ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2018 November 15; 10(11): 367-464

Published by Baishideng Publishing Group Inc

WJGO World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 10 Number 11 November 15, 2018

Contents

World Journal of Gastrointestinal Oncology
Volume 10 Number 11 November 15, 2018

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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
Baishideng Publishing Group Inc

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PUBLICATION DATE
November 15, 2018

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World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 November 15; 10(11): 367-369

DOI: 10.4251/wjgo.v10.i11.367

ISSN 1948-5204 (online)

EDITORIAL

Upgraded role of autophagy in colorectal carcinomas

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Author contributions: All authors participated in the writing and editing of the manuscript.

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

Manuscript source: Invited Manuscript

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Received: July 3, 2018
Peer-review started: July 3, 2018
First decision: July 19, 2018
Revised: August 1, 2018
Accepted: October 9, 2018
Article in press: October 9, 2018
Published online: November 15, 2018

Abstract

Autophagy is a basic catabolic process closely associated with degradation of cellular components. The role of autophagy in colorectal cancer (CRC) remains controversial. The mechanism of autophagy has been identified as protecting mechanism against tumorigenesis by isolation of damaged organelles or as cytoprotective provides energy in hypoxic regions of CRC tumors. Mutations in proto-oncogenes, such as *RAS* and *BRAF*, have been associated with autophagy initiation through signaling pathways of BRAF/MEK/ERK and PI3K/AKT/mTOR. A combination therapy of chemotherapeutic agents and autophagy inhibitors such as hydroxychloroquine or immunotherapy might represent a major step that could be evaluated as a putative novel therapeutic strategy in CRC patients.

Key words: Autophagy; Tumorigenesis; Clinical trials; Autophagy inhibitors; Colorectal cancer

Core tip: The significant role of autophagy in maintaining the balance of tumorigenesis and cancer cell death remains controversial. The last decade grown body of evidence support the notion that autophagy is a promising target for many malignant tumors, including colorectal cancer (CRC). A novel therapeutic approach which could involve autophagy inhibitors or immunotherapy plus chemotherapeutic drugs could open a new field for treating patients with CRC.

Koustas E, Sarantis P, Papavassiliou AG, Karamouzis MV. Upgraded role of autophagy in colorectal carcinomas. *World J Gastrointest Oncol* 2018; 10(11): 367-369 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/367.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.367

INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies leading to many cancer-related deaths worldwide. Some patients are initially diagnosed with metastatic CRC (mCRC), while 20% of CRC patients will eventually develop metastases, thus emphasizing the importance of novel effective treatment options[1].

Many studies have shown that CRC is closely associated with the cytoprotective mechanism of autophagy, a self-digesting process in cells. The last decade, many studies have identified and characterized autophagy as an important mechanism in mammalian systems, in healthy state and during carcinogenesis[2]. Cancer cells have the ability to use autophagy mechanism in trafficking of many oncogenic factors, such as chemotactic, pro-invasive or pro-inflammatory molecules and/or angiogenic molecules. Malignant tumors that use autophagy have the ability to change their microenvironment through the regulation of crosstalk between cancerous and stromal cells. This is a significant property which has been described in many chemotherapeutic treatment approaches[3]. Three different types of autophagy have been so far identified; macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy has been closely associated with the formation of phagophore which engulfs cytosolic proteins for degradation in lysosomes[4].

ROLE OF ONCOGENES IN AUTOPHAGY INITIATION

It is well experienced that the majority of mCRC patients eventually develop acquired resistance during their chemotherapy-based treatment. Oncogenes such as *EGFR*, *RAS* and *BRAF* have been characterized as key elements in the modulation of resistance mechanisms in mCRC. Additionally, these oncogenes regulate the cytoprotective mechanism of autophagy. *EGFR* is responsible for activation of signaling pathways that affect autophagy, among them PI3K-AKT-mTOR[5]. This pathway inhibits autophagy through the formation of PI3K-Beclin-1 homodimers. On the other hand, *BRAF*-depend signaling pathway (BRAF/MEK/ERK) has been shown to trigger autophagy *via* up-regulation of Beclin-1[6]. Moreover, several studies support the idea that *BRAFV600E* mutation induces the expression of autophagic markers; light chain 3 and Beclin-1 in CRC cells. Additionally, anti-EGFR MoAbs (such as cetuximab and panitumumab) induce autophagy which acts as a protective response in CRC cells. Several studies have described that mutant *RAS* can prevent the formation of autophagophore in autophagy machinery through the reduction of *BECN1* expression[7].

CONTROVERSIAL ROLE OF AUTOPHAGY IN CRC

The controversial role of autophagy in CRC development has been supported by a plethora of data. Cancer cells have been found to require high basal levels of autophagy for cell proliferation[8]. In already established tumors, autophagy has been associated with the hypoxic tumor regions where the metabolic demands are increased. The increasing levels of autophagy in hypoxic regions of tumors have also been associated with the modulation of immunosurveillance and immunosuppression in tumor microenvironment[9]. In addition, advanced tumors appear to be addicted in autophagy to maintain their energy balance. Through autophagy, cancer cells recycle intracellular components and build pro-tumorigenic factors. *KRAS*-dependent tumors also use autophagy machinery to maintain basic components to support cancer cells' growth under stressful condition[10].

AUTOPHAGY IN CLINICAL PRACTICE

The mechanism of autophagy has been suggested as a crucial modulator that can be targeted to improve the effect of anti-neoplastic drugs in several tumors, including mCRC. This notion has led to the development of agents that inhibit autophagy, thereby improving treatment outcome. The last decade many molecules that inhibit autophagy have been developed. Autophagy inhibitors, such as chloroquine and its analog hydroxychloroquine (HCQ), have been shown to decrease autophagy through the disruption of lysosomal function[6]. The anti-antineoplasmatic effect of these agents has been assessed in the clinical setting. Phase Ⅰ and Ⅱ clinical trials have already evaluated the efficacy of the combination of HCQ and chemotherapy (*e.g.*, oxaliplatin, fluouropirimidines) and anti-angiogenic agents (*e.g.*, bevacizumab) in mCRC patients. Furthermore, mCRC patients have achieved disease stabilization after combining HCQ with vorinostat[11]. Further elucidation of the effect of the currently existed as well as developing autophagy inhibitors in CRC patients is of paramount importance due to the dual role of autophagy in CRC.

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P- Reviewer: Brim H, He J, Kim TI, Lin JM **S- Editor**: Dou Y
L- Editor: A **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 November 15; 10(11): 370-380

DOI: 10.4251/wjgo.v10.i11.370

ISSN 1948-5204 (online)

REVIEW

Ampulla of Vater carcinoma: Molecular landscape and clinical implications

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Author contributions: Luchini C, Pea A, Scarpa A and Lawlor RT conceived of and designed the study; Pea A, Riva G, Lawlor RT and Luchini C performed the literature review; all authors contributed to the literature analysis and interpretation; Pea A, Scarpa A and Luchini C wrote the manuscript; all authors performed the final editing and gave approval of the manuscript in its present form.

Supported by the Italian Association for Cancer Research, No. 12182.

Conflict-of-interest statement: No potential conflict of interest.

Manuscript source: Invited Manuscript

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Received: June 1, 2018
Peer-review started: June 2, 2018
First decision: August 1, 2018
Revised: August 8, 2018
Accepted: October 8, 2018
Article in press: October 8, 2018
Published online: November 15, 2018

Abstract

Ampulla of Vater is a peculiar anatomical structure, characterized by the crossroad of three distinct epithelia: Intestinal, ductal pancreatic and biliary. Adenocarcinomas arising in this area represent an opportunity to understand the comparative biology of all periampullary malignancies. These neoplasms can exhibit intestinal, pancreaticobiliary or mixed features, whereas the subclassification based on morphology and immunohistochemical features failed in demonstrating a robust prognostic reliability. In the last few years, the molecular landscape of this tumor entity has been uncovered, identifying alterations that may serve as prognostic and predictive biomarkers. In this review, the histological and genetic characteristics of ampullary carcinomas are discussed, taking into account the main clinical and therapeutic implications related to this tumor type as well.

Key words: Pancreatobiliary; Intestinal; Mixed; *ELF3*; *TP53*; *KRAS*; Ampullary; Vater; Histotype

Core tip: Ampulla of Vater carcinomas comprise tumors with intestinal and/or pancreaticobiliary differentiation, but such histotypical classification is of little help for their prognostic stratification. Integration of the recently reported molecular profiles with histopathological and clinical information furnishes novel keys for fostering the development of a more efficient prognostic stratification and the identification of novel therapeutic strategies.

Pea A, Riva G, Bernasconi R, Sereni E, Lawlor RT, Scarpa A, Luchini C. Ampulla of Vater carcinoma: Molecular landscape and clinical implications. *World J Gastrointest Oncol* 2018; 10(11): 370-380 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/370.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.370

INTRODUCTION

Ampullary neoplasms represent a wide array of tumors arising in the ampulla of Vater, the most common of which is represented by ampulla of Vater carcinoma (AVC), although other rare malignancies, such as neuroendocrine tumors, may be encountered in this location[1-3]. AVC comprises 30% of pancreaticoduodenectomies and 20% of all tumor-related obstructions of the common bile duct[4-6]. Data from the surveillance, epidemiology, and end results registries have indicated an increased number of new diagnoses in the last years, with the average age at diagnosis ranging from 60 to 70 years old[6-8]. The etiology of ampullary carcinoma has not been clearly defined and an association with a noninvasive component displaying the adenoma-to-carcinoma sequence similar to colorectal carcinoma may be present[9,10].

The ampulla of Vater region presents very peculiar histological aspects, as it represents a crossroad of three different epithelia: Intestinal, ductal pancreatic and biliary. This kind of structure characterizes this area, with a unique complexity and morphological heterogeneity[1]. From the histological point of view, coupling morphological and immunohistochemical analyses, AVCs have been subgrouped into intestinal and pancreatobiliary subtypes based on the epithelium of origin; in case of coexistence of aspects of both subtypes, the mixed category has been introduced for a more precise classification[1,11-14]. However, the former classification has been challenged by lines of evidence showing a significant interobserver variability upon the interpretation of these patterns, and the mixed subtype being the predominant subgroup of AVCs, representing up to 40% of cases[15-17]. In addition, poorly differentiated tumors can further confound the histological classification[1]. The prognostic significance of this histological classification has been subjected to investigation with inconsistent results[15-18] that will be briefly discussed in this review.

In recent years, much progress has been made in characterizing the molecular alterations underlying AVC tumorigenesis, showing a complex mutational spectrum that supports only in part the distinction in different histological subtypes[14,17]. Molecular analysis showed alterations in overlapping pathways that may serve as foundation for developing new therapeutic approaches and may improve early prognostication models. In this review, we will discuss the histological and genetic landscape of AVCs and its clinical implications, with a specific focus on the treatment of choice and on the future perspectives related to this important topic.

HISTOPATHOLOGY

Gross appearance and location

According to the gross appearance and location, AVCs can be divided into three different categories: (1) intraampullary neoplasms, characterized by a intraluminal growth pattern, without extension out of the Oddi's sphincter; (2) periampullary neoplasms, with a significant vegetating component on the duodenal surface of the ampulla, usually adenomatous, noninvasive, and frequently characterized by an ulcerating part corresponding to the invasive component; and (3) mixed neoplasms, which show both intraampullary and vegetating growth[18-21]. In all of these cases, the ampullary region has a typical enlarged macroscopic appearance (Figure 1).

Histology and immunohistochemistry

In 2010, the World Health Organization revised the criteria for the pathological diagnosis of ampullary carcinoma to include three distinct histopathological subtypes on the basis of morphology and immunohistochemical characteristics: (1) the intestinal-type AVCs; (2) the pancreatobiliary-type AVCs; and (3) the mixed-type AVCs[1].

The intestinal type is frequently associated with a noninvasive component (duodenal adenoma). Its morphology is characterized by a colorectal-like architecture, with tubular or cribriform glands and central necrosis (Figure 2)[11,22]. The invasive component is usually smaller than in the pancreatobiliary type and less frequently exhibits adverse pathological factors and lymphovascular and perineural invasion[23-26]. This AVC subtype usually expresses intestinal immunomarkers, such as caudal-related homeodomain transcription factor 2 (CDX2), mucin2 (MUC2) and cytokeratin 20 (CK20)[27].

The pancreatobiliary type is morphologically similar to pancreatic ductal adenocarcinoma or to the cancer of the extra-pancreatic bile duct. Complex tubular glands composed of atypical cells and associated with a prominent desmoplastic stroma characterized this subtype (Figure 3)[11,22]. At immunohistochemistry, those cells stain positively for MUC1, MUC5AC and CK7[27].

A significant proportion of AVCs, ranging between 18% and 40%, presents a hybrid phenotype charac-

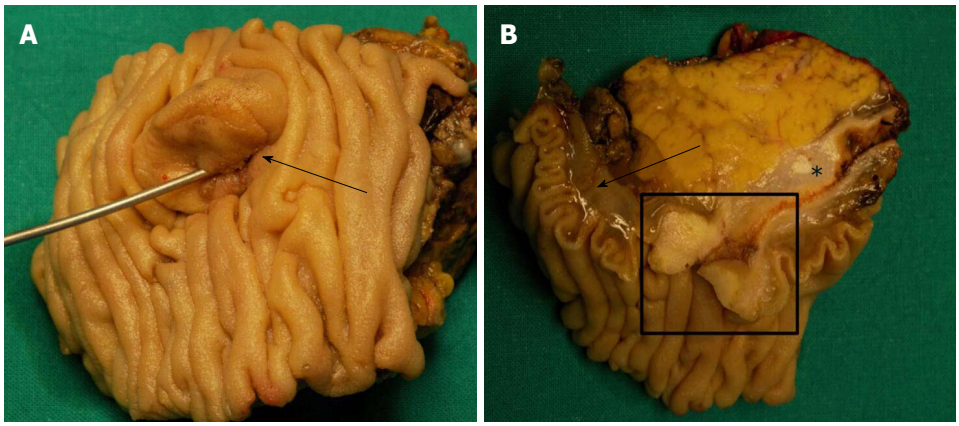

Figure 1 A classic example of the macroscopic appearance of a case of ampulla of Vater carcinoma. A: The ampullary area is markedly enlarged (black arrow); B: On the section surface, the ampulla of Vater carcinoma (black box), the adjacent duodenal wall (black arrow) and bile duct (asterisk) are clearly visible.

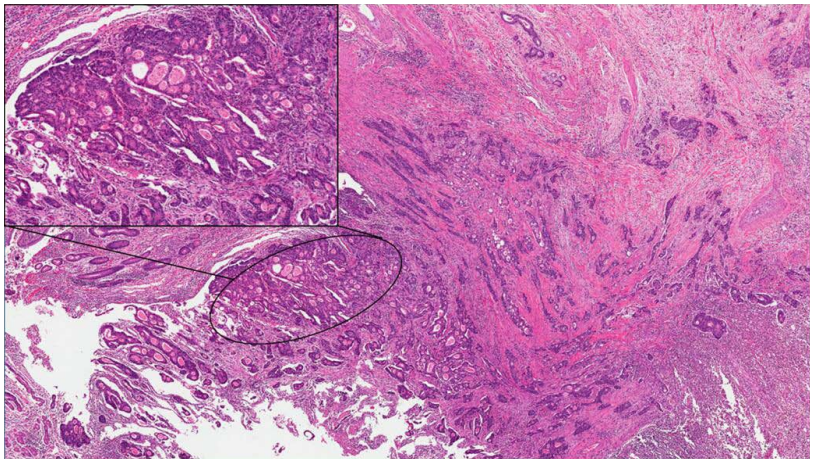

Figure 2 A classic example of intestinal-type ampulla of Vater carcinoma. At low magnification (2 × original magnification) and at higher magnification (the box in the upper left corner, 10 × original magnification) to better show its histological features. The lesion is composed of a colorectal-like architecture, with glands characterized by comedo-like necrosis.

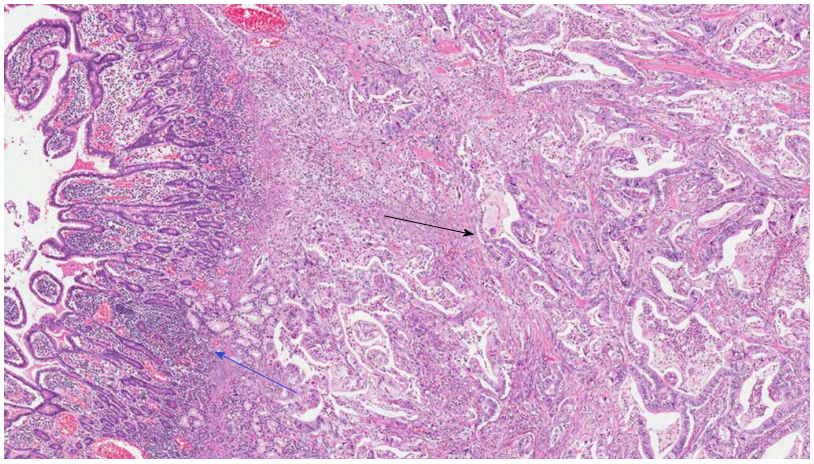

Figure 3 A classic example of pancreaticobiliary-type ampulla of Vater carcinoma (original magnification: 20 ×). The lesion is composed of ductal adenocarcinoma-like glands (black arrow) invading the duodenum (blue arrow).

terized by overlapping intestinal and pancreatobiliary features[28,29] and frequently by a nondistinctive immunohistochemistry (Figure 4)[28]. These aspects partially explain the high interobserver variability among pathologists in classifying AVCs subtypes[15,16,28].

