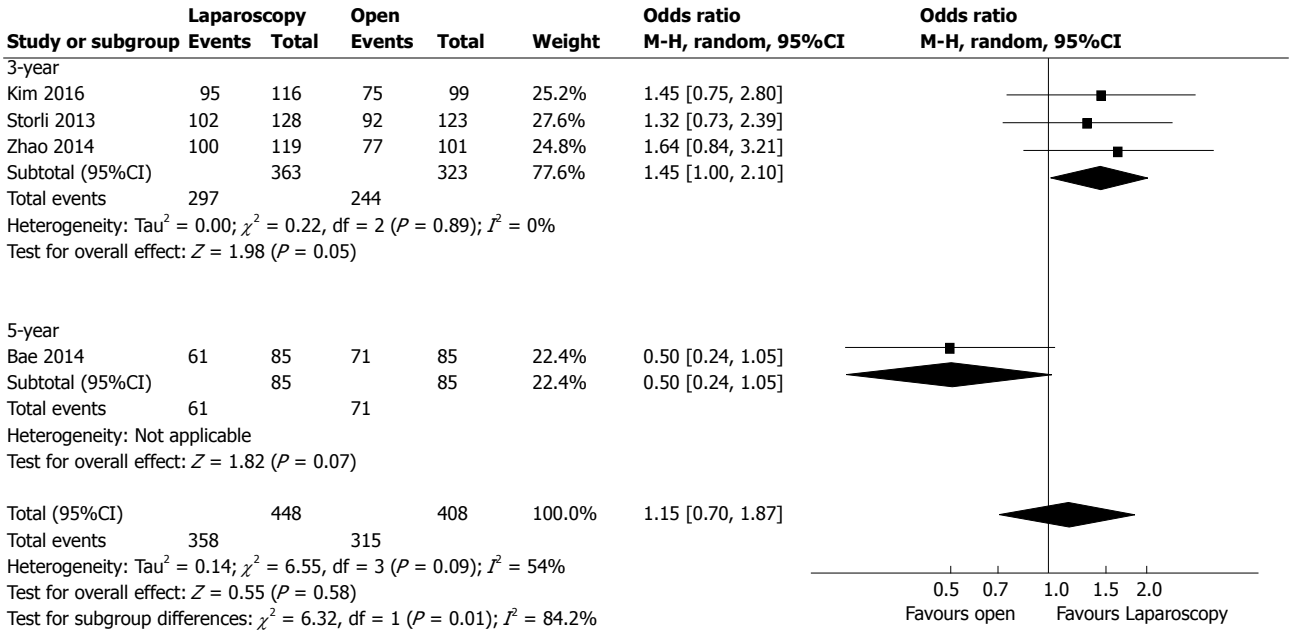

Figure 4 Meta-analysis of studies on disease-free survival of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

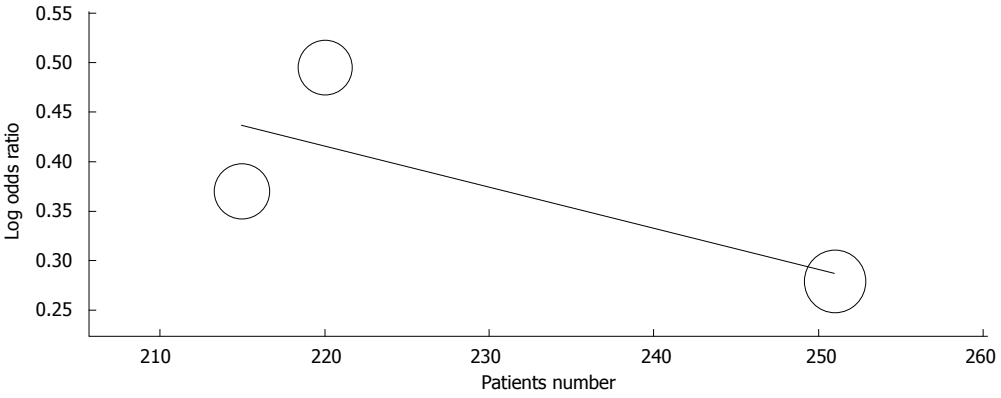

Figure 5 Meta-regression of studies on three-year disease-free survival of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

= 0.314, Figure 8A; and year of publishing of the study, Figure 8B).

Tumor to high tie distance

The mean distance from the tumor to the arterial high tie was reported by two studies that included 132 patients in the L-CME group and 120 patients in the O-CME group; we noted high heterogeneity among the studies (I^2 = 92%). Using the random-effects model, we did not find any statistically significant difference between the L-CME and O-CME groups (MD = 14.26 cm, 95%CI: -4.30 to 32.82, P = 0.13) (Figure 9).

Surface of the resected mesocolon

The surface of the resected mesocolon was reported by two studies with 132 patients in the L-CME group and 120 patients in the O-CME group. The surface of the resected mesocolon was larger in the L-CME group (MD = 11.75 cm^2, 95%CI: 9.50 to 13.99, P < 0.001) (Figure 10).

Complete mesocolic plane excision rate

One study reported the rate of complete mesocolic plane excision, with no statistically significant difference between the laparoscopic and open approach (OR = 0.77, 95%CI: 0.20 to 2.96).

Duration of surgery

The duration of surgery was reported by seven studies, with a high heterogeneity between data (I^2 = 94%). The L-CME group had a longer duration of surgery with a mean difference of 26.26 min (95%CI: 5.06 to 47.46, P = 0.02). Using Egger's test, no publication bias was found (t = 0.71, P = 0.26).

Incision length

The incision length was reported by two studies, including 586 patients in the L-CME group and 573 patients in the

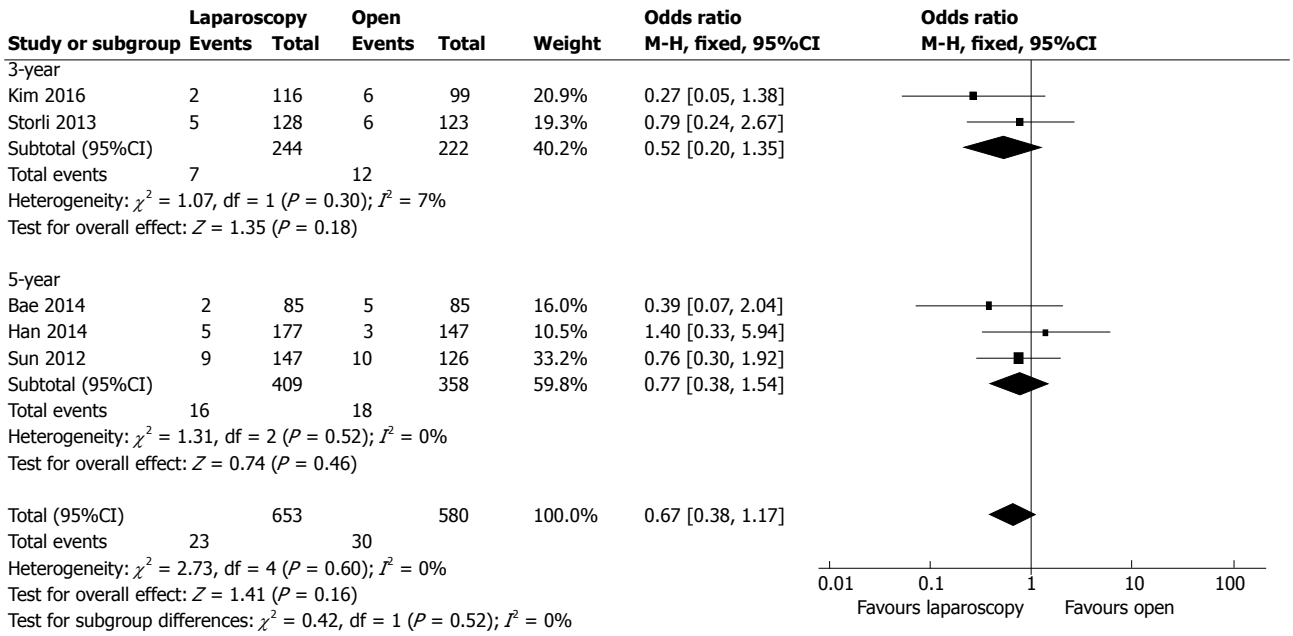

Figure 6 Meta-analysis of studies local recurrence rate of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