Different immunohistochemical panels have been

Table 1 Proposed immunohistochemical markers for ampulla of Vater carcinoma histological classification (adapted from Mafficini *et al*[16])

Immunohistochemical marker criteria present	Intestinal type	Pancreatobiliary type positive	Mixed/Ambiguous type	Note
Ang *et al*[12] (MUC1, MUC2, CDX2, CK20)	Positive CK20 or CDX2 or MUC2, and negative MUC1 Positive CK20 and CDX2, and MUC2 and any MUC1	Positive MUC1 and negative CDX2, and negative MUC2 and any CK20	All other combinations	
Chang *et al*[13] (MUC1, CDX2)	Positive CDX2 or negative MUC1	Negative CDX2 and positive MUC1	Not applicable	CDX2 positivity based on *H* score (percentage of positive cells × intensity of staining) > 35 MUC1 positivity based on any staining
Gingras *et al*[17] (MUC1, CDX2)	Ratio of the CDX2/MUC1 H score ⩾ 2	Ratio of the CDX2/MUC1 H score < 0.5	Ratio of CDX2/MUC1 H score ⩾ 0.5 and < 2	Use only MUC1 and CDX2 as per Chang *et al*[13], with H scores for both CDX2 and MUC1
Mafficini *et al*[16] (MUC1, MUC2, CDX2, CK20)	Positive CK20 or CDX2 or MUC2, and negative MUC1	Positive MUC1 and negative CDX2, and negative MUC2 and any CK20	All other combinations	

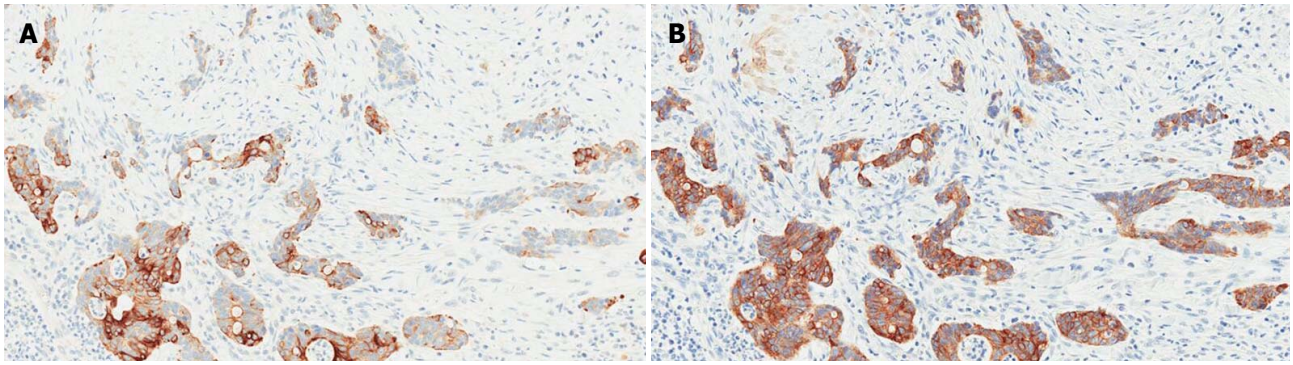

Figure 4 Immunohistochemical analysis of an ampullary adenocarcinoma of mixed subtype (original magnification 20 ×). A: Immunohistochemical analysis of an ampullary adenocarcinoma of mixed subtype, with cytokeratin 20 (CK20); B: Immunohistochemical analysis of an ampullary adenocarcinoma of mixed subtype, with cytokeratin 7 (CK7). This image highlights that, in the same area, some neoplastic glands may be positive not only for CK7 or for CK20, but for both markers even. The coexpression of an intestinal marker, such as CK20, and of a pancreatobiliary marker, such as CK7, supports the classification as mixed subtype.

suggested to overcome the difficulties in histological classification, also in order to stratify AVCs prognosis (Table 1)[12,13,15-17]. A 4-marker panel including MUC1, CK20, CDX2 and MUC2 has been proposed by Ang *et al*[12]. This panel has shown improved capacities in defining intermediate/mixed cases, although its correlation with clinical outcomes has not been evaluated. Chang *et al*[13] proposed a 2-marker panel, composed of CDX2 and MUC1, showing that the PB phenotype was associated with a poor prognosis. However, more recent studies questioning the accuracy and reproducibility of this method failed in identifying direct or significant prognostic correlations with the immunohistochemical patterns[15,16]. Notably, alterations in the "gastric" lineage marker MUC5AC have also been associated with poor outcome in AVCs, but further studies are needed to validate its prognostic role[15].

The morphological heterogeneity that characterizes a significant proportion of AVCs and the lack of a prognostic reliability of the histological classification, either individually or within immunohistochemical panels, led to the integration of molecular alterations into clinical practice in order to better define AVCs prognosis and treatment.

GENETIC LANDSCAPE

Although AVCs are usually sporadic neoplasms, they can also arise in the context of familial syndromes. Particularly, patients with familiar adenomatous polyposis (FAP) frequently develop duodenal adenomas and have a 100- to 200-fold increased risk of developing AVCs[7,30,31]. A previous seminal manuscript has indicated that sporadic AVCs differ from those occurring in FAP, according to frequency (17% *vs* 64%), as well as in the site of *APC* somatic mutations, suggesting a different molecular pathogenesis for the two conditions[32]. The molecular basis for AVCs initially concentrated on chro-

mosomal alterations, indicating chromosome 5 loss as an early event in AVC carcinogenesis, and chromosome 17p loss as a poor prognostic moderator[33,34].

Recent advances in sequencing technologies have permitted the in-depth characterization of the AVC molecular profile, providing important insights for the comprehension of the biology of this malignancy[14,16,17]. Particularly, two different whole exome sequencing analyses for a total of 240 patients have refined the knowledge about the mutational landscape of AVCs[14,17]. Both studies confirmed the presence of recurrent alterations in well-known AVC-related genes, including *TP53*, *KRAS* and those belonging to the Wnt-pathway, such as *APC*; at the same time, *ELF3* has been indicated as a novel AVC driver gene in this kind of tumor[14].

The association between driver mutations and histological subtypes has been evaluated with conflicting results. The *APC* gene, an important actor of the Wnt-signaling pathway, is frequently mutated in the intestinal subtype (50%-65% of cases), similar to colorectal cancer[35], while the pancreatobiliary type exhibits a higher prevalence of mutations in the pancreatic driver genes *KRAS*, *TP53* and *SMAD4*, with similar frequencies to pancreatic cancer[14,17,36].

Although histological subtypes show differences in prevalence for some genes (Table 2), important drivers, including *KRAS*, *TP53* and *ELF3*, can be found mutated in all histotypes. The lack of a specific genetic signature for the histological types suggests the existence of common biological mechanisms in the development of ampullary carcinoma, highlighting the heterogeneity of AVCs from the morphological to the molecular levels. This further calls for a reconsideration of the utility of the histological classification, since the genetic landscape indicates the lack of a specific distinction corresponding to morphology[16].

Both the recent whole-exome sequencing studies described inactivating mutations in the tumor-suppressor gene *ELF3*, in respectively 10% and 12% of cases[14,17]. In particular, Yachida *et al*[14] demonstrated with functional analyses a role of such a gene as an AVC driver. *ELF3* encodes an ETS-domain transcription factor that is implicated in the regulation of epithelial differentiation. Using immortalized epithelial cell lines derived from the common bile duct and duodenal mucosa and knocked down for *ELF3* expression, they demonstrated *ELF3* to enhance proliferation, motility and invasion, associated with the concomitant up-regulation of markers of epithelial-to-mesenchymal transition, such as vimentin, matrix metalloproteinase-1 (MMP1) and MMP9[14]. However, the exact functional role of *ELF3* as well as its potential role as a prognostic biomarker or target for therapy needs to be further investigated.

Interestingly, *ERBB2* amplification has been demonstrated in up 23% of cases[16,37]. In a recent report, it was observed in 13% of AVCs regardless of histological subtype and was virtually mutually exclusive with downstream mutations in *KRAS*/*NRAS*/*BRAF,* that are responsible for resistance of therapies targeting *ERBB2*[37].

Molecular profiling of AVCs has recently demonstrated a higher prognostic reliability than the histological subclassification. Indeed, analyzing a cohort of 80 AVCs, Mafficini *et al*[16] showed that *TP53* and *KRAS*, which were the most frequently mutated genes, were in respectively 41% and 35% of cases, were also independent prognostic predictors of survival regardless of histological subtypes. These data underline the importance of the mixed phenotype and the fact that the ampullary region is composed of various epithelia merging to form the complex epithelium of the ampulla. Common molecular alterations among different subtypes, such as *TP53* and *KRAS,* may indeed represent drivers of tumor progression at an early stage of disease. Whereas other genetic alterations, such as those belonging to the Wnt-pathway and those characterizing the pancreatobiliary type, such as *SMAD4* and *CDKN2A*, may occur at later stages of tumor growth[14,17].

Current treatment approaches do not distinguish patients based on subtypes[38,39], while molecular alterations may select patients that respond to different chemotherapeutic regimens, regardless of a clear histological differentiation[17]. In particular, clinical testing for Wnt-signaling and microsatellite instability (MSI) could be used to subclassify tumors for target therapies since therapies targeting the Wnt-pathway are in development and MSI-positive tumors may respond to immunotherapeutic approaches[17]. The detection of molecular alterations typical of late-stages may in the future support the choice of radical surgery with lymphadenectomy, rather than more conservative approaches. This highlights the importance of genetic analysis and the need of its future integration within the conventional pathology report.

TUMOR STAGING

The staging of AVCs is challenging due to the high complexity of this district and the three-dimensional spread pattern of tumors occurring in this region. In the new AJCC Cancer Staging System Manual, 8th edition[21], the pathological tumor (pT) stages have been reclassified, taking into account the degree of extensions and therefore improving the clinical and prognostic relevance of each pT stage (Table 3). In particular, new subsets for pT1, pT2 and pT3 have been introduced according to survival analyses and suggesting further prognostic variability[40]; the new pT4 stage comprises tumors involving peripancreatic arteries/axes, harmonizing with the exocrine pancreatic cancer staging system.

Metastatic lymph nodes are present in up to 60% of surgically resected AVCs[41-43], with a higher rate for pancreatobiliary than intestinal type carcinomas (55% *vs* 18%)[11]. The new staging system categorized the presence of nodal metastases in a three-tiered scale: N0 (no metastatic lymph node), N1 (one or two metastatic lymph nodes) and N2 (three or more metastatic lymph nodes); this subclassification has demonstrated a better predictive value in stratifying the prognosis than

Table 2 Frequency of significantly mutated ampulla of Vater carcinoma genes in different histotypes and compared to colorectal and pancreatic adenocarcinoma (adapted from Yachida *et al*[14])

Yachida *et al*[14]		Gingras *et al*[17]			Biankin *et al*[36] Pancreatic carcinoma, %	Colorectal Carcinoma (TCGA), %[35]
Intestinal type, %	Pancreato-biliary type, %	Mixed type, %	Pancreato-biliary type, %	Intestinal type, %		
APC (50)	*KRAS* (68)	*KRAS* (50)	*TP53* (72)	*TP53* (65)	*KRAS* (99)	*APC* (81)
TP53 (39)	*TP53* (67)	*APC* (50)	*KRAS* (65)	*KRAS* (46)	*TP53* (33)	*TP53* (60)
KRAS (39)	*SMAD4* (20)	*TP53* (41)	*SMAD4* (18)	*APC* (41)	*SMAD4* (16)	*KRAS* (43)
CTNNB1 (26)	*CTNNB1* (15)	*SMARCA4* (27)	*CDKN2A* (16)	*PIK3CA* (26)	*MLL3* (7)	*TTN* (31)
ARID2 (18)	*ERBB3* (14)	*PIK3CA* (23)	*PIK3CA* (13)	*SMAD4* (20)	*ATM* (5)	*PIK3CA* (18)
ERBB2 (14)	*GNAS* (12)	*SMAD 4* (23)	*ARID1A* (13)	*TGFBR2* (17)	*NALCN* (5)	*FBXW7* (14)
ACVR2A (13)	*CDH10* (12)	*SOX 9* (23)	*APC* (11)	*ARID2* (17)	*ARID1A* (4)	*SMAD4* (10)
SMAD4 (13)	*ELF3* (11)	*CDKN2A* (23)	*ATM* (10)	*ELF3* (7)	*SF3B1* (4)	*NRAS* (9)
GNAS (13)	*CDKN2A* (9)	*ARID1A* (18)	*TGFBR2* (10)	*CTNNB1* (17)	*TGFBR2* (4)	*TCF7L2* (9)
SOX9 (13)		*TGFBR2* (14)	*FBXW7* (8)	*NF1* (15)	*ARID2* (3)	*FAM123B* (7)

Table 3 Ampulla of Vater cancer staging AJCC 2017[21]

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to ampulla of Vater or sphincter of Oddi, or tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T1a	Tumor limited to ampulla of Vater or sphincter of Oddi
T1b	Tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T2	Tumor invades into the muscularis propria of the duodenum
T3	Tumor directly invades the pancreas (up to 0.5 cm) or tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T3a	Tumor directly invades pancreas, up to 0.5 cm
T3b	Tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to 1 to 3 regional lymph nodes
N2	Metastasis in > 3 regional lymph nodes

the previous dichotomous categories N0 (no metastatic lymph node) *vs* N1 (at least one metastatic lymph node). To reach a reliable value, the gross sampling of the surgical specimen should include a minimum of 12 lymph nodes[44]. However, since pancreatico-duodenal nodes are the most frequently involved and are usually resected within the specimen (pancreatico-duodenectomy), even if the minimum threshold of 12 is not met, pN0 should still be assigned. Notably, a preferential lymphatic spread from pancreatico-duodenal nodes to lymph nodes around the superior mesenteric artery has been suggested, highlighting the importance of a systemic and radical lymphadenectomy in this area[45].

The risk for lymph node metastases according to the T stage is clinically relevant since endoscopic ampullectomy has been proposed for early AVCs. Surgical series assessed a 8%-45% risk of lymph node metastases in tumors limited to ampulla of Vater and/or sphincter of Oddi (pT1a and pT1b, respectively, of the new staging system)[42,46-48]. The role of local excisions in surgically fit patients remains, being therefore controversial due to the relevant risk of lymph node metastases also in resected early cancers. Another pT-related issue regards the extra-nodal extension of nodal metastases, a histological feature indicating that the metastatic cells have reached the perinodal adipose tissue. In the new staging system, it has been not taken into account, whereas it has been demonstrated as an important prognostic factor in patients with AVC and other solid malignancies[49-57].

Other prognostic factors not included in the staging system but with a potential prognostic role are included among the histologic grading and the perineural invasion.

CLINICAL ASPECTS

In the majority of cases, AVCs are present with obs-

tructive jaundice, resulting in a high resectability rate at diagnosis[4,58,59]. Other symptoms, although less common, are upper gastrointestinal bleeding, pancreatitis and unspecific abdominal pain[60-62]. Ampullary tumors can even be incidentally discovered during endoscopic procedures or at cross-sectional imaging performed for other reasons. Despite the potentially high resectability rate, only up to 40% of patients undergo surgical resection[6], mostly due to the advanced age of presentation and the significant morbidity and mortality associated with pancreatic surgery.

The diagnostic work-up usually involves abdominal imaging using ultrasonography, computed tomography and/or magnetic resonance, aiming at excluding other causes of jaundice and at disease staging. Because of the anatomical location and the frequent small size of the tumor, an ampullary mass is often difficult to detect, but indirect signs such as pancreatic and/or bile duct obstruction/dilation can be observed[62,63].

Endoscopy plays a major role in the differential diagnosis of an altered papilla (either bulging or ulcerated) as well as in the local staging of the disease. Endoscopic biopsies are characterized by high false negative rates for adenocarcinoma, often underestimating the actual pathology[47,64], whereas endoscopic ultrasonography (EUS) guided-biopsies improve the diagnostic accuracy, assessing the correct pathology in almost 90% of the cases[65]. In the local staging of ampullary masses, EUS plays a primary role thanks to its capacities of estimating the depth of tumor infiltration within the duodenal wall and in predicting the presence of local node metastases[66-68], although their definitive demonstration is reserved for the histological examination.

ENDOSCOPIC *VS* SURGICAL TREATMENT

Radical resection represents, to date, the only established curative option for AVCs, while an endoscopic papillectomy is indicated for noninvasive tumors. A radical resection with an adequate lymphoadenectomy is usually recommended for invasive tumors, even if very small, due to the nonnegligible risk of lymph node metastasization or of incomplete tumor resection. The correct local staging is essential to guide further treatment decisions.

Endoscopic papillectomy

Endoscopic papillectomy is the treatment of choice for benign or noninvasive ampullary lesions. When EUS shows a lesion confined within the mucosa, and there are not histological features of invasion or of high-grade dysplasia upon biopsy, endoscopic ampullectomy should be performed[69,70]. The following histological examination of the endoscopic specimen must report the status of the resection margins and consider the potential presence of an invasive component[66,71,72]. In the case of high-grade dysplasia determined by endoscopic biopsy, an underlying adenocarcinoma on definitive pathology is present in 50%–100% of patients and usually in the context of voluminous intestinal-like villous adenomas, usually larger than tubular adenomas, and for which a radical endoscopic ampullectomy may be difficult[66,73].

However, endoscopic ampullectomy should be considered part of the diagnostic process and potentially curative in cases of high-grade dysplasia and clear resection margins at the final pathological evaluation of the specimen. Considering the significant morbidity and mortality associated with pancreatic surgery, endoscopic papillectomy has also been suggested for early ampullary carcinoma, in particular for pT1 tumors[46,48,68]. However, to date, this indication remains to date controversial, mainly due to the clinically relevant risk of lymph node metastases and the high rate of positive resection margins, reserving this procedure for patients unfit for surgical resection[74]. Endoscopic ampullectomy is a safe procedure, characterized by a relatively low rate (about 10%) of postprocedural complications, the most common being acute pancreatitis, followed by papillary stenosis, cholangitis and bleeding[75-78]. Most of these complications can be prevented by the placement of temporary pancreatic and biliary stents[77,79,80].

Surgery

Surgical ampullectomy has been proposed as an alternative to pancreaticoduodenectomy for selected patients with ampullary neoplasms[81]. This procedure is characterized by lower morbidity and mortality than major surgery, also allowing for performance of a partial lymphadenectomy (excluding the lymph nodes from the superior mesentery artery). However, its role in the treatment of AVCs is controversial, for the difficulties to obtain a radical resection[47,71,82]. Surgical ampullectomy shares the same complications of the endoscopic ampullectomy, with the risk of duodenal dehiscence and intra-abdominal collections as well as additional complications[71,83].

The current acceptable standard of care for resectable AVCs remains the pancreatico-duodenectomy, either with conventional or pylorus-preserving approach[42,46,47,84]. Surgery for AVCs is characterized by a high resectability rate, with close to 90% of cases undergoing laparotomy[7,24,85], but also by a higher rate of significant complications than pancreato-duodenectomies performed for pancreatic cancer. Such complications include pancreatic fistula, pneumonia, intra-abdominal infection, anastomotic leak, and delayed gastric emptying[86].

FUTURE PERSPECTIVES

The histological subtypes have revealed major issues on both interobserver reproducibility and its prognostic reliability. Since the ampulla of Vater is the crossroad of three distinct epithelia, the study of the tumors arising

in such a location represents a unique opportunity to better refine the knowledge about all periampullary cancers. The anatomical features of the ampulla of Vater may explain the histological heterogeneity of AVCs and the importance of also taking into account the mixed entity. Indeed, a significant part of this tumor type does not meet all the criteria for a definitive subclassification as intestinal or pancreaticobiliary-type. On the basis of such considerations, the integration of the molecular data appears as a fundamental step in understanding AVCs' biology, helping in better stratifying the prognosis, and highlighting potential targets for tailored therapy. Future therapeutic research studies should investigate, more in-depth, the AVCs histological and molecular features, which may represent the key to resolving intestinal-pancreaticobiliary heterogeneity.