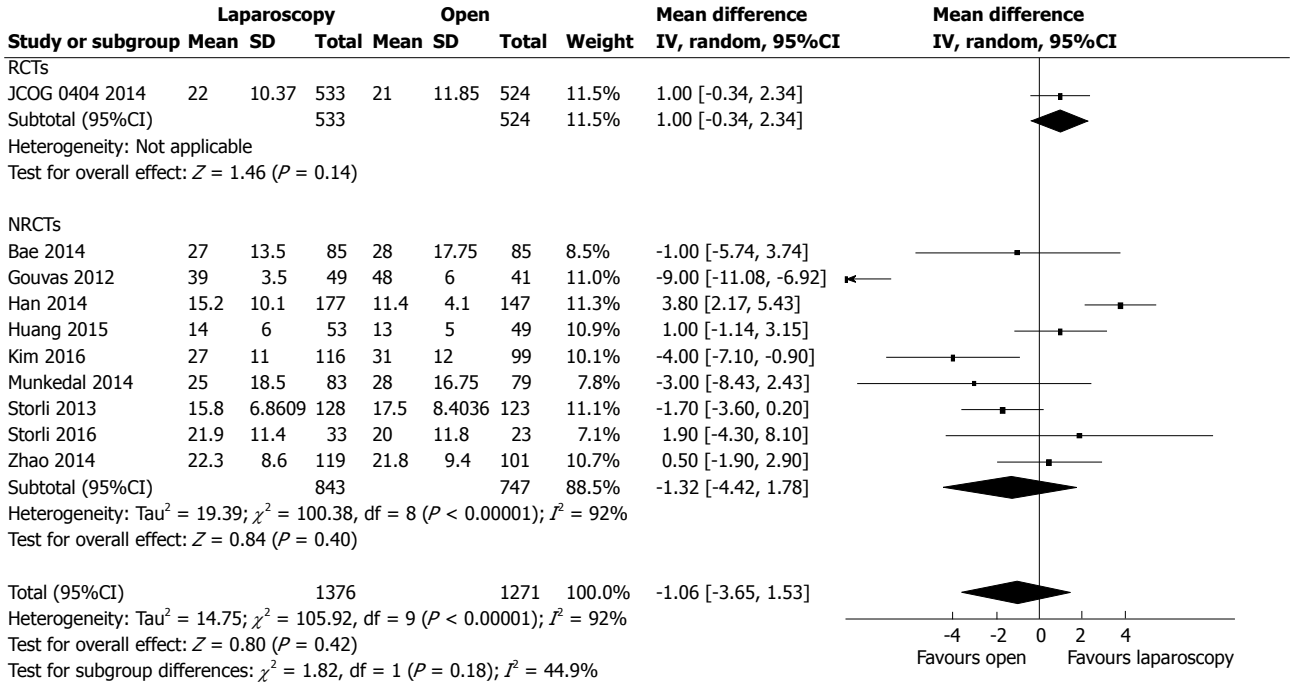

Figure 7 Meta-analysis of studies on lymphnodes retrieved of the specimen of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

O-CME group. Patients from the laparoscopic group had a shorter incision, with a mean difference of 14.01 cm (95%CI: -14.35 to -13.66, $P < 0.001$).

Blood loss

Intraoperative blood-loss data were presented by five studies, with 964 and 904 patients in the L-CME and O-CME, respectively. Due to the high heterogeneity of the data (I^2 = 89%) we have used the random-effect analysis. The laparoscopic approach was associated with statistical significant lower intraoperative bleeding, with a mean difference of 52.11 mL (95%CI: -78.57 to -25.65, $P < 0.001$). Using Egger's test, no publication bias was found (t = 0.17, P = 0.44). Should be noted the clinical significance of lower intraoperative blood loss associated with laparoscopic approach, which was translated in a lower need for transfusion rate (OR = 0.45, 95%CI: 0.27 to 0.75, P = 0.002). Two studies,

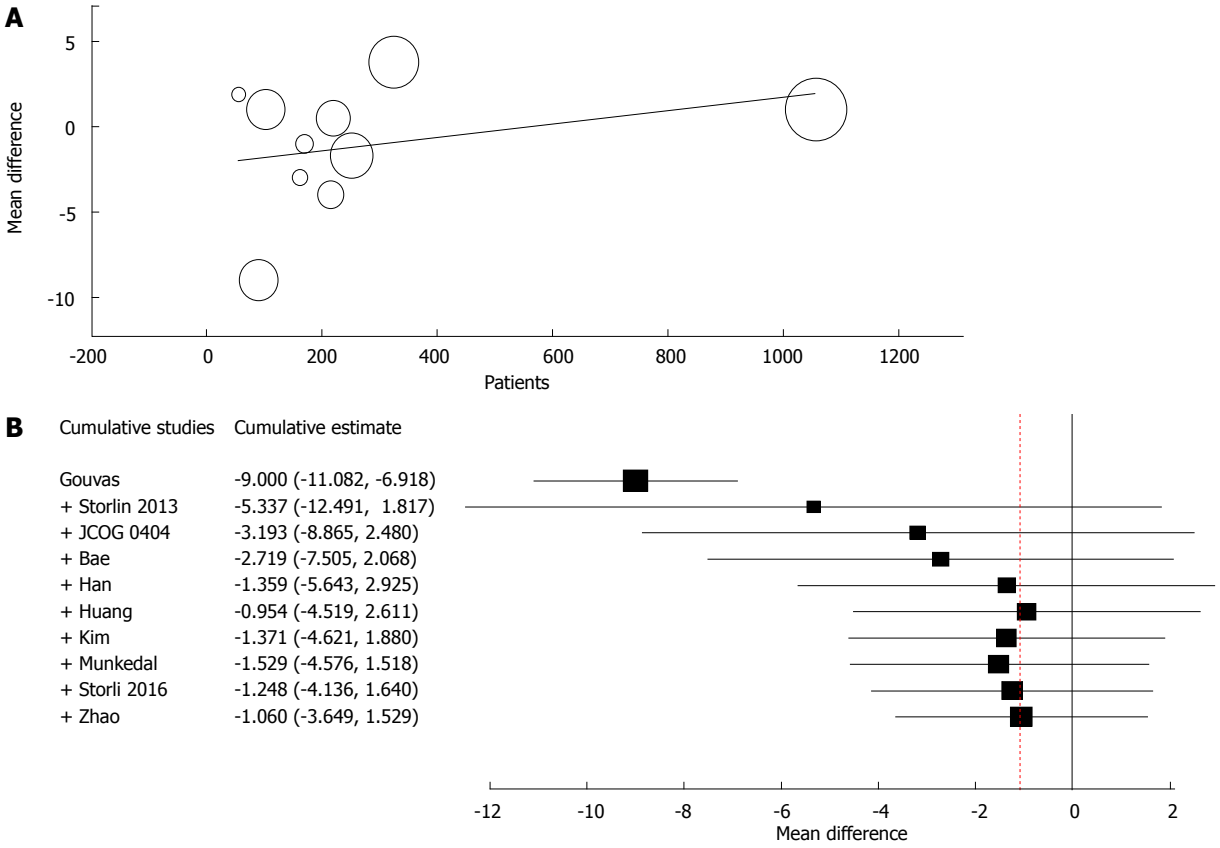

Figure 8 Results of statistical analysis. A: Meta-regression of studies on lymphnodes retrieved of the specimen according to the number of the included patients in each study; B: Cumulative meta-analysis according to the year of publishing of the article of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

	Laparoscopy			Open				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, random, 95%CI**	**IV, random, 95%CI**
NRCTs									
Gouvas 2012	152	30	49	148	21	41	46.0%	4.00 [-6.58, 14.58]	
Munkedal 2014	110	4	83	87	3.5	79	54.0%	23.00 [21.84, 24.16]	
Subtotal (95%CI)			132			120	100.0%	14.26 [-4.30, 32.82]	
Heterogeneity: Tau^2 = 165.76; χ^2 = 12.25, df = 1 (P = 0.0005); I^2 = 92%									
Test for overall effect: Z = 1.51 (P = 0.13)									
Total (95%CI)			132			120	100.0%	14.26 [-4.30, 32.82]	
Heterogeneity: Tau^2 = 165.76; χ^2 = 12.25, df = 1 (P = 0.0005); I^2 = 92%									
Test for overall effect: Z = 1.51 (P = 0.13)									
Test for subgroup differences: Not applicable									

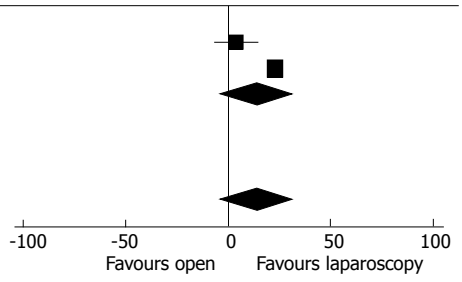

Figure 9 Meta-analysis of studies on tumor to arterial high tie (mm) distance of the specimen of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