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P- Reviewer: Sun LM, Bhatti A **S- Editor**: Dou Y
L- Editor: Filipodia **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2018 November 15; 10(11): 381-397

DOI: 10.4251/wjgo.v10.i11.381

ISSN 1948-5204 (online)

REVIEW

Laparoscopic and endoscopic cooperative surgery for gastric tumors: Perspective for actual practice and oncological benefits

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Author contributions: Aisu Y and Hori H wrote this review and contributed equally to this work; Aisu Y originally drew all schemas; all authors assessed previous papers and provided academic opinions. Aisu Y, Yasukawa D and Hori T performed the laparoscopic surgery; Hori T supervised this review; all authors approved the final version of the manuscript.

Conflict-of-interest statement: No author has potential conflicts of interest.

Manuscript source: Invited manuscript

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Received: August 22, 2018
Peer-review started: August 22, 2018
First decision: August 31, 2018
Revised: September 15, 2018
Accepted: October 11, 2018
Article in press: October 12, 2018
Published online: November 15, 2018

Abstract

Laparoscopic and endoscopic cooperative surgery (LECS) is a surgical technique that combines laparoscopic partial gastrectomy and endoscopic submucosal dissection. LECS requires close collaboration between skilled laparoscopic surgeons and experienced endoscopists. For successful LECS, experience alone is not sufficient. Instead, familiarity with the characteristics of both laparoscopic surgery and endoscopic intervention is necessary to overcome various technical problems. LECS was developed mainly as a treatment for gastric submucosal tumors without epithelial lesions, including gastrointestinal stromal tumors (GISTs). Local gastric wall dissection without lymphadenectomy is adequate for the treatment of gastric GISTs. Compared with conventional simple wedge resection with a linear stapler, LECS can provide both optimal surgical margins and oncological benefit that result in functional preservation of the residual stomach. As technical characteristics, however, classic LECS involves intentional opening of the gastric wall, resulting in a risk of tumor dissemination with contamination by gastric juice. Therefore, several modified LECS techniques have been developed to avoid even subtle tumor exposure. Furthermore, LECS for early gastric cancer has been attempted according to

the concept of sentinel lymph node dissection. LECS is a prospective treatment for GISTs and might become a future therapeutic option even for early gastric cancer. Interventional endoscopists and laparoscopic surgeons collaboratively explore curative resection. Simultaneous intraluminal approach with endoscopy allows surgeons to optimizes the resection area. LECS, not simple wedge resection, achieves minimally invasive treatment and allows for oncologically precise resection. We herein present detailed tips and pitfalls of LECS and discuss various technical considerations.

Key words: Minimally invasive surgery; Laparoscopic and endoscopic cooperative surgery; Facility-based; Gastrointestinal stromal tumor; Early gastric cancer

Core tip: Laparoscopic and endoscopic cooperative surgery (LECS) was first described as a treatment of gastric submucosal tumors in 2008, although a similar concept had been developed before that time. Thereafter, many researchers described LECS as a feasible technique for gastric resection, regardless of tumor location. LECS is a novel procedure that minimizes invasive damage to patients and preserves physiologic function of the residual stomach while securing oncological benefit. Currently, many physicians can fully utilize the advantages of LECS for gastric submucosal tumors located even at the esophagogastric junction by avoiding conventional total gastrectomy or proximal gastrectomy. This technique requires close cooperation between skilled surgeons and experienced endoscopists. Therefore, many tips and pitfalls should be discussed to accelerate this collaboration during LECS. We hope that the herein-described tips will benefit laparoscopic surgeons and interventional endoscopists who are interested in LECS.

Aisu Y, Yasukawa D, Kimura Y, Hori T. Laparocopic and endoscopic cooperative surgery for gastric tumors: Perspective for actual practice and oncological benefits. *World J Gastrointest Oncol* 2018; 10(11): 381-397 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/381.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.381

INTRODUCTION

Minimally invasive surgery is currently available for benign and borderline malignant tumors of the stomach[1-3]. Resection is a curative treatment for submucosal tumors (SMTs) and early gastric cancer (EGC)[4]. Many endoscopic physicians and general surgeons focus on the invention of novel tools and innovation of technical procedures[3,5,6]. Various therapeutic options have become well developed[2,3,5,7,8]. Interventional endoscopists continue to search for techniques with curative resectability [*e.g.*, endoscopic submucosal dissection (ESD)][9-11], and it was previously considered that endoscopic full-thickness resection is possible only by a surgical approach[12,13]. Since laparoscopy-assisted gastrectomy was first reported in 1994[14], a drastic evolution of laparoscopic surgery has occurred in parallel, and skilled laparoscopic surgeons now precisely perform minimally invasive segmental resection[15-18]. A smooth postoperative course, good functional outcome, and rapid recovery after such procedures have been established[15-17].

Each approach has its own strengths and limitations[3,10]. Hence, a hybrid approach (*i.e.*, cooperation between endoscopic intervention and laparoscopic surgery) was developed[3]. This technique aims to accumulate the strong points of intraluminal and intraperitoneal procedures and negate the technical limitations[3]. This novel concept has been described using different names (*e.g.*, hybrid laparoscopic, combined laparoscopic and endoscopic, laparoscopic-endoscopic rendezvous, and cooperative laparoscopicendoscopic procedures)[3,19-21]; however, use of these multiple terms might confuse endoscopic physicians and general surgeons. Despite the differing names, this hybrid concept focuses on a simultaneous approach via intraluminal and intraperitoneal pathways, subsequent precise resection with oncologic principles, and physiological closure of the defect[3,22,23].

Optimal resection techniques for gastric SMTs and EGC have been established based on the oncologic behaviors of these lesions[22,23]. Laparoscopic and endoscopic cooperative surgery (LECS), not simple wedge resection, achieves minimally invasive treatment and allows for precise resection of these tumors[3]. We herein focus on LECS with a review of previous literature and describe the actual procedures, including technical tips and pitfalls. Moreover, this hybrid approach is discussed with respect to extended indications, oncological benefits, and technical developments.

HISTORY

From an oncological viewpoint, the clinical and pathological behaviors of EGC and SMTs, including gastrointestinal stromal tumors (GISTs), have been well investigated[22,23]. Partial or segmental resection is considered acceptable based on oncologic principles[3,22,23]. General surgeons have an interest in minimally invasive treatment by laparoscopic local resection for SMTs and EGC[24-26]. Simple wedge resection is very easy to perform for most SMTs with extraluminal growth[27]; however, a laparoscopic approach is often difficult with respect to accessing the posterior wall, and postoperative stenosis may occur near the esophagogastric junction (EGJ) or pyloric ring.

Gastric cancer originates from the mucosa, and

some SMTs are accompanied by intraluminal growth. A dilemma faced by interventional endoscopists is that endoscopic full-thickness resection is impossible without surgical assistance[3,12,13]. In Japan, laparoscopic wedge resection using a lesion-lifting method was reported for treatment of SMTs with intraluminal growth and EGC[28-31], and a stabbing tool with a T-shaped bar was developed for partial lifting of the target wall[31,32]. However, this lesion-lifting method cannot minimize the resected area because the staple line cannot be determined by an intraluminal approach, and use of this method may increase the rate of positive surgical margins[21].

LECS has long been attempted for treatment of EGC and SMTs[21,33-35]. Interventional endoscopists and laparoscopic surgeons collaboratively explore the potential for curative resection (*i.e.*, a facility-based method) based on the abilities of the physicians at each individual institution[36]. In laparoscopy-assisted endoscopic resection, laparoscopic surgeons assist in resolution of accidental perforation or control of blood loss[37]. In endoscopic-assisted wedge resection, the target gastric wall is resected by linear staplers under intraluminal observation after laparoscopic mobilization of the stomach[37,38]. This combined resection procedure is the most commonly performed because of its technical simplicity[37,39]. Simple wedge resection and the lesion-lifting method are associated with difficulty in resection of tumors located in the posterior wall; thus, surgeons have also developed laparoscopic transluminal or intraluminal surgeries (*i.e.*, endoscope-assisted laparoscopic intraluminal surgery[32,40,41], endoscope-assisted laparoscopic transluminal surgery[42,43], and endoscope-assisted laparoscopic intragastric stapling[44-46])[3]. The resection line can be determined during transluminal or intraluminal surgeries, although these surgeries involve a gastric incision for creation of an intraluminal pathway and require advanced skills[3,21,32].

Novel cooperative laparoscopic and endoscopic techniques for gastric tumors (EGC and SMTs) have been developed mainly in Asian regions[34,47-50]. Procedures of both ESD and LECS originate in Japan, and this may be the reason why LECS is mainly developed in Asian countries so far. The term "LECS" was first reported in 2008[50]; thereafter, this combined procedure was commonly referred to as LECS. Previously established procedures (*e.g.*, the lesion-lifting method[31] and laparoscopy-assisted endoscopic resection[37]) might retrospectively be included as types of LECS procedures. Many physicians have demonstrated that LECS for gastric tumors (mainly SMTs) is feasible and safe.

LECS as described above involves intentional opening of the gastric wall and thus has a risk of tumor dissemination via gastric juice and contamination of the peritoneal cavity by enterobacteria[3,48,51]. LECS is therefore performed for gastric SMTs (mainly GIST), and the indications for LECS have been limited to cases without epithelial lesions including depressed lesions and/or ulcers[3,48]. To overcome this limitation and expand the indications for LECS, several modified LECS procedures have been developed (*e.g.*, inverted LECS[47], laparoscopy-assisted endoscopic full-thickness resection[52], nonexposed endoscopic wallinversion surgery[53-57], clean non-exposure technique[58], closed LECS[51], and lift-and-cut method[59]) and are currently applied to patients even with epithelial lesions. These novel LECS procedures are based on a clear concept of fullthickness resection without intentional perforation (*i.e.*, no exposure of gastric juice) for tumors accompanied by epithelial lesions.

SIMPLE WEDGE RESECTION BY A LINEAR STAPLER

Until LECS became well developed, simple wedge resection was generally conducted as a curative treatment for gastric SMTs. Wedge resection by a linear stapler has the advantage of avoiding the risk of intraoperative dissemination during laparoscopic surgery[60]. Another advantage of wedge resection is its technical simplicity and lack of requirement for advanced skills[3]. However, this simplicity easily results in rough resection and oncological inadequacy[61]. The simple wedge resection technique is associated with both excessive and inadequate resection of the gastric wall, which may lead to postoperative gastric stenosis, gastric dysfunction, and local recurrence[62,63]. Hence, simple wedge resection by a linear stapler is considered a technically easy but high-risk procedure[3,62].

CLASSIC LECS

LECS is a surgical technique that combines laparoscopic partial gastrectomy and ESD (Figure 1A). This combined technique is used mainly for gastric SMTs, such as GISTs. The simultaneous intraluminal approach with endoscopy allows surgeons to resect the gastric wall according to the appropriate cutting line without excessive or inadequate margins[63]. From an oncologic viewpoint, LECS optimizes the resection area by providing sufficient margins as a curative resection for gastric SMTs (Figure 1B). This is the most advantageous point of LECS compared with other approaches. Even if an SMT is located near the EGJ, optimal and precise resection by LECS may avoid the need for proximal gastrectomy.

As described above, modified LECS procedures using the concept of "no exposure" have been established for tumors accompanied by epithelial lesions[47,51-58]. The first documented version of LECS[50] has been categorized as "classic LECS" to distinguish it from other modified LECS procedures[48].

Table 1 Clinical outcomes of laparoscopic endoscopic cooperative surgery

Author	Ref.[1]	Published year	Patient number (case)	Age[2]	Gender (male/female)	BMI[2] (kg/m^2)	Procedures	Diagnosis	Size[2] (mm)	Conversion rate to gastrectomy or laparotomy (%)	Positive surgical margin (%)	Complications (treatment and case number)	Mortality	Recurrence rate (%)	Folow-up period[2] (mo)
Hiki *et al*	[50]	2008	7	53 ± 6	0/7	22.0 ± 1	Classic LECS	SMT	46	0	0	None	0	-	-
Kikuchi *et al*	[51]	2017	10	62	5/5	-	Closed LECS	SMT	24.1	0	-	Intra-abdominal abscess (n = 1)	0	0	12
Mitsui *et al*	[56]	2014	6	60	4/2	-	NEWS	SMT	34	0	0	None	0	0	8
Inoue *et al*	[58]	2012	24	66.2	-	-	Clean-NET	EGC	-	-	-	Gastric deformity (Reoperation, n=1)	0	0	-
Okumura *et al*	[59]	2017	28	67.6	8/20	-	Lift-and-cut method	GIST	33	0	0	None	0	0	26.6
Matsuda *et al*	[71]	2016	100	59.8	47/53	22.7 ± 3.3	Classic LECS	SMT	30.9	5	0	Leakage (n = 1) Postoperative stenosis (n = 2) Postoperative bleeding (n = 1)	0	0	25.3
Tsujimoto *et al*	[72]	2012	20	59.3 ± 11.9	10/10	21.8 ± 2.7	NEWS	SMT	37.9 ± 11	0	0	None	0	0	20.7
Kawahira *et al*	[73]	2012	16	61	4/12	22.1	Classic LECS	SMT	27.5	0	0	Lymphorrhea (n = 1)	0	0	-
Hoteya *et al*	[74]	2014	25	60	10/15	-	LECS	SMT in EGJ	32.3	0	0	None	0	0	18

[1]See the reference list; [2]Data were given as mean ± SD, or the median. BMI: Body mass index; Clean-NET: Clean non-exposure technique; EGC: Early gastric cancer; EGJ: Esophagogastric junction; GIST: Gastrointestinal stromal tumor; LECS: Laparoscopic endoscopic cooperative surgery; NEWS: Non-exposed endoscopic wall-inversion surgery; SMT: Submucosal tumor.

INDICATIONS

The indications for LECS should be considered based on the patient's disease, institutional ability, and individual skills[3,36]. Hence, the indications for LECS may be affected by both tumor- and facility-related factors[36]. Indication and contraindication for LECS are mainly considered based on three factors (*i.e.*, the tumor's characteristics, institutional ability and individual skills). Other clinical factors (*e.g.*, age, gender, body mass index and comorbidity) never affect the indication for LECS, and these factors in previous documents are summarized in Table 1. In our institution, all patients with a suspicious diagnosis of a gastric GIST routinely undergo gastrointestinal endoscopy, an upper gastrointestinal series, endoscopic ultrasound, and enhanced computed tomography to identify the size and location of the tumor. Moreover, a preoperative pathological diagnosis is made by ultrasound-guided fine-needle aspiration because the therapeutic strategy will be affected by the pathological assessment. For example, although lymph node dissection is not required for surgical treatment of GISTs[64], some SMTs (*e.g.*, carcinoid or submucosal carcinoma and submucosal adenocarcinoma) require lymph node dissection during surgery[65]. In our institution, patients diagnosed with EGC are treated by robot-assisted gastrectomy with lymph node dissection[66].

Classic LECS is mainly employed for gastric SMTs, and a GIST is a common target tumor. As described above, opening the gastric wall is associated with a risk of tumor dissemination via gastric juice[3,48,51], and classic LECS has limitations in the treatment of epithelial lesions[3,48]. From the viewpoint of tumor size, however, laparoscopic surgery for larger gastric GISTs is thought to carry a higher risk of tumor capsule injury[67]. The National Comprehensive Cancer Network and European Society for Medical Oncology argue that there is no good evidence in support of laparoscopic surgery for GISTs of > 5 cm[68], although skilled physicians emphasize that laparoscopic surgery

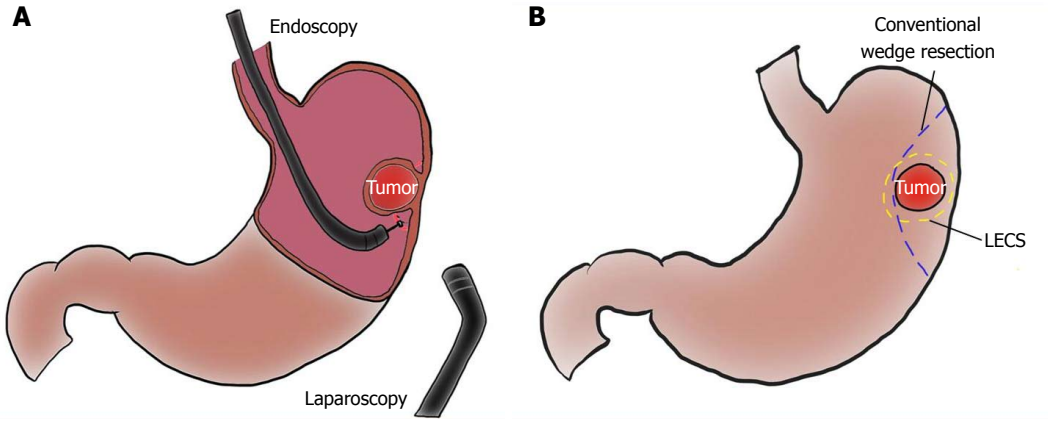


Figure 1 Schema of laparoscopic and endoscopic cooperative surgery, and comparison of resection line between laparoscopic and endoscopic cooperative surgery and conventional wedge resection. A: Laparoscopic and endoscopic cooperative surgery (LECS) is a combined procedure involving laparoscopy and endoscopy; B: The resection line of LECS minimizes the surgical margin, securing an adequate distance from the tumor. Conventional wedge resection is too close to the tumor and involves excessive wall dissection.

for gastric GISTs is safe and feasible regardless of tumor size[69,70]. In our institution, we generally apply laparoscopic surgery to gastric GISTs of ⩽ 5 cm in diameter, and we employ LECS only to intraluminal types without epithelial lesions. As a prerequisite, we routinely have detailed preoperative discussions with the patients and obtain adequate informed consent.

Skilled physicians have demonstrated that laparoscopic surgery can be applied to gastric GISTs of larger size and/or epithelial lesions if surgical and oncological safety (*e.g.*, tumor location, layers involved/occupied, expected malignancy of the tumor, institutional ability, and individual skills) are guaranteed[3,33,36,47,51-58,69,70]. Skilled physicians have also documented that LECS is feasible and safe for gastric SMTs in any location[37,50,71-74]. LECS was recently applied to duodenal SMTs[75]. However, application of LECS to SMTs near the EGJ should be carefully considered because laparoscopic suturing in this region requires advanced skill to avoid postoperative stenosis and leakage[34,76-78]. In fact, when the tumor covers more than one-third of the whole circumference of the EGJ, patients have a high rate of conversion to open surgery or proximal gastrectomy[71]. Tumor occupation of more than one-third of the whole circumference of the EGJ should be a contraindication for LECS. Although no definitive risk factors for anastomotic stenosis and postoperative leakage have been established, surgeons should not hesitate to convert to open surgery or proximal gastrectomy during laparoscopic surgery if surgical and oncological safety cannot be guaranteed.