	Laparoscopy			Open				Mean difference	Mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, fixed, 95%CI**	**IV, fixed, 95%CI**
NRCTs									
Gouvas 2012	190.6	71.6	49	197.6	190.6	41	0.1%	-7.00 [-68.69, 54.69]	
Munkedal 2014	126.9	7.08	83	115.13	7.49	79	99.9%	11.77 [9.52, 14.02]	
Subtotal (95%CI)			132			120	100.0%	11.75 [9.50, 13.99]	
Heterogeneity: χ^2 = 0.36, df = 1 (P = 0.55); I^2 = 0%									
Test for overall effect: Z = 10.25 (P < 0.00001)									
Total (95%CI)			132			120	100.0%	11.75 [9.50, 13.99]	
Heterogeneity: χ^2 = 0.36, df = 1 (P = 0.55); I^2 = 0%									
Test for overall effect: Z = 10.25 (P < 0.00001)									
Test for subgroup differences: Not applicable									

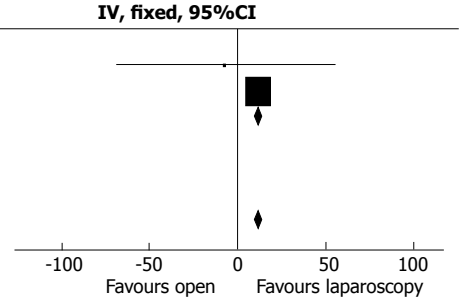

Figure 10 Meta-analysis of studies on resected mesocolon surface (cm^2) of the specimen of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

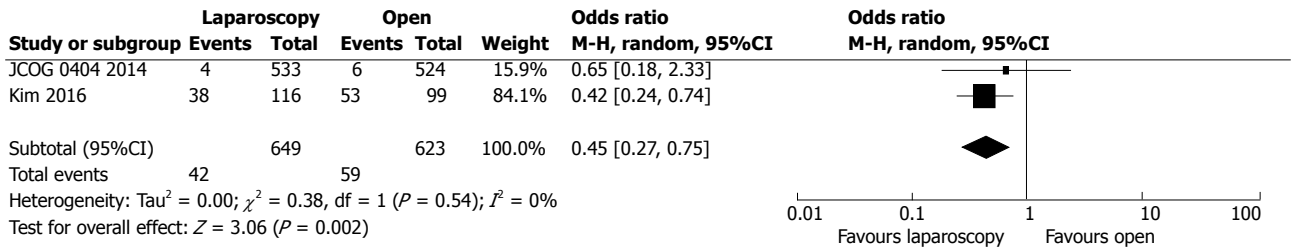

Figure 11 Meta-analysis of studies on transfusion requirements of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

including a total of 1272 patients, reported the need for blood transfusions, with a low heterogeneity between them (I^2 = 0%) (Figure 11).

Recovery of gastrointestinal function

The time to first flatus was reported by four studies, including 914 and 857 patients in the L-CME and O-CME, respectively. In the random-effects meta-analysis the laparoscopic approach was associated with a shorter time interval to first flatus, with a mean difference of 0.90 d (95%CI: -1.46 to -0.34, P = 0.002, I^2 = 97%).

The time to liquid diet was reported by five studies, with a high heterogeneity between them (I^2 = 98%). The time to liquid diet was shorter for the L-CME patients, with a mean difference of 1.84 d (95%CI: -2.93 to -0.74, P = 0.001).

Short-term morbidity and mortality

Seven studies presented the postoperative overall morbidity, and these studies included 1116 patients in the L-CME group and 1028 patients in the O-CME group. There was low statistical heterogeneity among the studies (I^2 = 0%). The L-CME procedure was associated with a lower postoperative morbidity (OR = 0.57, 95%CI: 0.46 to 0.71, P < 0.001) (Figure 12).

Wound complications, reported by eight studies, were significantly less frequent in the L-CME group (OR = 0.43, 95%CI: 0.30 to 0.61, P < 0.001). There was no statistical heterogeneity among the studies (I^2 = 0%).

There was no difference between the two groups regarding postoperative bleeding (OR = 1.20, 95%CI: 0.46 to 3.12, P = 0.71), anastomotic leakage (OR = 0.82, 95%CI: 0.0.54 to 1.25, P = 0.36), need for reoperation (OR = 0.59, 95%CI: 0.28 to 1.23, P = 0.16), and pulmonary complications (OR = 0.61, 95%CI: 0.20 to 1.84, P = 0.38).

The 30-d mortality was reported by six studies with 1158 patients in the L-CME group and 1079 patients in the O-CME group. There was low heterogeneity among the studies (I^2 = 0%). In the fixed-effects meta-analysis we observed no statistically significant difference between the L-CME and O-CME groups (OR = 0.42, 95%CI: 0.16 to 1.12).

Nine studies, with 1340 and 1233 patients in the L-CME and O-CME, respectively reported the hospital stay. There was a high heterogeneity between the studies (I^2 = 91%). In the random-effects meta-analysis we found a statistical significant lower hospital stay for laparoscopic group, with a mean difference of 4.07 d (95%CI: -5.87 to -2.28, P < 0.001).

Risk of bias across studies

We conducted sensitivity analysis to assess statistical heterogeneity based on excluding specific studies with a high risk of bias (Figure 13). There were no relevant changes in the overall effects of the quantitative synthesis. Our analysis of the funnel plots reveals no significant asymmetries for the studied outcomes (Figures 14 and 15).

DISCUSSION

Our meta-analysis revealed that laparoscopic CME with CVL for colon cancer offers the same quality of the resected specimen as the open approach, being superior in all perioperative results and at least non-inferior in long-term oncological outcomes. Although not addressed the complete mesocolic excision or D3 lymphadenectomy technique, the equivalence of laparoscopy in terms of resected lymphnodes was showed in four large, multicenter, studies-Clinical Outcomes of Surgical Therapy (COST), Conventional *vs* Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASSIC), Colon Cancer Laparoscopic or Open Resection I (COLOR I), and the Australasian Randomized Clinic Study Comparing Laparoscopic and Conventional Open Surgical Treatments for Colon Cancer (ALCCaS); the mean number of resected lymph nodes was 10.13 in the laparoscopic group and 10.14 in the open group[40-42]. An RCT from Taiwan comparing open with laparoscopic left-sided D2 resections for stage Ⅱ or Ⅲ colon cancer reported 16 ± 3 dissected lymph nodes in its laparoscopic group and 16 ± 6 in its open group[33]. The long-term oncological outcomes between the L-CME and O-CME groups were also comparable; there were no differences regarding the local and distant recurrence rate, the three- and five-year overall rates and the disease-free survival rates. In our study, the three-year overall and disease-free survival were superior in the laparoscopic group; however, should be noted the extensive experience in laparoscopy of the reporting centers. In Barcelona study, the laparoscopic approach was associated with a slight increase in survival rate, a faster postoperative recovery, and a shorter in-hospital stay duration[38]. In the COLOR

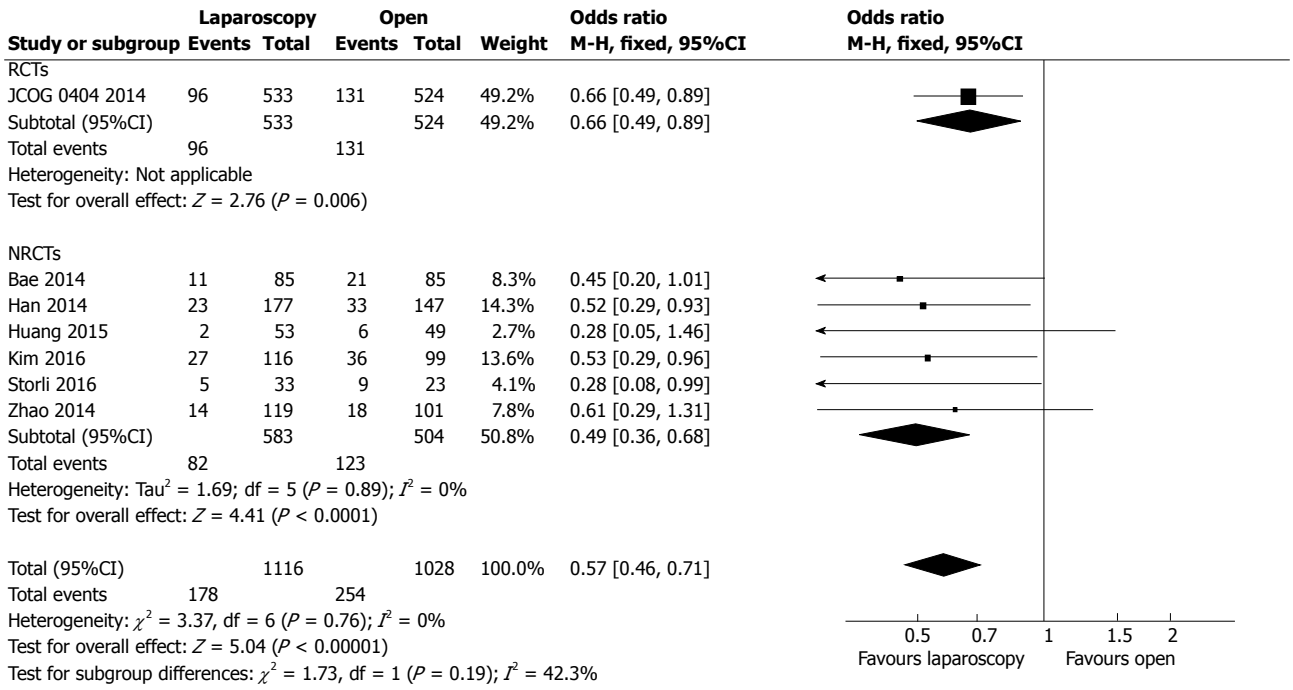

Figure 12 Meta-analysis of studies on postoperative overall morbidity of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

Leave-one-out summary
Continuous random-effects model
Metric: Mean difference
Model results

Studies	Estimate	Lower bound	Upper bound	Std. error	*P*-value
Overall	-1.749	-4.442	0.944	1.374	0.203
Han 2014	-2.462	-5.120	0.196	1.356	0.069
Kim 2016	-1.502	-4.379	1.375	1.468	0.306
Storlin 2013	-1.792	-4.871	1.287	1.571	0.254
Zhao 2014	-2.043	-5.046	0.960	1.532	0.182
JCOG 0404 2014	-2.148	-5.368	1.073	1.643	0.191
Bae 2014	-1.828	-4.694	1.037	1.462	0.211
Gouvas 2012	-0.524	-2.433	1.385	0.974	0.590
Huang 2015	-2.111	-5.139	0.916	1.545	0.172
Munkedal 2014	-1.646	-4.483	1.191	1.447	0.255
Storli 2016	-1.253	-4.011	1.506	1.408	0.373

Figure 13 Leave-one-out meta-analysis for the endpoint number of retrieved lymphnodes of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

study, 1248 patients were randomized for open or laparoscopic colon resection[46]. After a median follow-up of 53 mo, the combined three-year, disease-free survival rate was 74.2% in the laparoscopic group and 76.2% in the open group (P = 0.70). The combined three-year overall survival rate was 81.8% in the laparoscopic group and 84.2% in the open group (P = 0.45). The authors concluded that a difference in the three-year, disease-free survival rate could not be ruled out due to limitations of the study[46]. In the CLASSIC trial, 794 patients with colorectal cancer were randomized for open or laparoscopic resection[47]. An analysis of the subgroup of patients with colon cancer, 140 in the open group and 273 in the laparoscopic group, did not reveal any differences in terms of three-year overall survival rates (P = 0.51). After a median follow-up of 62.9 mo, there were no statistically significant differences in overall survival and disease-free survival rates[48]. In the COST study, 872 patients were randomized to receive an open or laparoscopic colectomy[49]. The 3- and 5-year follow-ups revealed no differences regarding recurrence rate and overall survival rates[49,50].

We found a longer duration of surgery in the laparoscopic group. However, all the perioperative outcomes, such as blood loss, need for transfusion, incision length, wound complications, and thirty-day overall morbidity were less frequent in the laparoscopic group. In the COST, CLASSIC, COLOR I, and ALCCaS trials, the mean duration of surgery was 145-180 compared to 95-135 min, the hospital stay was 5-10 *vs* 6-11 d, the 30-d morbidity was 21%-38% *vs* 20%-45%, and the 30-d mortality was 0.5%-4.0% *vs* 0.7%-5.0% in the

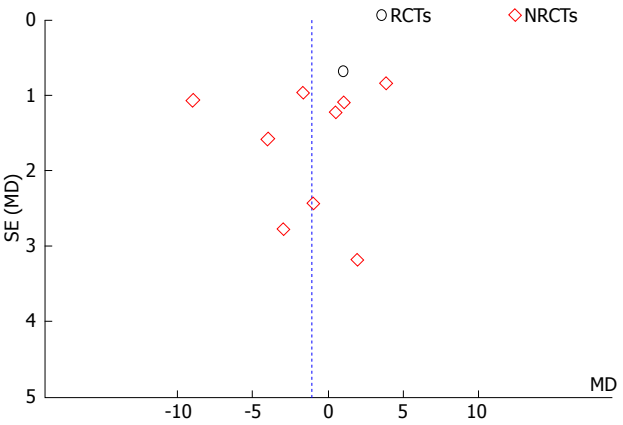

Figure 14 Begg's funnel plot for the endpoint number of retrieved lymphnodes of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer. RCTs: Randomized control trial; NRCTs: Non-randomized clinical studies.

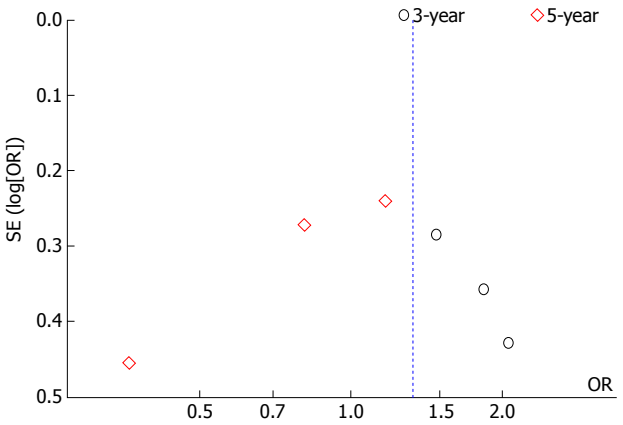

Figure 15 Begg's funnel plot for the endpoint overall survival of patients undergoing laparoscopic *vs* open complete mesocolic excision with central vascular ligation excision for colon cancer.

laparoscopic and open groups, respectively[40-42,49]. Liang *et al*[33] found a longer operative time for left-sided resections (224.4 ± 44.8 min *vs* 184.0 ± 30.6 min), less blood loss (54 ± 12 mL *vs* 240 ± 34 mL), a shorter wound incision (10.6 ± 1.6 cm *vs* 18 ± 3.1 cm) for the laparoscopic approach, but there were no statistically significant differences regarding total postoperative complications (20 *vs* 29, $P = 0.15$).

Our meta-analysis showed that patients from the laparoscopic group had a shorter hospital stay and a shorter recovery time to regain gastrointestinal function. This result is consistent with the current evidence that supported earlier recovery of bowel functioning and oral diet with an in-hospital stay duration 1.7 d shorter in the laparoscopic group[51]. The studies included in the current meta-analysis did not evaluate how surgery affected immune functioning. According to Liang *et al*[33], the postoperative proinflammatory response, evaluated by C-reactive protein and the erythrocyte sedimentation rate and postoperative immunosuppression and assessed by alteration of lymphocyte counts and the $CD4^+$/$CD8^+$ ratio, was significantly less in the laparoscopic group ($P < 0.001$).

An important concern regarding laparoscopic colon surgery is the reproducibility of results given the nature of multicenter, specialized centers and the heterogeneity of general surgeons. All surgical procedures from the studies included in this meta-analysis were performed by highly experienced or accredited surgeons. An analysis of the short-term outcomes of colon and rectal laparoscopic resections in Sydney South West Area Health Service revealed a lower morbidity (28.8% *vs* 54.4%, $P < 0.001$), fewer transfusions (0.4 units *vs* 0.7 units, $P = 0.0028$), a longer operative time (24.1 min, $P < 0.0001$) and a shorter length of stay (7 *vs* 10 d, $P = 0.0011$) for laparoscopic procedures[52]. Dobbins *et al*[53] published the results of laparoscopic resections for colon and rectal cancer from all of the public and private hospitals in New South Wales, Australia. The laparoscopic colon resections were associated with a reduced rate of extended stay (OR = 0.60, 95%CI: 0.49-0.72) and 28-d readmissions (OR = 0.86, 95%CI: 0.74-0.99). Survival benefits for laparoscopy, regarding cancer-specific survival, were observed in higher-caseload hospitals but not in lower-caseload hospitals[53].

The current meta-analysis has as a main limitation the clinical heterogeneity of the included studies, and caution should be exercised when interpreting its results. This meta-analysis involves several types of study designs, including retrospective, prospective, and RCT. There is an increased heterogeneity of the tumor localization on the colon, with the transverse colon cancers being excluded from the analysis in two studies, while the others included them into the right/extended right hemicolectomy group. Excepting the one randomized controlled trial, the experience in minimally invasive surgery of the surgeons from the laparoscopic group is not quantified, although all procedures were performed or supervised by trained colorectal surgeons. However, using random-effects meta-analysis, with subgroup analysis and meta-regression, we limited the variance of the included outcomes.

In summary, the current data suggest that the laparoscopic approach offers the same quality of resected specimens as the open approach in CME with CVL for colon cancer while maintaining all of the short-term benefits of a minimally invasive approach. Although a specimen-oriented surgical dissection in colon cancer *via* a laparoscopic approach is challenging, the magnification and predisposition to details of a minimally invasive technique are associated with a lower postoperative morbidity.