INITIAL SET-UP FOR INTERVENTIONAL ENDOSCOPY AND LAPAROSCOPIC SURGERY

LECS is performed under general anesthesia in the leg-open position. Both arms of the patient are fixed along the body to avoid interference with the procedures performed by the interventional endoscopists. The primary surgeon stands on the right side of the patient, and the assistant surgeon stands on the opposite side. The laparoscopist stands between the patient's legs. Both the interventional and assistant endoscopists stand beside the patient's head. The arrangement of various apparatuses and medical staff members in the operation room is shown in Figure 2A.

The patient is placed in the supine position with the head directed straight. The tracheal intubation tube has already been inserted through the mouth. Even if the patient's face can be slightly turned toward the left for endoscope insertion, the interventional endoscopists are repeatedly forced to handle the endoscope under unfamiliar situations (*i.e.*, supine body position, straight face direction, and competitive oral tube). Endoscopists must continuously perform very careful handling of the devices and patient, and placement of a flexible overtube (ST-SB1S; Olympus Medical Systems Corporation, Tokyo, Japan) is a solution for stress-free endoscopic maneuvers. Moreover, as described later, an overtube is a powerful tool for tumor removal *via* the mouth.

For the endoscopic intervention, an endoscopic system with fine vision and advanced apparatuses, including energy devices, is set up as for ESD. An insulation-tipped diathermic knife (ITknife2, KD-611L; Olympus Medical Systems Corporation) and soft coagulation system (VIO 300 D; Erbe, Tubingen, Germany) are prepared.

A camera port is placed on the umbilicus. Three additional ports (two 5-mm ports and one 12-mm port) are inserted into the left upper, left lower, and right upper quadrants, respectively, under pneumoperitoneum of 12 mmHg with a laparoscopic view. One additional 5-mm port in the right lower quadrant is acceptable, if

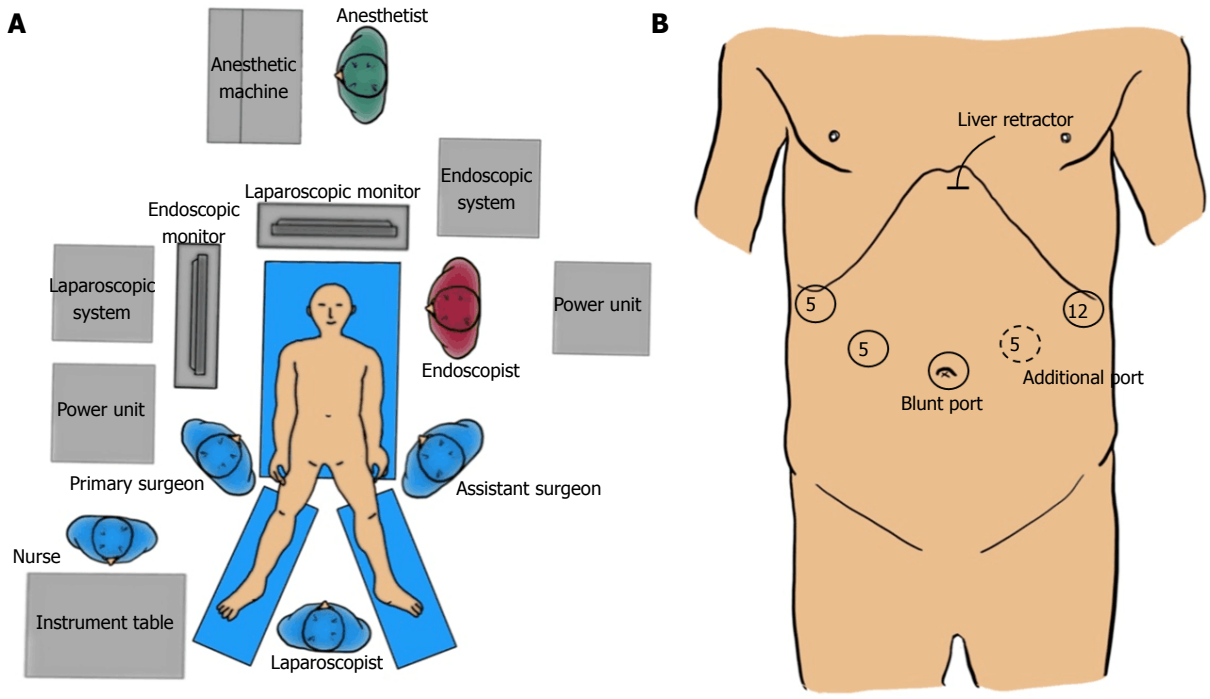


Figure 2 Set-up of staffs and devices in the operation theater and port placement. A: Apparatus position and staff placement in the operation room; B: Port placement.

necessary (Figure 2B).

During LECS, the laparoscopic surgeon should never forget that both the pneumoperitoneal pressure and light intensity are higher on the laparoscopic than endoscopic side. Under the conventional settings of usual laparoscopic surgery, interventional endoscopists cannot secure an adequate field because the stomach would collapse by pneumoperitoneal pressure and cannot obtain fine vision because the laparoscopic light would be too dazzling. The laparoscopic settings of these two factors should be optimally adjusted as necessary during LECS. In our institution, we adjust the light intensity manually as needed and downregulate the pneumoperitoneal pressure to 4 to 6 mm Hg while the interventional endoscope is being operated. However, the endoscopic setting is the same as or similar to that of usual ESD, according to the physician's preference.

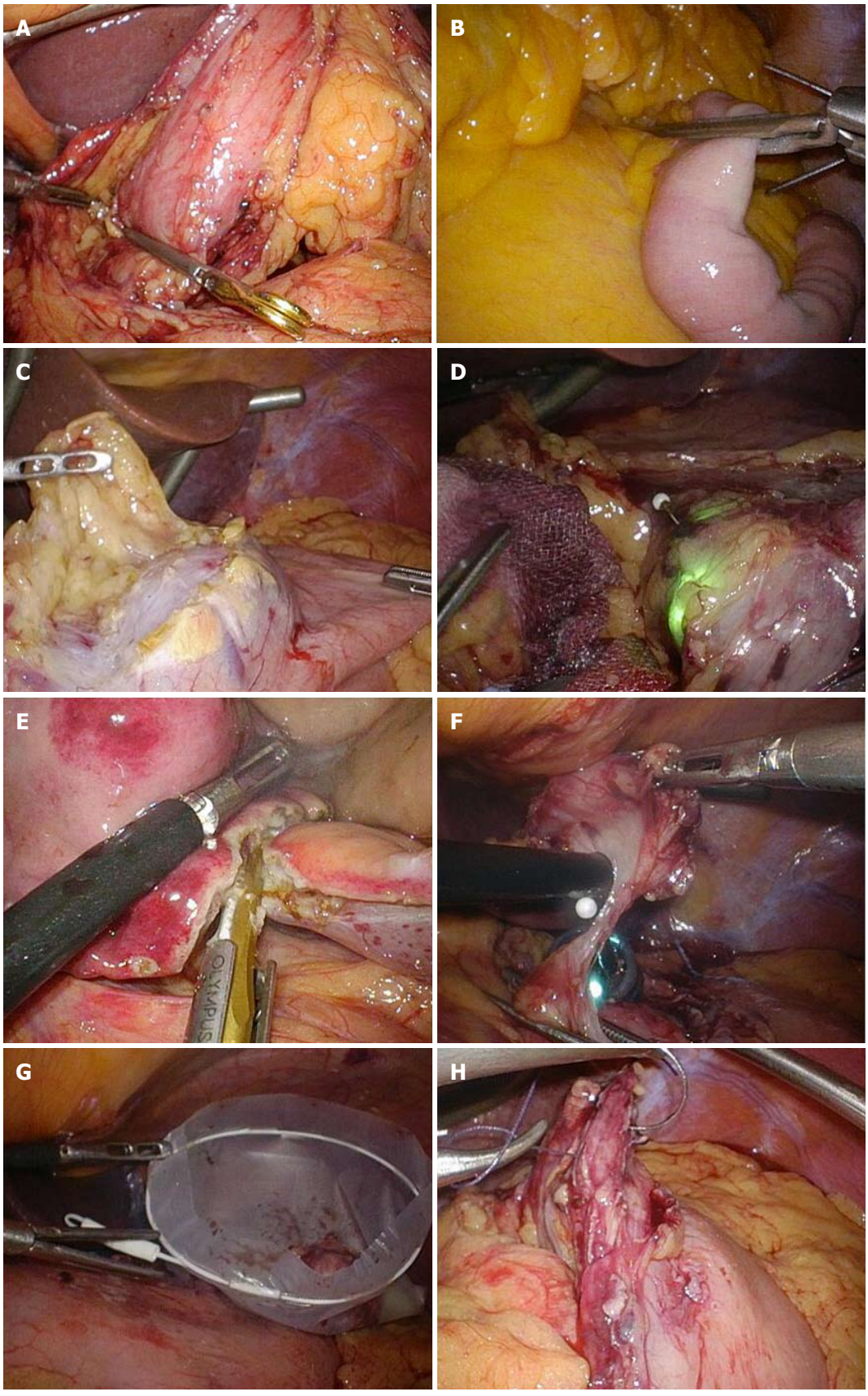
ANATOMICAL RECOGNITION

The stomach is fixed by ligaments and tendons that surround organs and structures such as the hepato-duodenal ligament, celiac axis, pancreatic capsule, crura of the diaphragm, and spleen. The target gastric wall should be mobilized ventrally with a free space made by carbon dioxide gas to ensure the safety of the interventional endoscopic procedure. Even subtle injury to the surrounding organs (*e.g.*, pancreas and aorta) during the endoscopic intervention should be avoided. Especially for SMTs at the posterior wall or EGJ, adequate dissection of the posterior side is key to good mobilization of the target stomach wall. In patients with GISTs, the target gastric wall is directly exposed because of rare metastasis to the regional lymph nodes[64].

PERITONEAL APPROACH BY A LAPAROSCOPIC VIEW

First, the tumor location is identified. Although gastric tumors are intraluminal, the tumor location can often be found from the extraluminal view because the gastric wall is slightly depressed or elevated. If the tumor location cannot be detected via the laparoscopic view, it should be confirmed by the endoscopic view. Excessive dilatation of the digestive tract by endoscopic insufflation of carbon dioxide should be prevented before the start of the intraluminal endoscopic investigation. Clamping of the antrum or jejunum should be performed using clamp forceps (PL541S; B. Braun Aesculap, Tokyo, Japan). Technically, placement of a jejunal clamp at about 10 cm on the anal side of the Treitz ligament is easier than placement of an antral clamp (Figure 3A and B), although an antral clamp provides a better surgical field by prevention of duodenal dilatation (Figure 3A). Notably, endoscopic insufflation into the intestines will remarkably disturb the laparoscopic field. In contrast, the stomach is well expanded by insufflation and clamping, providing an intraluminal working field for the endoscopic intervention.

The surrounding fat tissue and vessels of the gastric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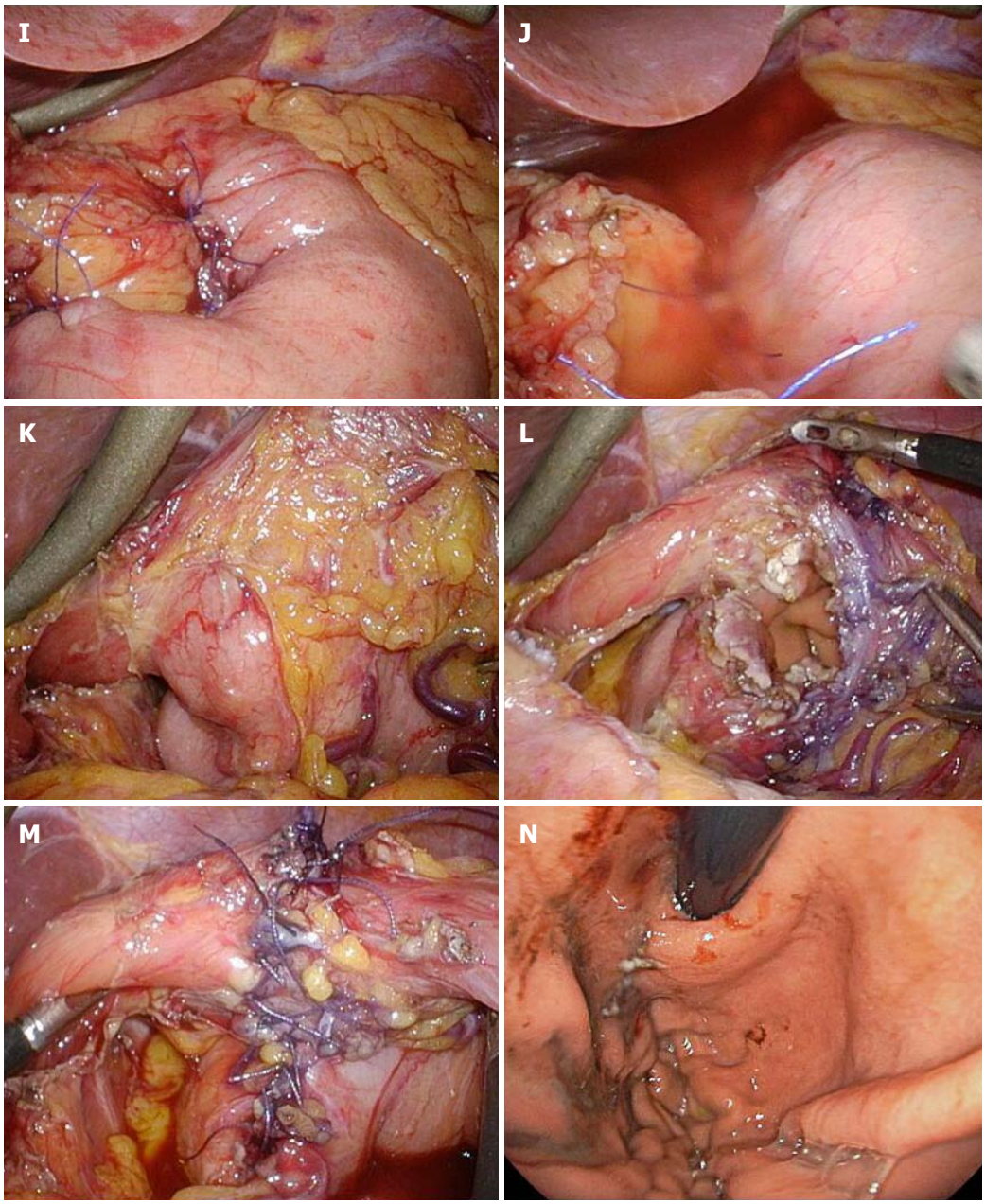

Figure 3 Intraoperative laparoscopic view of laparoscopic and endoscopic cooperative surgery. A and B: Clamping of the (A) antrum or (B) jejunum should be performed using clamp forceps. This allows for adequate gastric expansion that provides an intraluminal working field for the endoscopic intervention; C: The surrounding fat tissue and vessels of the gastric wall are dissected, and the target wall is then mobilized to the ventral side; D: The laparoscopic surgeon should mobilize the gastric wall and prevent it from touching any surrounding organs for a safe intraluminal intervention. The pneumoperitoneal pressure and light intensity of laparoscopy are decreased to avoid disturbing the endoscopist; E: The laparoscopic surgeon can dissect the proximal gastric wall on behalf of the interventional endoscopist, if necessary; F: The surgeon and the endoscopist cooperate to complete the operation while avoiding injury to the adjacent organs; G: The resected specimen is placed in a plastic bag and removed intraluminally using endoscopy; H: The mucosal layer is closed with a running 4-0 absorbable suture thread; I: The seromuscular layer is closed with interrupted 3-0 absorbable sutures; J: A leak test is performed after suturing. K: This image depicts a case involving a tumor located in the posterior wall near the EGJ; The target gastric wall is turned as much as possible with a marginal free space established by carbon dioxide gas. The right side of the EGJ has enough working space laparoscopically; L: The defect of the gastric wall tends to become larger than many physicians expect; M: The defect in the gastric wall is closed with the laparoscopic hand-sewn technique in a layer-to-layer fashion; N: Intraluminal view after suturing. The absence of stenosis and malformation is confirmed. EGJ: Esophagogastric junction.

wall are confirmed. To mobilize the stomach, omental fat tissue is cut while preserving the vessels coursing into the stomach (mainly gastroepiploic vessels). When excising the lesser omentum, the gastric branch of the vagus nerve should be maximally preserved to prevent postoperative gastroparesis. After the stomach mobilization, the stomach should be twisted until the target wall faces the ventral side to ensure the safety of the gastric wall during the endoscopic intervention (Figure 3C). Briefly, the target gastric wall never touches any surrounding organs (*e.g.*, pancreas and aorta) (Figure 3D). The ventrally mobilized target wall should then be exposed with a marginal free space established by carbon dioxide gas. Adequate dissection is performed

near the tumor and traced to the stomach, and the gastric wall around the tumor is exposed and mobilized to the ventral side. This process is very important to prevent unexpected injury to adjacent organs (*e.g.*, pancreas, liver, aorta, and spleen). Laparoscopic surgeons can dissect the proximal gastric wall with the assistance of interventional endoscopists, if necessary (Figure 3E). The surgeon and the endoscopist cooperate to complete the operation without injuring the adjacent organs (Figure 3F).

Determination of the cutting line with optimal margins based on the endoscopic findings is an oncological benefit. Although the cutting line is set by the interventional endoscopist, resection of the seromuscular layers can be performed with either the interventional endoscopists' insulation-tipped diathermic knife or the laparoscopic surgeon's ultrasonic coagulation shears. The resected specimen is placed in a plastic bag and removed intraluminally using endoscopy (Figure 3G).

The defect in the gastric wall is closed with a layer-to-layer laparoscopic hand-sewn technique. The mucosal layer is closed with a running suture using 4-0 absorbable suture thread (4-0 VICRYL, SH-1; Ethicon, Cincinnati, OH, United States). To prevent laxity of the running suture, an assistant surgeon holds the end of the last suture with a needle forceps, which has a strong grip force without any slip. The seromuscular layer is then closed with interrupted sutures using 3-0 absorbable suture thread (3-0 VICRYL, SH-1; Ethicon) (Figure 3H and I). When suturing is completed, a leakage test should be performed. The absence of air leakage should be confirmed by excessively inflating the stomach with endoscopy under adequate saline accumulation using a laparoscopic irrigation device (Figure 3J). The clamp forceps must be removed when the laparoscopic surgery is finished.