COMMENTS

Background

Complete mesocolic excision with central vascular ligation represents an extension to the colonic cancer of the already standardized resection for rectal cancer. It adheres to the same guiding principle that sharp surgical dissection, following embryological planes, with central vascular ligation, should improve oncological outcomes. The technical details of this new concept were published in 2007.

Research frontiers

A high-level evidence that laparoscopic approach offers the same quality of the resected specimen as open surgery for complete mesocolic excision with central vascular ligation for colon cancer is lacking.

Innovations and breakthroughs

Current evidence is consistent with a faster postoperative recovery for laparoscopic colectomies compared with the open approach; the former is not associated with any negative impact regarding local recurrence and survival rates. This study reveals that laparoscopy offers the same quality of the resected specimen as the open approach in complete mesocolic excision with central vascular ligation for colon cancer. The laparoscopic complete mesocolic excision with central vascular ligation is superior in all perioperative results and at least non-inferior in long-term oncological outcomes.

Applications

Due to all advantages of laparoscopy, the teaching and mentoring of minimally invasive techniques for colon resections should be accentuated, in order to increase the proportion of laparoscopic over open procedures.

Terminology

During complete mesocolic excision with central vascular ligation for right-sided tumors, the ileocolic and right colic vessels should be ligated at their origin from the superior mesenteric artery, medial (patient left-hand side) to the superior mesenteric vein. Transverse colon tumors require transection of the middle colic artery at its origin. Left-sided tumors require transection of the inferior mesenteric artery at its origin from the aorta.

Peer-review

This is an interesting meta-analysis and review of a highly debatable topic in surgery, the consensus about laparoscopic *vs* open surgery in high ligation.

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P- Reviewer: Horesh N, Gurkan A **S- Editor**: Cui LJ **L- Editor**: A
E- Editor: Lu YJ

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2017 December 15; 9(12): 492-496

DOI: 10.4251/wjgo.v9.i12.492

ISSN 1948-5204 (online)

CASE REPORT

Cystic metastasis from a mucinous adenocarcinoma of duodenum mimicking type Ⅱ choledochal cyst: A case report

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Author contributions: Kim YN and Song JS wrote the manuscript; Kim YN performed the pathological examination; Song JS edited the manuscript.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Chonbuk National University Hospital.

Informed consent statement: The study was performed after obtaining the patient's informed consent. The patient was treated according to the provisions of the Helsinki criteria.

Conflict-of-interest statement: Kim YN and Song JS declare no conflicts of interests.

Manuscript source: Unsolicited Manuscript

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Received: August 11, 2017
Peer-review started: August 12, 2017
First decision: August 30, 2017
Revised: August 31, 2017
Accepted: September 14, 2017
Article in press: September 14, 2017
Published online: December 15, 2017

Abstract

A 51-year-old male patient was referred to our hospital because of an incidentally detected cystic mass near the common bile duct (CBD). Imaging studies demonstrated a cystic mass that was suspected to communicate with the CBD. Gastroscopy showed irregular mucosal thickening with hyperemic change in the second portion of the duodenum. A type Ⅱ choledochal cyst combined with duodenal malignancy was suspected. The patient underwent surgical resection and the histological diagnosis was mucinous adenocarcinoma of the duodenum with cystic metastasis. Although its incidence is extremely rare, care should be taken to check for other sites of malignancy when a pericholedochal cystic mass is detected.

Key words: Duodenal cancer; Choledochal cyst; Cystic metastasis; Mucinous adenocarcinoma

Core tip: Mucinous adenocarcinoma is very rare in the

duodenum, and a cystic metastasis from mucinous adenocarcinoma of duodenum has never been reported. This is the first report of primary mucinous adenocarcinoma of duodenum with cystic metastasis. Although rare, careful evaluation with a high suspicion for other sites of malignancy is needed when a pericholedochal cystic mass is detected.

Kim YN, Song JS. Cystic metastasis from a mucinous adenocarcinoma of duodenum mimicking type Ⅱ choledochal cyst: A case report. *World J Gastrointest Oncol* 2017; 9(12): 492-496 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/492.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.492

INTRODUCTION

The small intestine is the longest gastrointestinal (GI) tract organ, reaching six to seven meters in average length. Despite its length and the large mucosal surface area of the small intestine, only 5% of malignant neoplasms of the GI tract occur in the small intestine[1]. Among them, primary adenocarcinoma of the duodenum represents approximately 25%-52% of malignant neoplasms of the small intestine and 4.6% were mucinous adenocarcinoma[2]. Choledochal cysts are rare, congenital dilatation of the extrahepatic or intrahepatic biliary tree. Among them, type Ⅱ choledochal cyst, a diverticulum of the common bile duct (CBD), is the rarest type. Here, we present a case of mucinous adenocarcinoma of the duodenum with cystic metastasis, which is extremely rare and was initially misinterpreted as a type Ⅱ choledochal cyst.

CASE REPORT

A 51-year-old male patient visited a local hospital because of dyspepsia and epigastric pain. Ultrasonography revealed a 4.5 cm sized cystic mass near the CBD and pancreatic head (Figure 1A). He was transferred to our hospital for further evaluation of the cystic mass. His medical history and laboratory findings were unremarkable. Tumor markers such as alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9 were within normal limits. Contrast-enhanced abdominal computed tomography (CT) showed a homogeneous low-density cystic mass with thin, smooth walls next to the CBD, and there were suspicions of a communication between the two structures (Figure 1B). Under the impression that the lesion was a type Ⅱ choledochal cyst, which is a discrete diverticulum of the extrahepatic bile duct, magnetic resonance (MR) imaging and endoscopic ultrasound (EUS) were done. The cystic mass showed low signal intensity on the T1-weighted MR image and high SI on the T2-weighted MR image with nearly imperceptible walls and there was no evidence of an enhancing solid portion in the cyst (Figure 1C). EUS also revealed a 4.5 cm sized cystic mass which seemed to be connected with the CBD, and gastroscopy showed irregular mucosal thickening with hyperemic change in the second portion of the duodenum (Figure 1D). Based on these findings, the patient underwent Whipple's operation under the impression the lesion was a type Ⅱ choledochal cyst with extrinsic compression of the duodenum, and the possibility of combined duodenal malignancy due to the mucosal lesion in the duodenum. An examination of the resected specimen revealed a duodenal cancer in the second portion of the duodenum 2.5 cm proximal to the ampulla of Vater, and the cystic mass did not show communication with the CBD (Figure 2A and B). The histological diagnosis was mucinous adenocarcinoma of the duodenum with cystic metastasis and subpyloric lymph node metastasis (Figure 2C and D). The postoperative course of the patient was uneventful. The patient was disease-free 12 mo after the initial diagnosis. However, the patient died 18 mo after the recurrence.

DISCUSSION

We initially suspected a type Ⅱ choledochal cyst combined with duodenal malignancy due to the mucosal lesion in the duodenum and the gastroscopic biopsy revealed a moderate degree of dysplasia. All of the imaging studies showed a well-marginated, homogeneously thin-walled cyst adjacent to the CBD which is regarded as a diverticulum of the extrahepatic bile duct, and the duodenal lesion was invisible. Since surgical resection is generally considered for the treatment of choledochal cysts, the patient underwent Whipple's operation, and the patient was confirmed to have mucinous adenocarcinoma of the duodenum with cystic metastasis and subpyloric lymph node metastasis.

Mucinous adenocarcinoma is one of the histologic subtypes of carcinoma and is very rare in the duodenum. A recent study from South Korea by Chang *et al*[3]. revealed that 54.8% of small intestinal carcinomas were located in the duodenum and 4.6% were mucinous adenocarcinoma. Due to its rarity, to the best of our knowledge, this is the first case report of primary mucinous adenocarcinoma of duodenum with cystic metastasis. Although there are several studies in the literature describing the imaging findings of small bowel carcinoma including duodenal carcinoma[3-6], there are no previous reports reporting the imaging findings of mucinous adenocarcinoma of the duodenum. According to previous studies, duodenal cancer typically appears as an irregular thickening of the duodenal wall with regional lymph node enlargement on CT. Since the duodenal lesion of our patient was flat and small (2.0 cm), the primary lesion in the second portion of the duodenum and metastatic lymph node in the subpyloric area were missed on initial imaging studies including CT and magnetic resonance imaging (MRI). In a retrospective review of CT and MRI, the metastatic lymph node in the subpyloric area was identified. However, the primary lesion was invisible.