The upper stomach is a common site of SMTs, especially GISTs[4,79]. GISTs are frequently located at the fornix/fundus and/or near the EGJ[76,79]. When tumors are located in the posterior wall near the EGJ or in the antrum near the pylorus, ventral mobilization of the stomach wall around the tumor is generally left incomplete. Two solutions are available in such cases. If the SMT has no epithelial lesion, one solution is utilization of the concept of transluminal and intraluminal surgeries, as described above. The gastric wall can be incised to approach the tumor in patients without a possibility of tumor dissemination. The other solution is endoscopic intervention performed under incomplete mobilization but secure surgical fixation of the stomach wall. Mobilization of the stomach is performed, and the target gastric wall is then turned as much as possible with a marginal free space created by carbon dioxide gas. The right side of the EGJ has enough laparoscopic working space[17]. In our institution, the stomach wall around the tumor is securely fixed by laparoscopic forceps, with a marginal free space even if this space is not located ventrally (Figure 3K). When the incision extends to the EGJ, the defect of the gastric wall tends to become larger than many physicians expect (Figure 3L). In such cases, closure of the larger defect should be started at the far side from the laparoscopic surgeons because the surgical field is unclear if the open defect remains on the far side (Figure 3H). Laparoscopic hand-sewn suturing is completed in a layer-to-layer fashion (Figure 3M). To avoid postoperative anastomotic stenosis, esophageal patency and gastric passage are endoscopically confirmed after suturing (Figure 3N). If the endoscope is set through the EGJ as a guide to prevent anastomotic stenosis, the EGJ caliber will be sustained during suturing. Notably, any damage or injury induced by the suture needles should be carefully avoided.

ORAL APPROACH BY ENDOSCOPIC VISUALIZATION

For an oral approach by endoscopic visualization, the location of the tumor is first confirmed (Figure 4A). The periphery of the tumor is then marked using argon plasma coagulation as close as possible to the tumor edge (Figure 4B). After injection of 10% glycerin mixed with indigo blue into the submucosal layer (Figure 4C), a small initial incision is made with a dual knife (Dual knife, KD-650L; Olympus Medical Systems Corporation), and the tip of an insulation-tipped diathermic knife is inserted into the submucosal layer. The whole circumference of the marked area is then cut using the insulation-tipped diathermic knife (Figure 4D). Finally, an intentional perforation is made (Figure 4E), and seromuscular dissection is circumferentially performed according to the determined line of the submucosal layer. The laparoscopic light is too dazzling for the endoscopic side (Figure 4F). The stomach rapidly collapses after gastric perforation, and thereafter, maintenance of an adequate intragastric field for endoscopic manipulation becomes difficult. Laparoscopic surgeons must help the endoscopist to appropriately perform these procedures, avoiding injury to the adjacent organs. According to determined cutting line with optimal margins, resection of the seromuscular layers can be performed by either the interventional endoscopist's insulation-tipped diathermic knife or the laparoscopic surgeon's ultrasonic coagulation shears. Especially when cutting the proximal side of the ventrally mobilized gastric wall, the interventional endoscopist may encounter some difficulties because of the reversed endoscopic image (Figure 5). Laparoscopic vision from the umbilicus may be a good solution to this problem. If necessary, the laparoscopic surgeon can dissect the proximal gastric wall on behalf of the interventional endoscopist. The absence of stenosis or malformation should be confirmed after suturing (Figure 4G).

The resected specimen is placed in a plastic bag (Rusch MemoBag; Teleflex, Tokyo, Japan) and removed

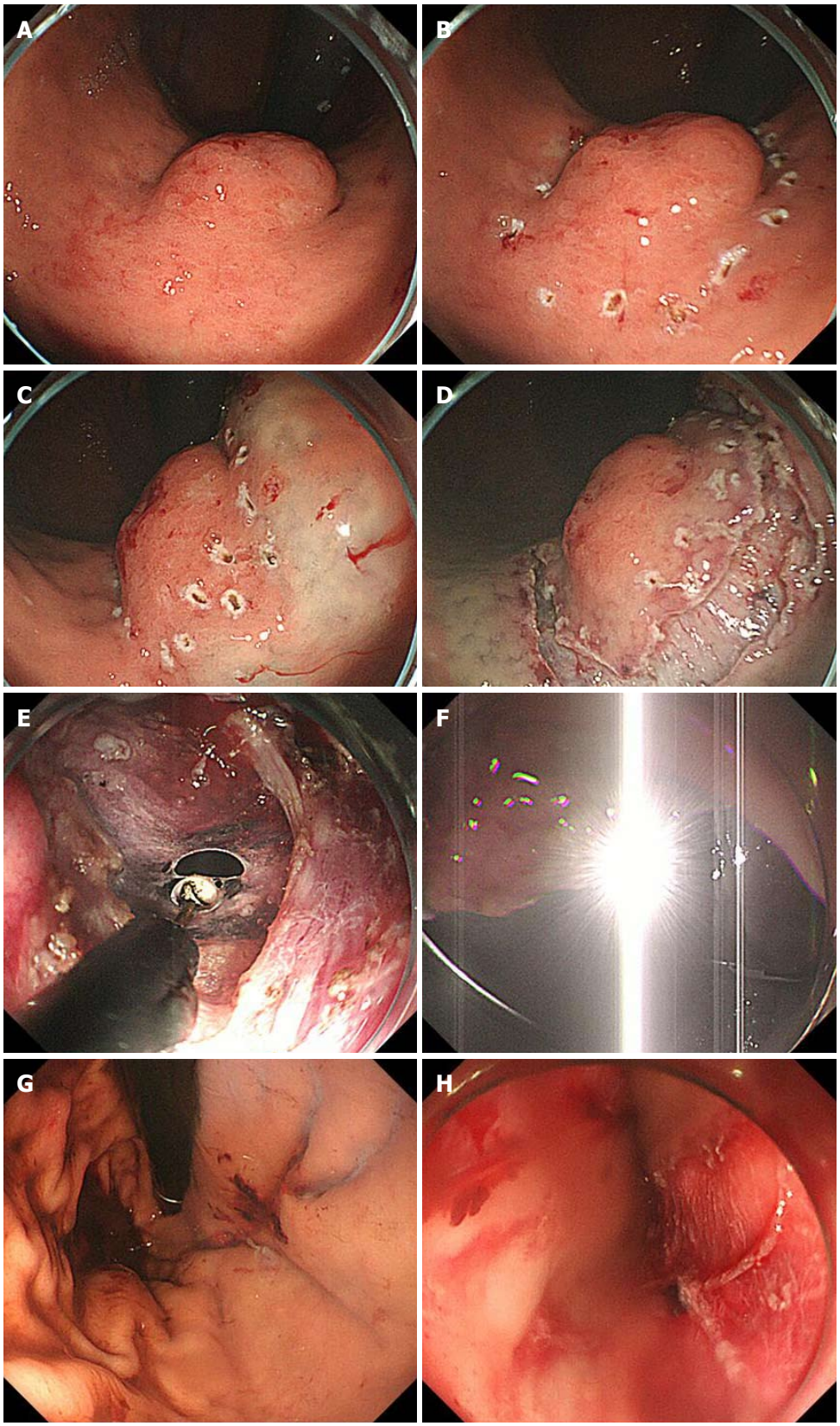

Figure 4 Intraoperative endoscopic view of laparoscopic and endoscopic cooperative surgery. A: First, the location of the tumor is confirmed; B: The periphery of the tumor is marked using argon plasma coagulation as close as possible to the tumor edge; C: Glycerin mixed with indigo blue is injected into the submucosal layer; D: The whole circumference of the marked area is cut using an insulation-tipped diathermic knife; E: An intentional perforation is made; F: The laparoscopic light is too dazzling for the endoscopic side; G: Intraluminal view after suturing. The absence of stenosis and malformation is confirmed; H: Esophageal mucosa injury by the plastic bag during specimen removal.

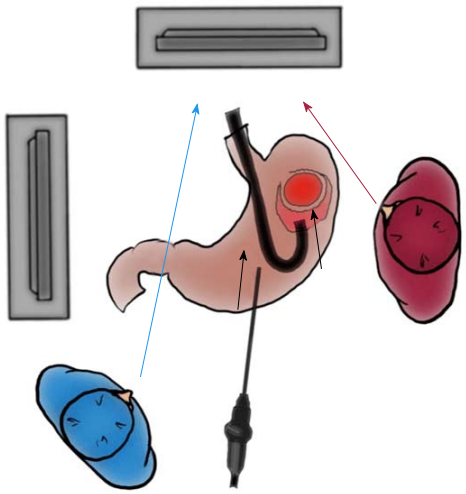

Figure 5 Importance of interventional endoscopist's line of vision while cutting the proximal side. The interventional endoscopist may experience some difficulties while cutting the proximal side of the gastric wall because of the reversed endoscopic image. If such difficulties are encountered, the endoscopist should turn his or her eyes to the laparoscopic monitor instead of the endoscopic monitor.

intraluminally using endoscopy if the size of the tumor is ⩽ 5 cm[20,80]. Larger tumors of > 5 cm are removed trough the umbilicus with a plastic bag. The thread of the bag is ligated to the nasogastric tube (Figure 6A) or held by a strong grasper (Figure 6B). The stored tumor is then removed through the mouth with utilization of the overtube.

The endoscope is inserted through the overtube. The overtube is used to protect the mucosal wall during the procedure and specimen removal. Appropriate use of an overtube is essential for successful LECS. The stored tumor in the bag is conically set in the overtube (Figure 7), and the overtube is removed with the tumor bag. Hence, injury to the esophageal mucosa can be avoided during specimen removal (Figure 4H).

KEY POINTS AND TECHNICAL PITFALLS

Placement of an overtube has some advantages for repeated endoscopic insertion and tumor removal through the mouth. The cutting line is determined with an optimal circular margin according to the intraluminal findings. This is an oncological benefit of LECS. Laparoscopic pressure and light are stronger than those of endoscopy. Hence, laparoscopic surgeons must pay closer attention to avoid disturbances during endoscopic interventions. The stomach is dissected from related ligaments and omentum, and the target gastric wall is ventrally mobilized. The target gastric wall should be exposed with a marginal free space by carbon dioxide gas and should never touch any surrounding organs for safe intraluminal intervention. To cut the proximal side of the ventrally mobilized gastric wall, laparoscopic vision from the umbilicus may be adequate for endoscopic maneuvers. The laparoscopic surgeon can dissect the proximal gastric wall on behalf of the interventional endoscopist if the interventional endoscopist experiences some difficulties. After tumor removal, the defect is closed in a layer-to-layer fashion. Because laxity of running suture results in leakage, an assistant surgeon holds the end of the last suture with a needle forceps, which has a strong grip force. A leak test can be performed with enough air pressure. To avoid excessive dilatation of the small intestine due to insufflation of carbon dioxide gas from endoscopy, clamp forceps are placed on the antrum or jejunum. This clamp should be removed at the end of surgery.

POSTOPERATIVE COURSE

Patients begin drinking on postoperative day 1 and eating on postoperative day 2. If the postoperative course is uneventful, the patients can be discharged around postoperative day 7. In previous studies, the postoperative hospital stay was 4.6 to 10.5 d[37,71-74,81]. The postoperative hospital stay tends to be prolonged in patients with tumors involving the EGJ[74], and postoperative obstruction due to stenosis is a major concern in patients with lesions near the cardia.

ONCOLOGICAL ADVANTAGES

In LECS, the tumor is resected with careful observation from both the intraluminal and extraluminal side. Consequently, the surgical margins from the tumor are guaranteed, and excessive gastric wall resection is minimized (Figure 8A)[50,81]. Previous important studies reported no recurrent cases (Table 1). Conventional simple wedge resection with only an extraluminal approach results in excessive and unnecessary resection of the gastric wall (Figure 8B-D). It may also have a risk of unexpected crushing of the tumor with the stapler because it is an intraluminally blinded procedure.

LIMITATIONS OF LECS

Many researchers have reported that LECS is feasible and safe for the treatment of gastric SMTs[37,71-74,81]. The main limitation of LECS is the possibility of tumor dissemination during opening of the gastric wall, and contamination with gastric juice into the abdominal cavity may occur. This is why LECS can only be applied to gastric SMTs without epithelial lesions. To overcome this weakness, several procedures based on the concept of "no exposure" have been developed, such as inverted LECS[47], laparoscopy-assisted endoscopic full-thickness resection[52], nonexposed endoscopic wallinversion surgery[53-57], the clean non-exposure technique[58], closed LECS[51], and the lift-and-cut method[59]. Closed LECS, endoscopic resection after plate statement under seromuscular layers, is an effective technique[51].

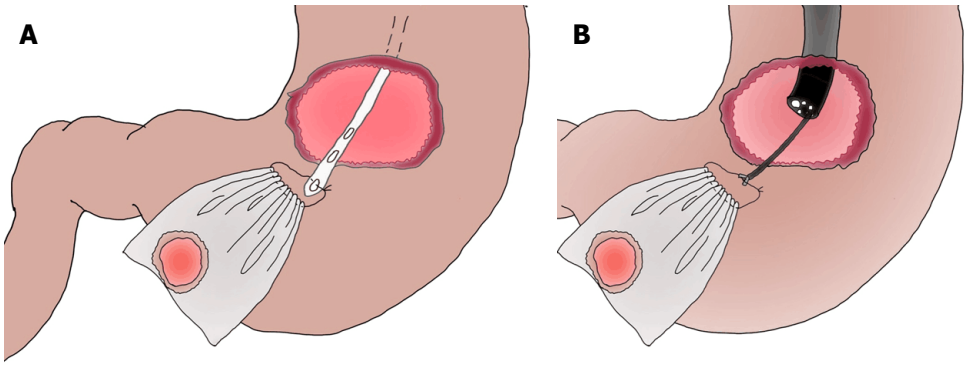

Figure 6 Options of specimen removal with plastic bag. A: Specimen removal with a nasogastric tube; B: Specimen removal with an endoscopic forcep.

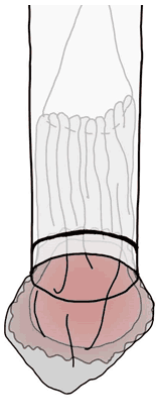

Figure 7 Effective use of an overtube when removing the specimen. The tumor encased in the bag should be sheathed as much as possible in the overtube and removed through the mouth along with the overtube. Hence, injury to the esophageal mucosa by the plastic bag during specimen removal can be avoided.

FACILITY-BASED PRIORITY BETWEEN SURGEONS AND PHYSICIANS

LECS is a combined procedure involving laparoscopic surgery and endoscopic intervention performed in an institution-based manner[36]. However, the balance between the surgeons' technique and the endoscopists' skill will vary depending on each facility. Although close cooperation is essential, and collaboration of skilled surgeons and experienced endoscopists is ideal. Skills are set within each institution, and the best facility-based service should be considered on an individual basis[36]. Whether the surgeons or endoscopists will take the initiative and proceed with the operation differs among individual facilities. This does not mean that if a skilled doctor is on one side, the other doctor can be unskilled. Of course, both must be skilled.

From a surgical viewpoint, experience alone is not enough for reliable laparoscopic surgery[16]. Laparoscopic surgeries without reconstructive procedures (*e.g.*, cholecystectomy and appendectomy) do not require advanced techniques, and these surgeries have therefore rapidly spread worldwide. In contrast, complicated laparoscopic surgeries (*e.g.*, gastrectomy and proctectomy) have not yet become typical procedures because of the need for skilled surgeons. LECS is not a markedly difficult procedure, although special skills of laparoscopic suturing are required. The laparoscopic closure is technically challenging. Minimally educated and poorly experienced surgeons who are not familiar with suturing in the abdominal cavity under laparoscopy and have no choice except to use staplers should not pursue this procedure. Ironically, simple wedge resection with linear staplers may accomplish the concept of "no exposure"[60], and employment of a linear stapler itself is actually an effective option to avoid tumor dissemination[60]. This is a critical issue; i.e., that the oncological benefits of LECS are ignored by misuse of simple wedge resection.

MORTALITY AND MORBIDITY

Clinical outcomes (*e.g.*, oncological resectability, mortality, morbidity and follow-up term) in previous important documents were summarized in Table 1. LECS has demonstrated no mortality and a low incidence of postoperative complications[48,81], and we speculate that strict performance of the leakage test may play an important role to avoid leakage.

Even subtle stenosis or obstruction of the upper digestive tract will easily result in refractory symptoms after surgery, and the risk factors for stenosis or obstruction remain undefined. There is no evidence of a lower frequency of postoperative stenosis or obstruction in LECS, conversions to proximal gastrectomy and open surgery have been reported, and a good operative course after double-flap technique anastomosis during proximal gastrectomy has been documented[82].

FUTURE POTENTIAL OF LECS

Although LECS has a risk of tumor dissemination, its application for treatment of EGC has been reported

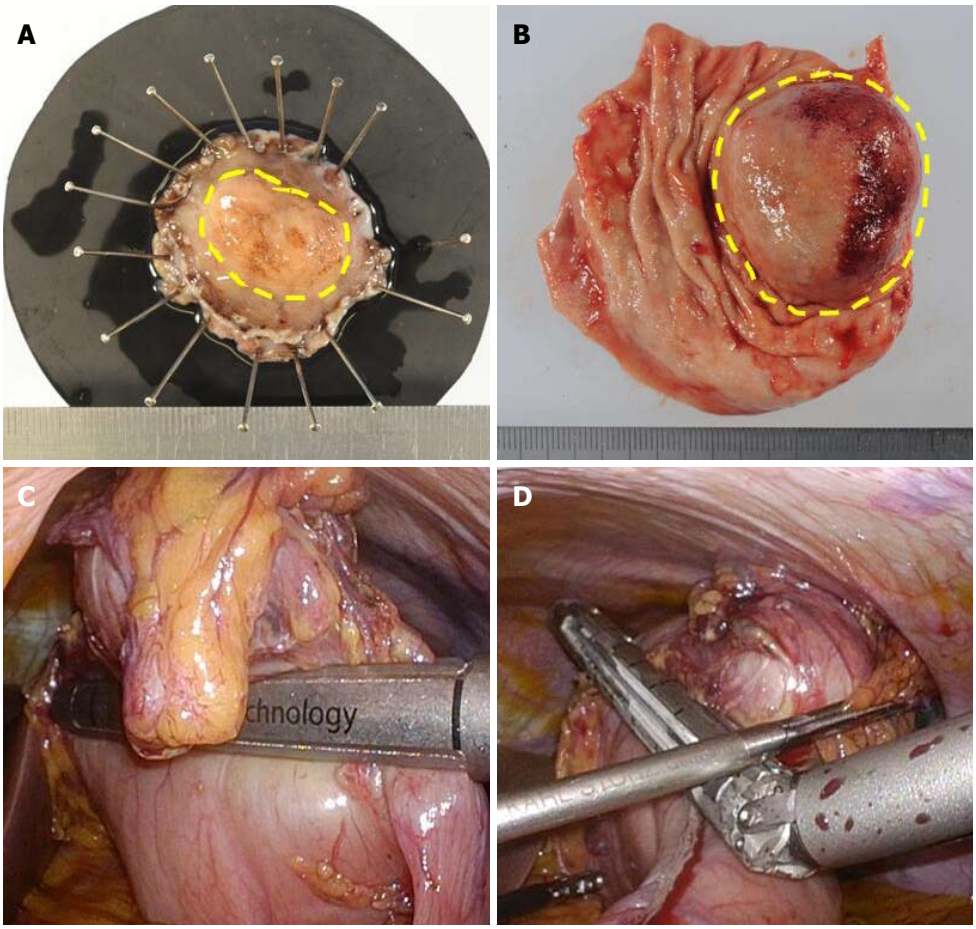

Figure 8 Comparison of surgical margins between laparoscopic and endoscopic cooperative surgery and conventional wedge resection. A: Specimen of Laparoscopic and endoscopic cooperative surgery (LECS). The surgical margin from the tumor is kept at the proper distance; B: Specimen of conventional wedge resection. Simple wedge resection causes both excessive and inadequate resection of the gastric wall, which may lead to postoperative gastric stenosis, gastric dysfunction, and local recurrence; C and D: Intraoperative view of conventional wedge resection with a linear stapler. The resection line is as shown in Figure 1B. The specimen has a portion too close to the tumor and a portion far from the tumor.

by some researchers[47,57]. Laparoscopic-assisted endoscopic full-thickness resection is also an established procedure[83]. LECS without lymph node dissection for EGC has been applied to limited cases involving technical difficulties when performing ESD such as severe ulcer-related scarring, an unfavorable tumor location, and a large tumor size. However, patients with lymph node metastasis have not been included. LECS for EGC has also been attempted according to the concept of sentinel lymph node dissection[84]. Sentinel lymph node biopsy for EGC is reportedly useful when deciding whether to perform lymph node dissection[85]. If the sentinel lymph node concept is established in the surgical treatment for gastric cancer, the indications for LECS for EGC could be expanded in the future, which could result in increasingly successful gastric cancer treatment. Gastrectomy with lymph node dissection for older patients with gastric cancer, especially those aged $\geqslant$ 85 years, has been highly associated with mortality during the postoperative course[86]. To prevent postoperative morbidity and mortality, maintaining an appropriate balance in the surgical procedure and range of lymph node dissection is very important based on the patient's general condition, comorbidities, and assumed risk. For selected patients, LECS may be useful as a palliative or symptom-alleviating measure.

ADVANCED TECHNIQUES AND COSMETIC ADVANTAGES

Stab and incisional wounds should be considered as distinct from each other[16,87]. The tumor cased in the bag can be sheathed as much as possible in the overtube (Figure 7), and tumor removal through the mouth can omit the need for an incisional wound. To reduce the need for incisional wounds, natural orifice transluminal endoscopic surgery is currently challenged[88,89].

Robot-assisted excision (da Vinci Surgical System; Intuitive Surgical, Inc., Sunnyvale, CA, United States) regardless of tumor size and location has been reported[90]. Additionally, single-port robotic surgery (Single Port Robotic Surgical System, da Vinci Sp; Intuitive Surgical, Inc.) is currently available.

CONCLUSION

LECS can be safely introduced in a facility-based manner by either surgeons or endoscopists with advanced skills. LECS is a function-preserving surgery with oncological safety and is mainly indicated for gastric SMTs if educated, experienced, and skilled physicians are available. LECS has various possibilities for further developments.

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P- Reviewer: Huerta-Franco MR, Kopljar M **S- Editor**: Ma RY
L- Editor: A **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2018 November 15; 10(11): 398-409

DOI: 10.4251/wjgo.v10.i11.398

ISSN 1948-5204 (online)

MINIREVIEWS

Conversion surgery for gastric cancer patients: A review

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Author contributions: Zurleni T and Rausei S designed the study, edited and revised the manuscript; Zurleni T, Gjoni E and Altomare M reviewed the literature and drafted the study; all authors equally contributed to this paper for the final approval of the final version.

Conflict-of-interest statement: All authors stated they have no conflicts of interest to disclose.

Manuscript source: Invited manuscript

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Received: June 27, 2018
Peer-review started: July 1, 2018
First decision: July 17, 2018
Revised: September 25, 2018
Accepted: October 7, 2018
Article in press: October 7, 2018
Published online: November 15, 2018

Abstract

Gastric cancer (GC) is the third most common cancer-related cause of death worldwide. In locally advanced tumors, neoadjuvant chemotherapy has recently been introduced in most international Western guidelines. For metastatic and unresectable disease, there is still debate regarding correct management and the role of surgery. The standard approach for stage IV GC is palliative chemotherapy. Over the last decade, an increasing number of M1 patients who responded to palliative regimens of induction chemotherapy have been subsequently undergone surgery with curative intent. The objective of the present review is to analyze the literature regarding this approach, known as "conversion surgery", which has become one of the most commonly adopted therapeutic options. It is defined as a treatment aiming at an R0 resection after chemotherapy in initially unresectable tumors. The 13 retrospective studies analyzed, with a total of 411 patients treated with conversion therapy, clearly show that even if standardization of unresectable and metastatic criteria, post-chemotherapy resectability evaluation and timing of surgery has not yet been established, an R0 surgery after induction chemotherapy with partial or complete response seems to offer superior survival results than chemotherapy alone. Additional larger sample-size randomized control trials are needed to identify subgroups of well-stratified patients who could benefit from this multimodal approach.

Key words: Metastatic gastric cancer; Gastric cancer; Conversion surgery; R0 resection; Stage IV gastric cancer; Palliative chemotherapy; Unresectable gastric cancer

Core tip: Conversion surgery is defined as a surgical treatment with the goal of R0 resection in initially unresectable gastric cancer patients after response to chemotherapy. Although the heterogeneity of metastatic disease factors makes it difficult to identify true prognostic variables, a survival benefit has been

demonstrated in several reports. Further prospective large-scale studies seem to be necessary to improve patient selection and to validate this promising multimodal therapy.

Zurleni T, Gjoni E, Altomare M, Rausei S. Conversion surgery for gastric cancer patients: A review. *World J Gastrointest Oncol* 2018; 10(11): 398-409 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/398.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.398

INTRODUCTION

Gastric cancer (GC) is known to be the third most common cancer-related cause of death worldwide[1]. Surgical treatment with adequate extended lymphadenectomy is associated with good outcomes in early stages. However, in advanced GC, prognosis remains poor. Neoadjuvant chemotherapy (NAC) has been suggested for resectable, locally advanced GC based on well-known Randomized Controlled Trial (RCT)s[2,3]. Despite many enrolled patients having lower esophagus or esophagogastric junction involvement and surgery not always including a standard extended lymphadenectomy, there was a survival advantage of NAC plus surgery compared to surgery alone. Therefore, NAC, or preferably preoperative chemotherapy, has been recently introduced as an option in most treatment guidelines[4-9].

The SEER database shows that one third of Western patients with GC have unresectable disease, and different strategies have recently been adopted to manage advanced unresectable cancer[10]. Generally, in these cases, surgery is upfront considered as a palliative treatment for obstruction or bleeding.

Palliative chemotherapy remains the main treatment strategy of IV stage GC patients[11]. Although the median survival time (MST) of these patients has improved due to development of new chemotherapeutics agents, it is still unsatisfactory. Therefore, patients who demonstrated a response to chemotherapy have begun to be subsequently surgically treated with curative intent. This approach in stage IV patients, called "conversion surgery", is becoming one of the most common therapeutic options discussed in the literature over the last decades. The aim of the present review was to define the effective usefulness of this strategy, to identify its crucial aspects and to highlight critical issues and implications for future perspectives.

Literature search

We analyzed articles published in English from 1997 to 2017 using the following key words: Conversion surgery, conversion therapy, R0 resection stage IV GC, unresectable GC. We excluded case reports and case series, ultimately obtaining 13 articles for 13 studies. We first analyzed stage IV factors singularly to define major current therapeutic strategies for any selected patient, and then, we considered oncological outcomes of palliative chemotherapy through experiences derived from several trials. Therefore, we focused on the emerging role of conversion therapy as a new treatment option for metastatic gastric cancer patients.

STAGE IV GC

Stage IV GC is a heterogeneous biological condition with a mixture of distant metastases, including hematologic, lymph nodal and/or peritoneal. To reduce this heterogeneity, the Japanese Gastric Cancer Association (JGCA) and the Union Internationale Contre le Cancer (UICC) minimized differences between their classifications and categorized similar groups[12-16]. However, these systems do not seem sufficient to derive any significant clinical suggestions.

In the recent classification introduced by Yoshida *et al*[17] with the proposal to identify objective principles for conversion surgery, stage IV patients were subdivided into 4 new categories (Figure 1). Initially, the presence of macroscopic peritoneal dissemination is considered as a different biological and prognostic finding compared with hematological metastases. Patients without peritoneal involvement belong to category 1 (potentially resectable metastases) and category 2 (marginally resectable metastases). Patients with macroscopic peritoneal metastases are stratified into category 3 (unresectable except certain situations) and category 4 (incurable metastases). Below we highlight different critical aspects in terms of staging, treatment and prognosis of different potential metastatic patterns in stage IV GC.

Peritoneal metastases

Synchronous peritoneal carcinomatosis (PC) is the most frequent site of metastasis in stage IV GC. PC occurs in 14%-43% of GC patients and represents 35% of all synchronous metastases[18,19]. The prognosis of PC in GC is worse than that for other metastatic sites[20,21]. Peritoneal dissemination of GC is a dynamic multistep process that involves several molecules acting in a coordinated way. As reported in a recent review by Kanda *et al*[22], there are 4 steps in peritoneal dissemination: (1) migration to the abdominal cavity after detachment of cells from the tumor; (2) adaptation to the abdominal microenvironment; (3) adhesion to mesothelial cells and invasion of the baseline membrane; and (4) growth and angiogenesis of the tumor. These molecular mechanisms are very challenging because identification of a single pathway is not necessarily correlated with disease prognosis.

Survival of patients with PC is poor, despite the progress of chemotherapy. Hence, PC is often considered a determinant for a "real" curative treatment possibility,

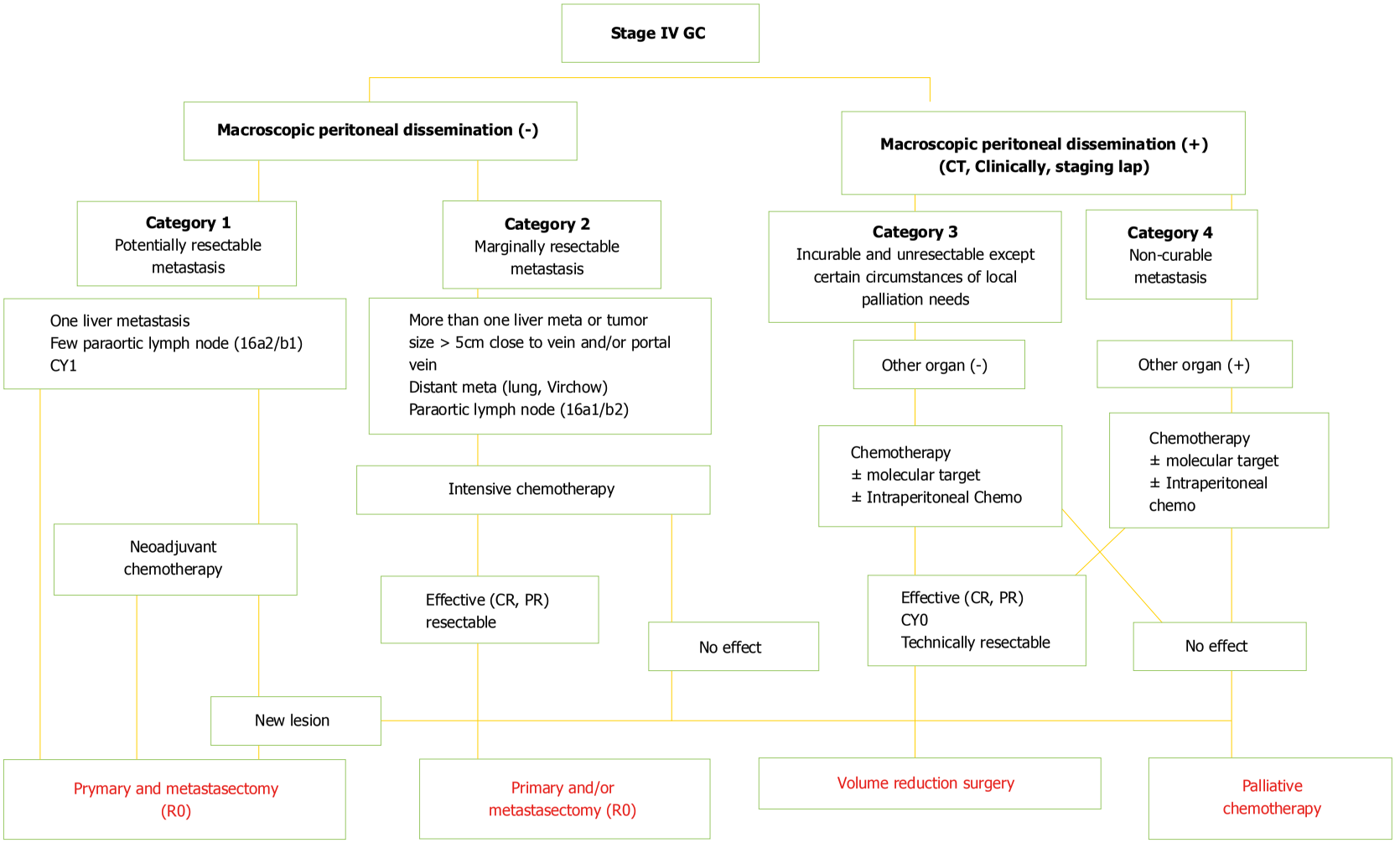

Figure 1 Biological categories proposed by Yoshida *et al*[17]. GC: Gastric cancer.

and several scoring systems on extension of PC have been validated to accurately discriminate treatment options, stratify patients prognosis, and, consequently, correct statistical analyses[23-25]. Okabe *et al*[26] noted that in curatively (R0) resected patients, after disappearance of limited peritoneal dissemination treated with induction therapy (S-1 plus cisplatin), MST was significantly longer (43.2 mo) than in patients who underwent non-curative resection (12.6 m), as well as in patients without surgery (10.3 m). To increase chemotherapy efficacy for PC, the literature suggests an additional benefit of hyperthermic intraperitoneal administration of drugs (hyperthermic intraperitoneal chemotherapy, HIPEC)[27-31].

Recent advances in multimodal treatment for patients with peritoneal dissemination are highlighted by Ishigami *et al*[32] in the PHOENIX-GC trial that, although failing to show statistical superiority for intraperitoneal paclitaxel plus systemic chemotherapy, suggested possible clinical benefit for this treatment option. In a systematic review of 10 studies considering 441 patients treated with cytoreductive surgery plus HIPEC, a median overall survival of 15 mo after radical (R0) cytoreduction was shown by Gill *et al*[33]. Consistently, the phase Ⅲ randomized trial by Yang *et al*[34] and the GYMSSA trial reported improved survival rates with surgery plus HIPEC compared with surgery alone[35].

Distant metastasis

Many patients with stage IV GC have multiple metastatic sites. Usually, the first site of metastasis occurring through the hematogenous pathway is the liver. Systemic chemotherapy is a standard treatment approach for GC patients with liver metastases[36], recommended by both the National Comprehensive Cancer Network (NCCN) Guidelines and the Japanese Guidelines[37,38]. Surgical resection has been recently reported to prolong survival in highly selected patients[39-41]. Li *et al*[42] reported a 100% response rate after chemotherapy with weekly DCF regimen before curative gastrectomy in 8 patients. A multidisciplinary approach, including surgery in selected GC patients when the liver is the only site of metastasis, is associated with interesting results[43]. However, treatment of synchronous or metachronous hepatic metastases is not well standardized in GC patients. Once combined with gastrectomy and extended lymphadenectomy, there are no differences in 5-year survival after resection of synchronous and metachronous liver metastases[44]. Considering metachronous metastases, patients submitted to surgery benefit from better selection and exhibit good survival over short and medium terms[45]. Surgical treatment of the best subgroups of candidates can achieve good results that should encourage surgeons and medical oncologists[41,46].

Lymph node metastases

A proper lymphadenectomy during surgical resection is a milestone for GC treatment. Patients with para-aortic lymph node (PAN) metastases, or bulky nodes around the hepatic, splenic, or celiac arteries are considered unresectable. Some retrospective studies demonstrated the presence of PAN metastases in greater than 20% of patients undergoing D2 + PAN dissection, and 5-year survival rates of patients with PAN metastases do not exceed 20%[47,48]. Furthermore, a phase Ⅲ trial JCOG9501 comparing D2 nodal dissection with or without PAN dissection for GC concluded that prophylactic PAN dissection does not improve survival rates[49]. Interestingly, patients with macroscopic metastases in these nodes were excluded from analysis, resulting in a low incidence of metastatic n° 16 nodes in patients receiving PAN dissection. This "selection bias" left open the issue of prognostic efficacy of removal of PAN station in PAN metastatic patients[50]. On the other hand, since 2000, three phase Ⅱ trials (JCOG0001, JCOG0405 and JCOG1002) have explored preoperative/induction chemotherapy and PAND gastrectomy for bulky N2/N3 gastric cancer[51-54]. The JCOG0001 study reported a low 3-year survival rate (27%) after 2-3 cycles of irinotecan and cisplatin followed by surgery. Conversely, the JCOG0405 trial demonstrated an excellent response rate (up to 64.7%) with 3-year survival of 58.8% in patients who received 2-3 cycles of cisplatin and S-1 before surgery. Similarly, in the JCOG1002 study, among 52 eligible patients, 48 underwent surgery, 44 with R0 resection (84.6%), after 2-3 cycles of docetaxel, cisplatin and S-1 with a pathological response rate of 50%.