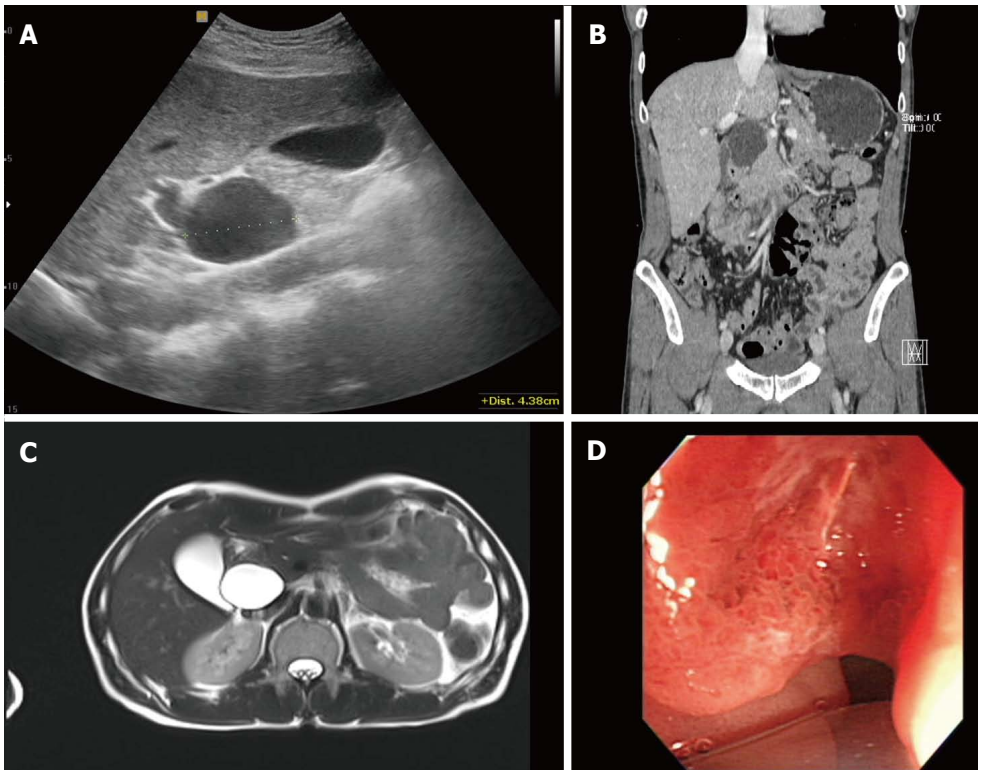

Figure 1 Evaluation of clinical findings. A: Ultrasonography of upper abdomen shows a 4.5 cm sized anechoic cystic mass adjacent to the head of the pancreas and common bile duct; B: Coronal multiplanar reformatted image of contrast-enhanced abdominal computed tomograph shows a homogeneous low-density cystic mass with thin, smooth walls abutting the common bile duct, with possible communication between the two structures; C: Axial T2-weighted magnetic resonance image demonstrates the cystic mass as a homogeneously high signal intensity lesion with thin walls, and there was no evidence of mural nodularity in the cystic mass; D: Endoscopic image of the duodenum shows irregular mucosal thickening with hyperemic change in the second portion of the duodenum.

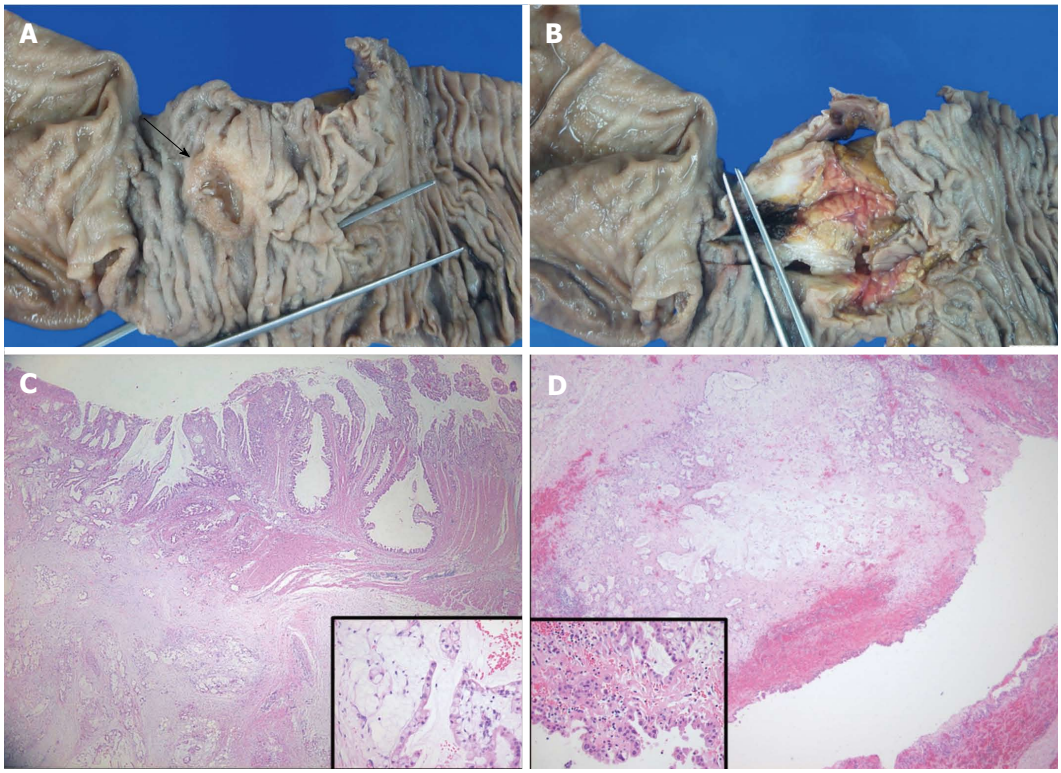

Figure 2 Gross specimen and pathological findings. A: The ulcerofungating mass measuring 2.4 cm × 2.0 cm (arrow), 2.5 cm distant from the ampulla of vater, is observed in the duodenum; B: The cut surface reveals a grey-white mass that abuts the head of the pancreas; C: Histologically, the duodenal mass proved to be an infiltrative adenocarcinoma with subserosal invasion, note the abundant extracellular mucin with floating neoplastic epithelium (Inset); D: Photomicrograph of the cystic mass shows invasive tumor cells in the lining of the cyst and the surrounding soft tissue which is a definite malignant feature (Inset).

Choledochal cysts are a rare congenital anomaly of the intrahepatic or extrahepatic biliary tree and is known to occur in 1 in 100000 to 1 in 150000 live births[7]. Choledochal cysts occur more frequently in Asian populations, with more than two-thirds of all reported cases originating in Asia. Traditionally, choledochal cysts presented predominantly in young age with the triad of abdominal pain, palpable right upper quadrant mass, and intermittent jaundice. Nonetheless, recent analyses show increasing numbers of adults presenting with choledochal cysts[8]. According to Todani's classification, choledochal cyst can be divided into 5 types: Type Ⅰ, a cystic or fusiform dilatation of the CBD, which is subdivided into saccular, segmental, and diffuse types; type Ⅱ, a diverticulum arising from the CBD; type Ⅲ, choledochocele or a bulbous dilation of the terminal CBD within the ampulla of Vater; type Ⅳ, multiple intrahepatic and extrahepatic cysts; and type Ⅴ, intrahepatic bile duct cysts or Caroli disease[9]. Among them, type Ⅱ cysts are the most rare form of choledochal cysts, usually making up less than 2%-5% of cases[10]. They usually manifest as a pericholedochal cystic mass, of various shapes, some being gallbladder-like, and others being diverticulum-like. Choledochal cysts have been associated with an approximately 20 to 50-fold increase in biliary malignancies when compared with the general population[11]. The risk of malignancy in type Ⅱ choledochal cysts has been estimated to range from 7%-9%, which is a slightly lower than the risk for other types of choledochal cysts (14.3% in the third decade)[12]. Current recommendations for management of choledochal cysts is surgical resection regardless of cyst type, including hepaticojejunostomy, Whipple procedure, partial liver resection, or liver transplantation[13].

In conclusion, we have described the first case of a mucinous adenocarcinoma of the duodenum with cystic metastasis. Even though the incidence of this particular type of cancer is extremely low, careful evaluation with a high suspicion for other sites of malignancy must be done when a pericholedochal cystic mass is detected incidentally.

ARTICLE HIGHLENGTHS

Case characteristics

A 51-year-old male patient was admitted because of incidentally detected cystic mass near the common bile duct (CBD).

Clinical diagnosis

About 4.5 cm sized cystic mass near the CBD, with irregular mucosal thickening in the second portion of the duodenum.

Differential diagnosis

Type Ⅱ choledochal cyst combined with duodenal malignancy.

Laboratory diagnosis

Laboratory findings were unremarkable, including tumor markers such as alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9.