PALLIATIVE CHEMOTHERAPY

As specified above, according to current guidelines, palliative chemotherapy is the main strategy for treatment of stage IV GC patients. These cases have always represented the ideal setting for use of many new combinations of chemotherapeutic agents, both in Japan and in Western countries[55-67]. The median overall survival observed in these studies varies between 3 and 17 mo. In the SPIRIT trial, an overall survival of 13 mo was reported using S-1 plus cisplatin, which is defined as the standard treatment for metastatic GC in Japan[56]. In Western countries, the treatment most commonly used for metastatic GC is a combination of chemotherapy regimens, including fluoropyrimidine plus a platinum agent, though epirubicin or docetaxel can also be combined[64,66]. Recent developments in chemotherapeutic and molecular targeted agents have added new clinical issues in the management of incurable GC. As reported in the ToGA trial, Trastuzumab plus chemotherapy in HER2-positive patients improved overall median survival from 11.1 to 13.8 mo[60]. In addition, histological biomarkers have been identified to predict survival among GC patients[68]. Recently, palliative chemotherapy seemed further validated compared with palliative surgery by results of the REGATTA trial. In fact, although some authors emphasized the beneficial role of palliative gastrectomy[69,70], in this RCT, Fujitani *et al*[71] demonstrated no survival benefit for palliative gastrectomy prior to chemotherapy in advanced GC patients with a single non-curative factor. However, the methodological biases of the REGATTA trial negatively affect reliability of its results and weaken its potential clinical implications[72]. Therefore, at the moment, for stage IV GC patients, we have no strong evidence to consider the results of palliative chemotherapy satisfactory. On the other hand, we also have no reliable data to suggest definitely abandoning surgery.

FROM SALVAGE SURGERY TO CONVERSION THERAPY

The heterogeneous presentation of stage IV GC characteristics makes it difficult to identify the best therapeutic strategy for these tumors due to their different biological behaviors. On the other hand, given the poor results achieved with chemotherapy alone, in order to further improve survival of these patients, new therapeutic approaches have been considered. Based on experiences of the multidisciplinary treatment of metastatic colorectal cancer, in the last 2 decades, many studies have been conducted to evaluate efficacy of the combination of chemotherapy and surgery for stage IV GC. Surgical resection for advanced tumors has historically been called "radical", "salvage", "adjuvant" or "secondary" gastrectomy. More specifically, the concept of conversion surgery has been recently treated by Yoshida[17] to define a treatment aiming to R0 resection after chemotherapy in initially unresectable patients.

Tables 1 and 2 show patient characteristics and treatment options analyzed in the considered studies, as well as survival results. Below, we discuss in chronological order the main results of these studies, with particular focus on potential prognostic factors in conversion surgery strategy.

Examined studies

Probably, the first report of conversion surgery was in 1997 by Nakajima *et al*[73]. Thirty patients with incurable GC were treated with combined chemotherapy and radical surgery. Survival of patients with curative resection was 55.6% at 5 years. Long-term survivors were exclusively found among patients with distant metastatic lymph nodes. PC and extra-abdominal lesions did not respond to chemotherapy and, hence, did not reach surgery[73].

Yano *et al*[74] analyzed 34 patients with inoperable GC who underwent NAC. Eight patients among 14 who received salvage surgery exhibited curative resection. Histological type, T4 as non-curative factors, clinical response, and salvage surgery were significant prognostic factors. T4 unresectable lesions and paraaortic node metastases showed high dissolution rates after chemotherapy, whereas peritoneal and distant metastases did not[74]. A study on combined treatment with S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV GC was conducted by Satoh *et al*[75]. Their results showed that 26 patients among 44 who received preoperative chemotherapy underwent R0 surgical resection. Interestingly, all 12 patients with pre-cy1 as a single pre-stage IV factor achieved R0 resection with a 2-year OS of 75%[75].

In 2012, Kanda *et al*[76] reported a good response rate to S-1 chemotherapy in patients with incurable GC who were submitted to secondary surgery. Twenty-six patients of 28 underwent R0 resection. The results showed that 1-, 3-and 5-year survival were 82.1, 45.9 and 34.4%, respectively. Multivariate analysis revealed histological lesion length to be the only significant prognostic factor[76]. According to reports from Han *et al*[77], 22/34 M1 patients with one initial metastatic site who responded to induction chemotherapy exhibited good survival outcomes after R0 resection, with resection rates of 88% and 44% for one and two metastatic sites, respectively. MST of R0 was 22.9 mo, with a 3-year overall survival of 41.4%. Concerning gastric cancer patients with peritoneal seeding, Kim *et al*[78] published results of 18 conversion patients in which 10 received R0 resection after chemotherapy. MST and 3-year OS of R0 patients were 37 mo and 50%, respectively. Unexpectedly, 8 patients who received non-curative resection had longer survival rates than did other patients who continued chemotherapy[78].

Fukuchi *et al*[79] reported a series of 40 out of 151 patients who underwent conversion surgery. In 32 of them, it was possible to perform R0 resection with a 5-year OS of 49% (MST: 62 mo). By multivariate analysis, the presence of just one non-curative factor and R0 resection were significant independent predictors for good OS[79].

Kinoshita *et al*[80] analyzed the effects of conversion gastrectomy after docetaxel, cisplatin and S-1 (DCS) combined chemotherapy. Of 57 patients, 42 were categorized as unresectable, while 15 patients were potentially resectable cases, with a single incurable factor (16 a2-b1 metastases or < 3 peripheral liver metastases). The 3-year OS rate of potentially resectable cases was 92.9%, compared with 35.1% of unresectable cases[80].

In a multi-institutional retrospective study, Sato *et al*[81] highlighted pathological response as a significant independent predictor for OS. He determined that 33/100 patients were able to undergo conversion therapy. Almost eighty-five of them received an R0 resection after DCS chemotherapy with a pathological response rate of 78.8%. Five-year OS in R0 patients was 48.6%[81].

Ten patients with one incurable factor were retrospectively analyzed by Einama *et al*[82]. All cases were considered resectable after chemotherapy, achieving R0 resection. The authors reported a longer survival of surgical patients compared with those who received chemo alone (MST 29 mo). Non-invasive macroscopic type, higher differentiation, and absence of peritoneal dissemination were all favorable survival predictors[82].

Another study concerning conversion surgery after combination chemotherapy of docetaxel, cisplatin, and S-1 from Mieno *et al*[83] reported that 74.2% of the study population (23/31) underwent R0 resection in patients with stage IV GC initially deemed unresectable. Fifty-eight point one percent of patients had extra regional

Table 1 Patient characteristics and onco-surgical treatments

Reference	Period	Population (conversion surgery)	Median - age	Unresectable criteria						Chemotherapy	Surgery	Lymphadenectomy (D2 or more)	Ro
				P1	H1	Cy1	PAN/N3	T4	Other				
Nakajima *et al*[73], 1997	1989-1995	30 (19)	53	9 (30%)	11 (37%)		23 (77%)	8 (27%)	3 (10%)	FLEP	NS	NS	9 (30%)
Yano *et al*[74], 2002	May 1994-Dec 1999	34 (14)	54.4 (31-73)	26 (76%)	4 (12%)		10 (3.4%)	12 (35%)	1 (0.3%)	FEMTXP or THP-FLPM	NS	NS	8 (24%)
Satoh *et al*[75],2012	May 2003-Mar 2008	51 (44)	63 (35-79)	24 (49%)	3 (6%)	12 (23%)	7 (14%)		5 (10%)	S1 + Cisplatin	TG (58%) DG (21.5%)	82%	26 (51%)
Kanda *et al*[76],2012	Apr 2000-Mar 2008	31(28)	65.5 (49-79)	7 (25%)	4 (14.3%)		15 (54%)	9 (32%)		S1 + Cisplatin or Paclitaxel or Irinotecan	TG (42.89%) DG (57.1%)	96.30%	26 (93%)
Han *et al*[77], 2014	Jan 2000-Dec 2009	34 (34)	56 (28-71)	7 (14%)	5 (10%)		15 (29.4%)		7 (14%)	5-FU + Platinum or 5-FU + Platinum + Taxane	NS	NS	26 (76.5%)
Kim *et al*[78], 2014	Jan 2003-Dec 2012	43 (18)	52.8 (32-72)	43 (100%)						5-FU + Cisplatin or S1 + Cisplatin	TG (72.2%) DG (27.7%)	100%	10 (55%)
Fukuchi *et al*[79], 2015	Feb 2003-Dec 2013	151 (40)	66 (31-79)	11 (28%)	5 (13%)	3 (8%)		6 (15%)	26 (65%)	S1 + Cisplatin or S1 + Paclitaxel	TG (72.5%) DG (27.5%)	NS	32 (80%)
Kinoshita *et al*[80], 2015	Apr 2006-Mar 2012	57 (34)	65 (30-78)	15 (26%)	18 (32%)		23 (40%)		2 (3.5%)	DCS	TG (64.7%) DG (26.5%)	50%	27 (79%)
Sato *et al*[81], 2017	Dec 2002-Apr 2014	100 (33)	63 (26-78)	33 (33%)	29 (29%)		61 (61%)	14 (14%)	11 (11%)	DCS I line, CPT-11 II line	TG (84.8%) DG (12.1%)	100%	28 (85%)
Einama *et al*[82],2017	Jan 2009-Dec 2015	10	70.5 (59-86)	3 (30%)	1 (10%)	1 (10%)	4 (40%)	1 (10%)		S1 + CDDP or DOC	TG (40%) DG (30%)	100%	10 (100%)
Mieno *et al*[83],2017	Oct 2006-Dec 2012	31 (31)	63 (35-78)	25%	16%		58%	26%		DCS + DS (Docetaxel-S1) in responder patients	TG (74.2%) DG (22.6%)	77%	23 (74%)
Yamaguchi *et al*[84], 2017	2001-2013	259 (84)	61.7 (21-78)	35 (41%)			37 (44%)		34 (40%)	DCS or S1 or S1 + Cisplatin or S1 + Taxane	TG (82.1%) DG (17.9%)	NS	43 (51%)
Morgagni *et al*[85], 2018	Apr 2005-Aug 2016	73 (22)	69 (59-74)							Epirubicin + Cisplatinum + 5-FU or Oxaliplatin + 5-FU or Docetaxel + Oxaliplatin + 5-FU or Other	TG (72.7%) DG (22.7%)	91.90%	22 (100%)

P1: Peritoneal carcinomatosis; H1: Hepatic metastases; Cy1: Positive cytology; PAN: Para-aortic node metastases; TG: Total gastrectomy; DG: Distal gastrectomy; DCS/DS: Docetaxel-Cisplatin-S1/Docetaxel-Cisplatin; FEMTXP: Fluorouracil, epirubicin, methotrexate, cisplatin; THP-FLPM: Pirarubicin, 5-FU, Leucovorin, Cisplatin, mitomycin C; FLEP: 5-FU + Leucovorin + Etoposide; CDDP: Cisplatin; DOC: Docetaxel; NS: Not specified.

lymph node as unresectable factor[83].

In a study by Yamaguchi *et al*[84], 84 patients among 259 with stage IV GC received conversion surgery after chemotherapy. Patients were classified into four categories

Table 2 Overall survival and median survival time

Reference	Years	OS (rate)			MST (mo)		
		CHT	CHT + surgery		CHT	CHT + surgery	
			R1/R2	R0		R1/R2	R0
Nakajima *et al*[73], 1997	2/3-yr				4.7	6.5	
	5-yr			55.6			
Yano *et al*[74], 2002[2]	2/3-yr						
	5-yr						
Satoh *et al*[75], 2012	2/3-yr		43	75[1]			19.2
	5-yr						
Kanda *et al*[76], 2012	2/3-yr		0	45.9			29
	5-yr			34.4			
Han *et al*[77], 2014	2/3-yr			41.4		7.8	22.9
	5-yr						
Kim *et al*[78], 2014	2/3-yr	0	0	50	8	18	37
	5-yr						
Fukuchi *et al*[79], 2015	2/3-yr				14	30	62
	5-yr	1	15	49			
Kinoshita *et al*[80], 2015	2/3-yr	0	16	63.5	9.6	29.9	
	5-yr						
Sato *et al*[81], 2017	2/3-yr	18.7			15.7	21.7	47.9
	5-yr	0	0	48.6			
Einama *et al*[82], 2017	2/3-yr						29
	5-yr						
Mieno *et al*[83], 2017	2/3-yr	56.9		73.1		56.1	
	5-yr						
Yamaguchi *et al*[84], 2017	2/3-yr				11.3	21.2	41.3
	5-yr						
Morgagni *et al*[85], 2018	2/3 yr	0		39.4	14		38[3]
	5 yr						

[1]R0 in only pre-Cy1 patients; [2]No data are specified but a *P* value < 0.0003 is shown between resected and not-resected 5-years OS rate; [3]Patients who had cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy had an MST of 50 mo. OS: Overall survival; MST: Median survival time; CHT: Chemotherapy.

previously published by the same authors[17]. Survival results of this series rose from 24.7 to 31.0 of MST. Patients who underwent R0 resection had an MST of 41.3 mo[84]. Recently, Morgagni *et al*[85] reported a Western series of 22 patients among 73 unresectable subjects who underwent R0 resection after induction chemotherapy. Gastrectomy plus HIPEC was performed in 9 patients. The 1- and 3-year survival rates were 63.6% and 39.4%, respectively[85].

DISCUSSION

Gastric cancer is known to be a heterogeneous disease. Dissemination may occur directly to the peritoneum, through the hematogenous and lymphatic systems. Moreover, the method whereby cancer cells enter into the portal circulation varies, resulting in significant variability of metastatic patients both for the site and the amount of tumor. Consequently, few metastatic patients are eligible for conversion surgery. Moreover, frequent coexistence of different factors of incurability make it difficult to identify true prognostic variables, as well as the rate of response to chemotherapeutic treatments. Despite progress in chemotherapy providing significant hope with new drug agents, the response rates of metastatic GC patients remain unsatisfactory with non-optimal patient compliance. The definition of initial unresectable criteria and post-chemotherapy resectability has yet to be established. In many cases, the line between neoadjuvant and induction chemotherapy remains unclear. Therefore, analysis of experiences on conversion surgery in stage IV GC is very challenging due to the heterogeneity of series, makes it very difficult to compare results from different studies. Furthermore, the majority of analyzed studies have been performed in Eastern Asia (only one in Italy). As such, this could represent a potential bias for reliable evaluation independent of differences in chemotherapy schedules, quality of surgery, and patient biology, for example. Undoubtedly, the Regatta trial taught us that even a palliative gastrectomy increases patient morbidity compared with chemotherapy alone. Hence, a strict selection of patients who could potentially benefit from conversion surgery seems mandatory. Yoshida *et al*[17] proposed a biological classification to stratify all stage IV GC patients to respond to this need (Figure 1). Probably, long-term survivors can be found mostly in the first three categories, though the small number of patients in the first category can be explained by this unusual condition. Actually, these patients are likely to benefit from NAC.

Although analyzed studies were retrospective and

limited with respect to number of patients enrolled, the possibility of curative resection seems a crucial aspect. The literature reports R0 resection rates ranging from 24%-100% (Table 1), and these numbers are closely correlated with prognosis (Table 2). Thus, the survival benefit derived from R0 resections might justify a predictable increase in morbidity compared with survival from medical therapy alone. Interestingly, even non-curative resection often results in superior survival compared to chemotherapy alone. Consistent with this suggestion from the literature, quality of life (QOL) after conversion (even if non curative) surgery remains an intriguing issue to be analyzed. In this regard, a meta-analysis conducted by Lasithiotakis *et al*[86] underlined the relevant role of QOL outcomes after palliative gastrectomy.

Consistent with considerations by Yoshida *et al*[17], the presence of only one-site of metastasis is one of the most important prognostic factors according to most analyzed studies. In this literature review, lymph node metastases and positive cytology on peritoneal washing as unresectable factors are also related to better prognoses after conversion surgery when partial or complete response to chemo was observed. In this regard, while the more reliable (and later) evaluation of pathological response was demonstrated to be correlated with survival after conversion therapy, we have no unquestionable prognostic data and no objective criteria for clinical response assessment. Indeed, another determining factor is the detection of the best timing to operate (or to decide to not operate). Generally, surgery occurs when the tumor decreases in sizes and before it develops any drug resistance. For this determinant decision making step, cooperation between oncologists and surgeons is mandatory for general management of patients (and not the tumor alone). Regarding type of surgery and extension of lymphadenectomy, total or distal gastrectomy (also with multivisceral approach) aiming at R0 resection was generally associated with D2 or more extended lymphadenectomy. We believe that a proper and standardized D2 lymphadenectomy could achieve optimal results with acceptable morbidity/mortality. Finally, whether chemotherapy is required after an R0 resection is an issue that needs clarification.

In conclusion, the survival efficacy of conversion surgery may dramatically improve when combined with targeted chemotherapy. Perhaps new cytotoxic and molecular targeted agents and progress in sensitive molecular biomarker development could shift treatment from standardized to personalized, leading to further improved outcomes. The promising results of this multimodal therapy are increasingly gaining the attention of medical and surgical oncologists in planning further studies. Although it seems hard to design a valuable trial due to the difficulty of enrolling patients, it appears mandatory to demonstrate the effectiveness of this strategy in stage IV GC patients, or at least in well-selected and stratified stage IV patient subgroups. On the other hand, given that long-time survivors exist, we are convinced that the multidisciplinary discussion should always be recommended on a case-by-case basis. In conclusion, it is well known that some decades ago patients affected by unresectable GC represented a large population on whom medical oncologists applied new and promising therapies without great success. Today, the strategy of conversion surgery induces oncologists to consider that surgery could still have a role, even after almost "hopeless" systemic therapy.

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P- Reviewer: Arigami T, Barreto SG, Caboclo JF, Fujita T, Ierardi E
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2018 November 15; 10(11): 410-420

DOI: 10.4251/wjgo.v10.i11.410

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of primary tumor localization in stage II and III colon cancer

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Author contributions: All authors helped perform the research; Sakin A wrote the manuscript, and performed procedures and data analysis; Sakin A and Secmeler S wrote the manuscript, drafted study conception and design, and performed experiments and data analysis; Arici S and Geredeli C contribution to writing the manuscript, drafting conception and design; Sakin A, Yasar N, Demir OG, Demir C and Cihan S contribution to writing the manuscript; Sakin A, Cihan S, Yasar N and Can O contribution to writing the manuscript, drafting conception and design.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital.

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

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

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: August 13, 2018
Peer-review started: August 13, 2018
First decision: August 24, 2018
Revised: September 14, 2018
Accepted: October 17, 2018
Article in press: October 17, 2018
Published online: November 15, 2018

Abstract

AIM

To investigate the effects of tumor localization on disease free survival (DFS) and overall survival (OS) in patients with stage Ⅱ-Ⅲ colon cancer.

METHODS

This retrospective study included 942 patients with stage Ⅱ and Ⅲ colon cancer, which were followed up in our clinics between 1995 and 2017. The tumors from the caecum to splenic flexure were defined as right colon cancer (RCC) and those from splenic flexure to the sigmoid colon as left colon cancer (LCC).