Imaging diagnosis

Findings from gastroscopy, ultrasonography, computed tomograph, and magnetic resonance imaging led to a diagnosis of type Ⅱ choledochal cyst with extrinsic compression of the duodenum, and the possibility of combined duodenal malignancy.

Pathological diagnosis

Mucinous adenocarcinoma of the duodenum with cystic metastasis and subpyloric lymph node metastasis.

Treatment

Whipple's operation.

Related reports

Mucinous adenocarcinoma of the duodenum is very rare, and this is the first case report of primary mucinous adenocarcinoma of duodenum with cystic metastasis.

Experiences and lessons

Although rare, careful evaluation with a high suspicion for other sites of malignancy is needed when a pericholedochal cystic mass is detected.

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P- Reviewer: Agrawal S, Espinel J, Sitarz R **S- Editor**: Chen K
L- Editor: A **E- Editor**: Lu YJ

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2017 December 15; 9(12): 497-501

DOI: 10.4251/wjgo.v9.i12.497

ISSN 1948-5204 (online)

CASE REPORT

Extrapancreatic solid pseudopapillary neoplasm followed by multiple metastases: Case report

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Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

Informed consent statement: Patients were not required to give informed consent to the study because the participant is deceased.

Conflict-of-interest statement: We have no pertinent financial relationships to disclose.

Manuscript source: Unsolicited manuscript

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Received: June 24, 2017
Peer-review started: June 26, 2017
First decision: August 7, 2017
Revised: August 24, 2017
Accepted: November 3, 2017
Article in press: November 3, 2017
Published online: December 15, 2017

Abstract

Solid pseudopapillary neoplasm (SPN), also known as Gruber-Frantz tumor, is a rare form of neoplasm that almost exclusively occurs in the pancreas and in young females. While the potential of malignancy is low for SPN, these tumors can mimic other diseases and require a meticulous investigation and a standard treatment by total surgical resection. We present an unusual case of SPN arising in the mesentery of a 40-year-old man with subsequent multiple metastases. Histopathological examination showed similar properties of the mesenteric neoplasm to those of SPN in pancreas. Although the mass was surgically removed, the patient died of recurrent disease 4 years after the initial presentation. We speculate that SPN originates from pancreatic progenitor cells. Further histopathological analyses are required for the prediction of SPN recurrence after resection.

Key words: Solid pseudopapillary neoplasm; Mesentery; Metastasis

Core tip: Solid pseudopapillary neoplasm (SPN) has been recognized by World Health Organization since 2010, and classified as a low malignant potential neoplasm. Such neoplasm is characterized by the presence of a mutation in the gene that encodes β-catenin. β-catenin is an important factor in the Wnt signaling pathway (β-catenin-dependent Wnt signaling). The identification of extrapancreatic SPN, especially in the mesentery, indicates a possible endoderm link between pancreatic progenitor cells and SPN cells.

Wu H, Huang YF, Liu XH, Xu MH. Extrapancreatic solid pseudopapillary neoplasm followed by multiple metastases: Case

report. *World J Gastrointest Oncol* 2017; 9(12): 497-501 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/497.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.497

INTRODUCTION

Solid pseudopapillary neoplasm (SPN) is a rare and indolent type of neoplasm that occurs in pancreas; SPN forms 0.3% to 2.7% of all pancreatic exocrine tumors. A large body of SPN indices are found in young female patients, and well-circumscribed. A margin negative surgical resection shows curative result in majority of cases[1-3]; recurrence after surgical resection is reported in 2% to 10% of patients[4,5]. Patients with unresectable SPN may have a long-term survival (5 years), and require complex chemo- and radio-therapy treatments; the efficacy of adjuvant therapies in the SPN treatment remains largely unknown and a clinical challenge. Thus, it is important to differentiate the risk of recurrence in SPN patients. An extrapancreatic development of SPN is a rare incident; only 16 cases of extrapancreatic SPN have been reported so far worldwide (Table 1). In the present article, we report a patient, in whom SPN was found in the mesentery; no invasion or attachments to adjacent organs was observed. To the best of our knowledge, this article is the first to report a SPN case in the mesentery.

CASE REPORT

A 40-year-old Chinese male came to hospital on November 15, 2012. His main complaint was abdominal distention that lasted over 6 mo. His physical examination revealed a 30 cm soft mass in the abdomen. An abdominal computed tomography (CT) scan exhibited solid and mixed cystic lesions, measuring > 28 cm diameter (Figure 1). Patient's blood test results were unremarkable. On November 22, 2012, the patient underwent an exploratory laparotomy, and the tumor protruding from the mesentery was completely excised. At that time, no invasion or attachments to adjacent organs was observed. In addition, the postoperative course was uneventful. The resected specimen of the mesenteric tumor was 25 cm × 15 cm × 28 cm, and showed a multilobulated structure with rich microvasculature. Microscopic characterization of the tumor showed that the tumor formation was a mix of solid and pseudopapillary areas. There was no evidence of pancreatic tissue in the analyzed sample. Further, the specimen was positive for alpha-1-antitrypsin, vimentin, CD56 and β-catenin immunostaining, whereas negative for S-100, neuron-specific enolase, E-cadherin, calretinin, progesterone receptor, chromogranin, and pancytokeration (Figure 2). Such results led to the diagnosis of SPN in the mesentery. Following 3.5 years, the patient continued to complain about abdominal distention and occasional polypnea. An abdominal CT scan exhibited multiple tumors in peritoneum, greater omentum, and colonic wall (Figure 3). Meanwhile, cells in the pleural effusion were found positive for alpha-1-antitrypsin, vimentin, CD56 and β-catenin. It was clear that the patient was suffering from recurrence of the disease. Before the surgical operation to clean the recurrent tumors, the patient received the treatment of 60 mg cisplatin by hyperthermic intraperitoneal chemotherapy (HIPEC). Unfortunately, there was no response to the treatment, and the patient was transferred to the palliative care unit. Soon after the patient's physical conditions worsened, we lost the patient on November 2016, 4 years after the initial surgery.

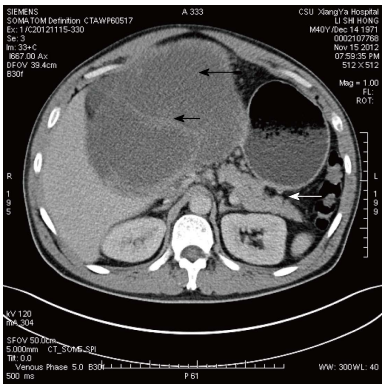

Figure 1 An abdominal computed tomography scan exhibited solid and mixed cystic lesions, measuring > 28 cm diameter (black arrow). The tumor was apart from the pancreas (white arrow).

DISCUSSION

SPN has been recognized by the WHO classification as a low malignant potential neoplasm in 2010[3]. It was first named as Gruber-Frantz tumor and after that it had been called the pancreatic solid papillary epithelial neoplasm, pancreatic papillary cystic neoplasm, pancreatic solid cystic tumor and solid pseudopapillary tumor. The differential diagnosis of SPN may include: pseudocyst, pancreatic mucinous neoplasms, well-differentiated ductal adenocarcinoma, pancreatic endocrine neoplasm, and acinic cell carcinoma. The pathogenesis of SPN remains unclear. Likewise, genetic events that contribute to the development of SPN are yet to be discovered. There are two basic proposals for the SPN origin: (1) genital ridge-related cells and (2) pancreatic progenitor cells[1,6]. To note, an important proportion of SPN cases show mutations in the somatic β-catenin coding gene (*CTNNB1*)[7-9]. Such mutations can affect Wnt signaling pathways as well as self-renewal capability of stem cells[10]. SPN cells were reported to be positive for β-catenin, vimentin, alpha-1-anti-trypsin, CD10, CD56, and progesterone receptors by immunohistochemical analysis[11]; however this staining pattern fails to reveal a clear phenotypic relationship between SPN and any of the defined cell lineages of the pancreas. Thereby, it can be speculated as SPN cells show multipotential differentiation. According to the study concerned with the embryonic development of the human pancreas, dorsal and ventral pancreatic buds were reported to proliferate

Table 1 Review of extra-pancreatic solid pseudopapillary neoplasm

Ref.	Age	Sex	Location	Size (cm)	Procedure	Follow-up
Miyazaki *et al*[19]	22	F	Retroperitoneum	7	Laparoscopy	6 mo NED
Hibi *et al*[20]	45	M	Omentum	15	Laparoscopy	96 mo DOD
Deshpande *et al*[21]	17	F	Left ovary	25.5	Open surgery	72 mo NED
	57	F	Right ovary	3	Open surgery	NA
	21	F	Left ovary	14	Open surgery	NA
He *et al*[22]	39	F	Right ovary	6	Laparoscopy	36 mo NED
Fukunaga *et al*[23]	46	F	Omentum	5	Laparoscopy	3 mo NED
Ishikawa *et al*[24]	13	F	Mesocolon	4	Open surgery	36 mo NED
Guo *et al*[25]	47	F	Retroperitoneum	16	Open surgery	14 mo NED
Geng *et al*[26]	37	F	Retroperitoneum	8	Open surgery	NA
Zhu *et al*[27]	22	F	Retroperitoneum	6	Laparoscopy	14 mo NED
Chen *et al*[28]	47	F	Left ovary	6	Open surgery	18 mo NED
Cheuk *et al*[29]	25	F	Right ovary	16.5	Open surgery	144 mo NED
Walter *et al*[30]	32	F	Stomach	10	Open surgery	24 mo LWD
	73	M	Duodenum	14	Open surgery	3 mo DOD
Stoll *et al*[31]	48	F	Left ovary	8	Open surgery	9 mo NED
Present case	40	M	Mesentery	28	Open surgery	48 mo DOD

NED: No evidence of disease; DOD: Dead of disease; LWD: Live with disease; NA: Not available; F: Female; M: Male.

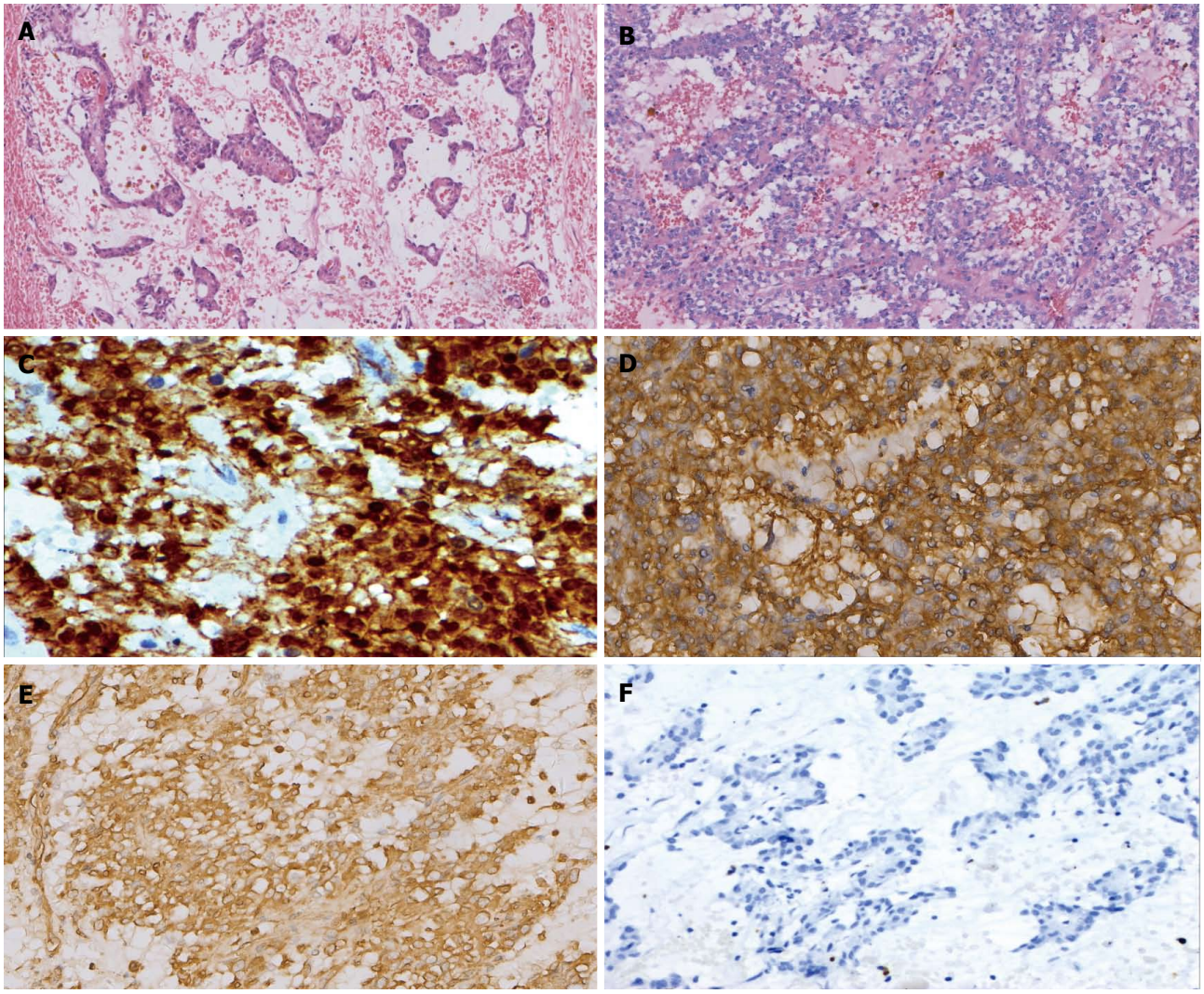

Figure 2 Histological and immunohistochemical findings of the tumor (× 200). The tumor cells are arranged in solid sheets, pseudopapillary and microcysts (A and B: Hematoxylin-eosin stain), and are immunohistochemically positive for alpha-1-antitrypsin (C), β-catenin (D: Cytoplasmic and nuclear staining), CD56 (E), whereas negative for chromogranin (F).

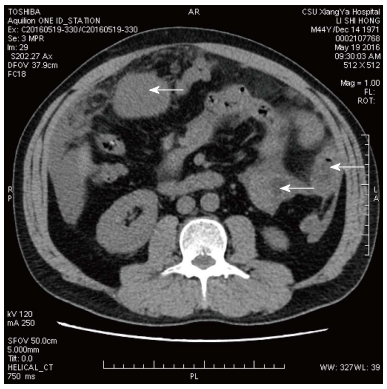

Figure 3 An abdominal computed tomography scan exhibited multiple tumors in peritoneum, greater omentum, and colonic wall (white arrow).

from gut epithelium of endoderm during the 4th week of gestation. Dorsal pancreas fuses with ventral pancreas at the 7th week of gestation due to the rotation of the stomach and duodenum development[12]. Identification of extrapancreatic SPN in the ovary, retroperitoneum and the omentum, as listed in Table 1, indicates a possible endoderm link, substantiated by the migration of pancreas during embryogenesis. We therefore believe that extrapancreatic SPN originates from pancreatic progenitor cells.

In SPN patients, tumor resection confers an 8 year survival rate in 85% of cases; nevertheless, local recurrence or distant metastases can occur in some patients[13]. Histological and clinical parameters for prediction of disease recurrence after the initial surgical operation remain a challenge as there is still no consensus in the medical community. Many clinicians and researchers have been working to determine such criteria. For example, Kang *et al*[14] listed: (1) a tumor size larger than 8 cm; (2) cellular atypia; (3) vascular invasion; (4) perineural invasion; (5) systemic metastasis; and (6) peritoneal seeding as significant prognostic factors for tumor recurrence in a multicenter study. A case series study conducted by Yang *et al*[15] showed that vascular invasion, extra-pancreatic invasion, lymph node metastasis, and Ki-67 index $\geqslant$ 4% are associated with SPN recurrence. It is important to note that a rupture of the tumor or laparoscopic biopsy may seed the tumor cells into the peritoneal cavity, and could be an etiological factor responsible for the peritoneal recurrence[16]. Nonetheless, a recurrence prediction scoring model require more investigation. Such model will help clinicians to distinguish a high-risk group from low-risk group. Likewise, there is still no consensus on the treatment strategy in patients with SPN recurrence. A previous report described a 35 years old woman relapsing 8 mo after the resection of an SPN, which ruptured preoperatively. The patient firstly underwent a complete cytoreductive surgery, but relapsed within 8 mo, and received another cytoreductive surgery combined with HIPEC (oxaliplatin and irinotecan). At 31 mo of follow-up, the patient showed no evidence of disease recurrence[17]. Thus, a complete cytoreductive surgery combined with HIPEC stands as an important treatment solution for high-risk group of SPN. Further, another report concluded that SPN are radiosensitive, and can be successfully treated by using radiation therapy[18]. Future clinical and molecular studies are required to provide more precise tools to predict the biological behavior of SPN.

ARTICLE HIGHLIGHTS

Case characteristics
Abdominal distension.

Clinical diagnosis
Abdominal mass.

Differential diagnosis
Pancreatic mucinous neoplasms.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Mesenchymal neoplasm.

Pathological diagnosis
Solid pseudopapillary neoplasm (SPN).

Treatment
Complete cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.

Related reports
Grading and staging play an important role in treatment and prognosis.

Term explanation
SPN: Solid pseudopapillary neoplasm.

Experiences and lessons
Future clinical and molecular studies are required to provide more precise tools to predict the biological behavior of SPN.

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P- Reviewer: Ikura Y, Lin J, Ramia JM, Şendur MAN **S- Editor**: Ji FF
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