RESULTS

The median age of the patients was 58 years (range: 19-94 years). Male patients constituted 54.2%. The rates of RCC and LCC were 48.4% (n = 456) and 51.6% (n = 486), respectively. During the median follow-up of 90 mo (range: 6-252 mo), 14.6% of patients developed recurrence and 9.1% of patients died. In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, DFS was similar in terms of primary tumor localization (stage Ⅱ; P = 0.547 and P = 0.481, respectively; stage Ⅲ; P = 0.976 and P = 0.978, respectively). In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, OS was not statistically significant with respect to primary tumor localization (stage Ⅱ; P = 0.381 and P = 0.947, respectively; stage Ⅲ; P = 0.378 and P = 0.904, respectively). The difference between median OS of recurrent RCC (26 ± 6.2 mo) and LCC (34 ± 4.9 mo) cases was eight months (P = 0.092).

CONCLUSION

Our study showed no association of tumor localization with either DFS or OS in patients with stage Ⅱ or Ⅲ colon cancer managed with or without adjuvant therapy. However, post-recurrence OS appeared to be worse in RCC patients.

Key words: Colon cancer; Tumor localization; Adjuvant treatment; Overall survival; Disease free survival

Core tip: It is well known that metastatic right colon cancer is more aggressive than left colon cancer. However, the effects of tumor location on the decision of adjuvant therapy and survival are not clearly known in early stage disease. In this retrospective study, we investigated the effects of tumor location on disease free survival and overall survival in patients with and without adjuvant therapy for stage Ⅱ-Ⅲ colon cancer. There was no difference for disease free survival or overall survival between patients with right or left localized colon cancer, but we established that right localized tumors were more aggressive than left side after recurrence.

Sakin A, Arici S, Secmeler S, Can O, Geredeli C, Yasar N, Demir C, Demir OG, Cihan S. Prognostic significance of primary tumor localization in stage II and III colon cancer. *World J Gastrointest Oncol* 2018; 10(11): 410-420 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/410.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.410

INTRODUCTION

Colon cancer (CC) is a common and fatal disease. It is estimated that about 95520 CC cases are diagnosed annually in the United States. CC is the third most common cancer in men and the second most common cancer in women. Despite a declining mortality since 1990, it ranked the third in women and the second in men in cancer-related deaths. From 1992 to 2012, the incidence of men and women under the age of 50 diagnosed with CC increased by 2.1% per year. These increases were primarily seen in left-sided cancers, and particularly in rectal cancer (3.9% per year). Approximately 39% of the cases are local, and 37% are locoregional at diagnosis. Seventy to 80% of patients with locoregional disease at diagnosis are suitable for curative surgery. While surgery is essential for curative treatment, some patients have recurrence even after curative surgery. The prognosis is worse after recurrence. For this reason, it is important to identify reliable factors for identification of patients at high risk of recurrence[1,2].

The proximal and distal segments of the colon possess different embryological origins. The segment extending from the caecum to the proximal two-thirds of the transverse colon develops from the midgut. The part from the distal third of the transverse colon to the rectum develops from the hindgut. While the right colon consists of the caecum, ascending colon, hepatic flexure, and transverse colon, the left colon consists of the splenic flexure, descending colon, and sigmoid colon. Blood supply, innervation, and lymphatic drainage anatomically differ between the right and left colon. Considering these differences in anatomy and embryological origin, variation in clinical features may be identified for the same disease of the colon[2].

It has been known for many years that right CC (RCC) and left CC (LCC) represent dissimilar tumors with differences in epidemiology, biology, pathology, and clinical outcomes. Recently, the relationship between tumor localization and prognosis in metastatic disease has been investigated. These studies, however, primarily focused on responses to chemo- or targeted therapy[3,4]. For this reason, it is still not clear for patients and clinicians whether tumor localization is an important additional risk factor in locoregional disease.

In our study, we aimed to examine the association of tumor localization to disease free survival (DFS) and overall survival (OS) in patients who underwent curative surgery for stage Ⅱ and Ⅲ CC.

MATERIALS AND METHODS

Patients

This retrospective study included patients who were followed up in the oncology outpatient clinic of Okmeydani Training and Research Hospital between 1995 and 2017. Clinical and pathological data were obtained from medical patient records. Those with rectal cancer, another malignancy distinct from CC, multiple primary tumors, metastatic disease, patients under 18 years and those without sufficient data were not included in the

study. A total of 942 patients with full medical records and a pathological diagnosis of stage Ⅱ-Ⅲ CC were identified. The study was approved by the institutional ethics committee.

Data collection

Data obtained from medical records included the age, gender, alcohol or tobacco use, type of surgery (emergent or elective), presence of diabetes mellitus (DM) or hypertension (HT), histological characteristic (adenocarcinoma, mucinous adenocarcinoma), grade, primary tumor localization, stage, pathological tumor stage (pT), pathological node stage (pN), lymph node status ($\geqslant$ 12 or < 12), numbers of excised and involved lymph nodes, presence of perineural invasion (PNI) or lymphovascular invasion (LVI), surgical margin positivity, use of adjuvant therapy, adjuvant therapeutic regimen, recurrence, and most recent status (exitus-alive). Patients were re-staged according to the 8th tumor, node, and metastasis staging manual 2017 of the American Joint Committee on Cancer/Union for International Cancer Control. Patients were divided into two groups, right colon and left colon. Tumors extending from the caecum to the splenic flexure were classified as RCC, those from the splenic flexure to the sigmoid colon as LCC. Age was grouped as < 65 and $\geqslant$ 65 years. Grades were grouped as 1 + 2 and 3. pT was grouped as 1 + 2, 3 and 4. DFS was estimated as the time elapsed from diagnosis to local recurrence or systemic metastasis. OS was estimated as the time from diagnosis to death. OS2 was defined as the time from recurrence to death.

Statistical analysis

SPSS 15.0 for Windows software package was used for statistical analysis. Descriptive variables were expressed with mean, standard deviation, minimum, and maximum values for numerical parameters, and with number and percentage values for categorical parameters. Numeric variables in two independent groups were analyzed by a Student's *t*-test when the data were normally distributed and by Mann Whitney *U* test when the normal distribution condition was not met. Comparisons of rates in groups were made with chi-square. Monte Carlo simulation was applied when conditions were not met. The survival analyses were performed with Kaplan Meier. Determinants were analyzed by Cox regression. In univariate analysis, a forward stepwise model was used for values with $P <$ 0.250. An overall 5% alpha error level was used to infer statistical significance.

RESULTS

The rates of RCC and LCC were 48.4% (n = 456) and 51.6% (n = 486), respectively. Male patients constituted 54.2%. The median patient age was 58 years (range: 19-94 years). Nearly one-third of patients (32.5%) were equal to or above 65 years old (Table 1).

Twenty-six patients (2.8%) had a family history of CC in their first-degree relatives. The history of smoking and regular alcohol use was present in 45.8% (n = 350) and 5.2% (n = 49) of patients, respectively. Emergency surgery was performed in 151 patients (16%). DM and HT were present in 9.9% and 23.7% of the study population, respectively (Table 1).

Analysis of tumor histology showed mucinous adenocarcinoma in 17.3% of patients, grade Ⅲ tumor in 6.7% of patients, and stage Ⅱ disease in the majority of patients (60.2%). The rates of pT3 and pT4 were 79.8% and 6.1%, respectively. The mean number of lymph node dissections performed was 17.57 $\pm$ 10.8, where lymph node involvement was 1.48 $\pm$ 4.0. The rate of lymph node dissection below 12 was 31.4%. The number of patients with pN2 and pN1 were 102 (10.8%) and 273 (29%), respectively. PNI and LVI positivity was found in 21.7 and 32.2% of patients, respectively. Eight patients (0.8%) had positive surgical margins (Table 1).

Postoperative systemic therapy was initiated in 734 patients (77.9%), 67.2% (n = 493) of which received 5-FU-based (5-fluorouracil + leucovorin, capecitabine) and 32.8% (n = 241) received oxaliplatin-based (capecitabine + oxaliplatin, 5-fluorouracil + leucovorin + oxaliplatin) regimens. A total of 695 patients (94.7%) completed planned adjuvant chemotherapy regimens (Table 1).

During the median follow-up of 90 mo (range: 6-252 mo), 138 (14.6%) patients developed recurrence, and 40 (29.0%) of recurrences were locoregional and 98 (71.0%) were distant and 95 (9.1%) of patients died. Metastasectomy was performed for 48 of patients with recurrence (Table 1).

No statistical difference existed between RCC and LCC in terms of gender, smoking and alcohol use, history of DM and HT, tumor grade, stage, pT stage, pN stage, LVI and PNI positivity, positive surgical margins, adjuvant therapy use, the regimen used for adjuvant therapy, rates for recurrence (locoregional or distant), metastasectomy and death. Rate of mucinous adenocarcinoma histology, rate of LN number of $\geqslant$ 12, and the mean number of LNs dissected were significantly higher in the RCC group (P = 0.002, $P <$ 0.001, and $P <$ 0.001, respectively) (Table 1).

At all stages, 1, 3, 5, 10, and 15-year DFS and OS rates were 97.9%, 89.8%, 87.0%, 84.4%, 82.7% and 99.8%, 96.7%, 92.4%, 86.7%, 86.6%, respectively. In stage Ⅱ RCC and LCC, rates of DFS at 1, 3, 5, 10, and 15 years were 98.9%, 93.9%, 93.1%, 92.0%, 90.3% and 98.0%, 94.5%, 91.8%, 90.5%, 90.5%, respectively. In stage Ⅲ RCC and LCC, rates of DFS at 1, 3, 5, 10, and 15 years were 96.2%, 83.6%, 79.4%, 75.0%, 73.2% and 96.8%, 81.9%, 78.2%, 74.4%, 72.2%, respectively (Table 2).

In stage Ⅱ RCC and LCC, rates of OS at 1, 3, 5, 10, and 15 years were 99.3%, 96.2%, 94.5%, 92.7%, 92.7% and 99.7%, 99.3%, 97.0%, 93.8%, 92.1%,

Table 1 Comparison of clinical and pathological data according to tumor localization

		All patients (n = 942)		RCC (n = 456)		LCC (n = 486)		
		n	%	*n*	%	*n*	%	*P*
Age (yr)	< 65	636	67.5	304	66.7	332	68.3	0.590
	⩾ 65	306	32.5	152	33.3	154	31.7	
Gender	Male	511	54.2	250	54.8	261	53.7	0.730
	Female	431	45.8	206	45.2	225	46.3	
Family history	No	916	97.2	439	96.3	477	98.1	0.790
	Yes	26	2.8	17	3.7	9	1.9	
Smoking status	No	592	62.8	277	60.7	315	64.8	0.192
	Yes	350	37.2	179	39.3	171	35.2	
Alcohol use status	No	893	94.8	434	95.2	459	94.4	0.614
	Yes	49	5.2	22	4.8	27	5.6	
Mode of surgery	Elective	791	84	400	87.7	391	80.5	0.002
	Emergent	151	16	56	12.3	95	19.5	
DM	No	845	89.7	407	89.3	438	90.1	0.527
	Yes	93	9.9	48	10.5	45	9.3	
HT	No	717	76.1	344	75.4	373	76.7	0.329
	Yes	223	23.7	112	24.6	111	22.8	
Histology	Adenocarcinoma	779	82.7	356	78.1	423	87	< 0.001
	Mucinous adenocarcinoma	163	17.3	100	21.9	63	13	
Tumor grade	Well and moderately	879	93.3	420	92.1	459	94.4	0.151
	Poorly	63	6.7	36	7.9	27	5.6	
Tumor stage	Ⅱ	567	60.2	271	59.4	296	60.9	0.644
	Ⅲ	375	39.8	185	40.6	190	39.1	
pT stage	T1-2	133	14.1	57	12.5	76	15.6	0.267
	T3	752	79.8	374	82	378	77.8	
	T4	57	6.1	25	5.5	32	6.6	
The number of removed lymph nodes	< 12	296	31.4	102	22.4	194	39.9	< 0.001
	⩾ 12	646	68.6	354	77.6	292	60.1	
pN	N0	567	60.2	269	59	298	61.3	0.589
	N1	273	29	133	29.2	140	28.8	
	N2	102	10.8	54	11.8	48	9.9	
PNI	Negative	728	78.3	354	78.5	374	78.1	0.879
	Positive	202	21.7	97	21.5	105	21.9	
LVI	Negative	629	67.8	303	67.3	326	68.2	0.777
	Positive	299	32.2	147	32.7	152	31.8	
Surgical margin	Negative	928	98.5	449	98.5	479	98.6	0.096
	Positive	8	0.8	6	1.3	2	0.4	
Adjuvant treatment	No	208	22.1	94	20.6	114	23.5	0.293
	Yes	734	77.9	362	79.4	372	76.5	
Adjuvant treatment regimen	5-FU-based	493	67.2	243	67.1	250	67.2	0.978
	Oxaliplatin-based	241	32.8	119	32.9	122	32.8	
Completion rate of adjuvant treatment		695	94.7	344	95	351	94.4	0.685
Tumor recurrence	No	804	85.4	389	85.3	415	85.4	0.971
	Yes	138	14.6	67	14.7	71	14.6	
	Locoregional recurrence	40	29	21	31.3	19	26.8	0.553
	Systemic recurrence	98	71	46	68.7	52	73.2	
Metastasectomy		48	34.8	24	35.8	24	33.8	0.804
Status	Exitus	95	9.1	51	11.2	44	9.1	0.278
	Alive	847	90.9	405	88.8	486	90.9	
		Median	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**	
Age (yr)		58	19-94	57	19-89	58	21-94	0.141
Follow-up (mo)		90	1-252	90	1-252	90	5-235	
		mean	**SD**	**mean**	**SD**	**mean**	**SD**	
Number of removed lymph nodes		17.57	10.843	19.78	11.059	15.5	10.223	< 0.001
Number of metastatic lymph nodes		1.46	4.068	1.41	2.86	1.5	4.944	0.743

DM: Diabetes mellitus; HT: Hypertension; Max: Maximum; Min: Minimum; LCC: Left colon cancer; LVI: Lymphovascular invasion; *n*: Number of patients; pN: Pathological lymph node stage; PNI: Perineural invasion; pT: Pathological tumor stage; RCC: Right colon cancer.

respectively. In stage Ⅲ RCC and LCC, rates of OS at 1, 3, 5, 10, 15 years were 100.0%, 95.5%, 86.2%, 78.9%,

Table 2 Disease free survival and overall survival rates (%) at 12, 36, 60, 90, 120 and 180 mo according to tumor localization

	All patients (%)	RCC (%)		LCC (%)	
DFS (mo)		Stage II	Stage III	Stage II	Stage III
12	97.9	98.9	96.2	98.0	96.8
36	89.8	93.9	83.6	94.5	81.9
60	87.0	93.1	79.4	91.8	78.2
90	84.9	92.6	75.9	91.3	76.7
120	84.4	92.0	75.0	90.5	74.4
180	82.7	90.3	73.2	90.5	72.2
OS (mo)					
12	99.8	99.3	100.0	99.7	100.0
36	96.7	96.2	95.5	99.3	94.4
60	92.4	94.5	86.2	97.0	87.9
90	89.5	94.0	82.5	94.4	86.4
120	87.6	92.7	78.9	93.8	82.9
180	86.6	92.7	78.9	92.1	82.9

LCC: Left colon cancer; OS: Overall survival; RCC: Right colon cancer; DFS: Disease free survival.

78.9% and 100.0%, 94.4%, 87.9%, 82.9%, 82.9%, respectively (Table 2).

In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, DFS was similar in terms of primary tumor localization (stage Ⅱ; log rank $P = 0.547$ and log rank $P = 0.481$, respectively; stage Ⅲ; log rank $P = 0.976$ and log rank $P = 0.978$, respectively). In stage Ⅲ disease, there was no statistically significant difference for DFS in patients receiving 5-FU-based or oxaliplatin-based regimens according to tumor location (log rank $P = 0.518$ and log rank $P = 0.638$, respectively) (Figure 1).

In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, OS was not statistically significant with respect to primary tumor localization (stage Ⅱ; log rank $P = 0.381$ and log rank $P = 0.947$, respectively; stage Ⅲ; log rank $P = 0.378$ and log rank $P = 0.904$, respectively). In stage Ⅲ disease, there was no statistically significant difference for OS in patients receiving 5-FU-based or oxaliplatin-based regimens according to tumor location (log rank $P = 0.113$ and log rank $P = 0.806$, respectively) (Figure 2). No statistically significant difference was detected between median survival after recurrent/metastatic (OS2) RCC (26 ± 6.2 mo) and LCC (34 ± 4.9 mo) cases (log rank $P = 0.092$) (Figure 3).

Univariate analysis for DFS showed statistically significant factors as age ⩾ 65 years, presentation with ileus, stage, pT stage, pN stage, dissected LN < 12, PNI, LVI, surgical margin positivity, and adjuvant therapy ($P = 0.001$, $P = 0.003$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.008$, and $P = 0.041$, respectively). In multivariate analysis, age ⩾ 65 years, presentation with ileus, stage, dissected LN < 12, PNI, LVI, and adjuvant therapy were detected as statistically significant factors ($P = 0.001$, $P = 0.011$, $P < 0.001$, $P = 0.012$, $P < 0.001$, $P = 0.003$, and $P = 0.005$, respectively) (Table 3).

Univariate analysis for OS revealed statistically significant factors as age ⩾ 65 years, HT, stage, pT stage, pN stage, PNI, LVI, and adjuvant therapy ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.017$, respectively). In multivariate analysis, age ⩾ 65 years, stage, PNI, LVI, and adjuvant therapy were found to be statistically significant factors ($P < 0.001$, $P = 0.036$, $P = 0.001$, $P < 0.001$, and $P = 0.011$, respectively) (Table 4).

DISCUSSION

In this trial, we aimed to investigate whether tumor location had prognostic significance in patients who underwent curative surgery for stage Ⅱ or Ⅲ CC with or without adjuvant therapy. In our study, we found that primary tumor localization had no effect on DFS and OS. A number of studies have been conducted in different regions of the world to describe the differences between RCC and LCC[5-10]. The data related to the prognosis of RCC and LCC are contradictory in recent studies[5-9,11]. Most studies reported patients with RCC as likely to be older, often female, in advanced stages, and poorly differentiated[6-12].

In their study of 1224 patients, Mik *et al*[5] reported that RCC patients were older than LCC patients, with a median age of 67.8 years. LCC patients were likely to have operations for emergent indications. The number of dissected lymph nodes were reported to be higher in RCC (11.7 ± 6 *vs* 8.3 ± 5, $P = 0.0001$)[5]. In another study, the likelihood of RCC was associated with increased age. In addition, T4 tumor, poor differentiation rate, and presence of venous invasion were detected to be significantly higher in RCC[6]. In our study, the median age was 58 years (range: 19-94 years). Similarly, in our study, LCC patients were more likely to have operations for emergent indications. Likewise, mucinous type was significantly more common in RCC. Unlike other studies, we did not detect significant differences between RCC and LCC in terms of age, gender, pT stage, stage, LVI, and PNI[5-9,11-13].

Lim *et al*[7] followed 414 patients with stage Ⅰ-Ⅲ

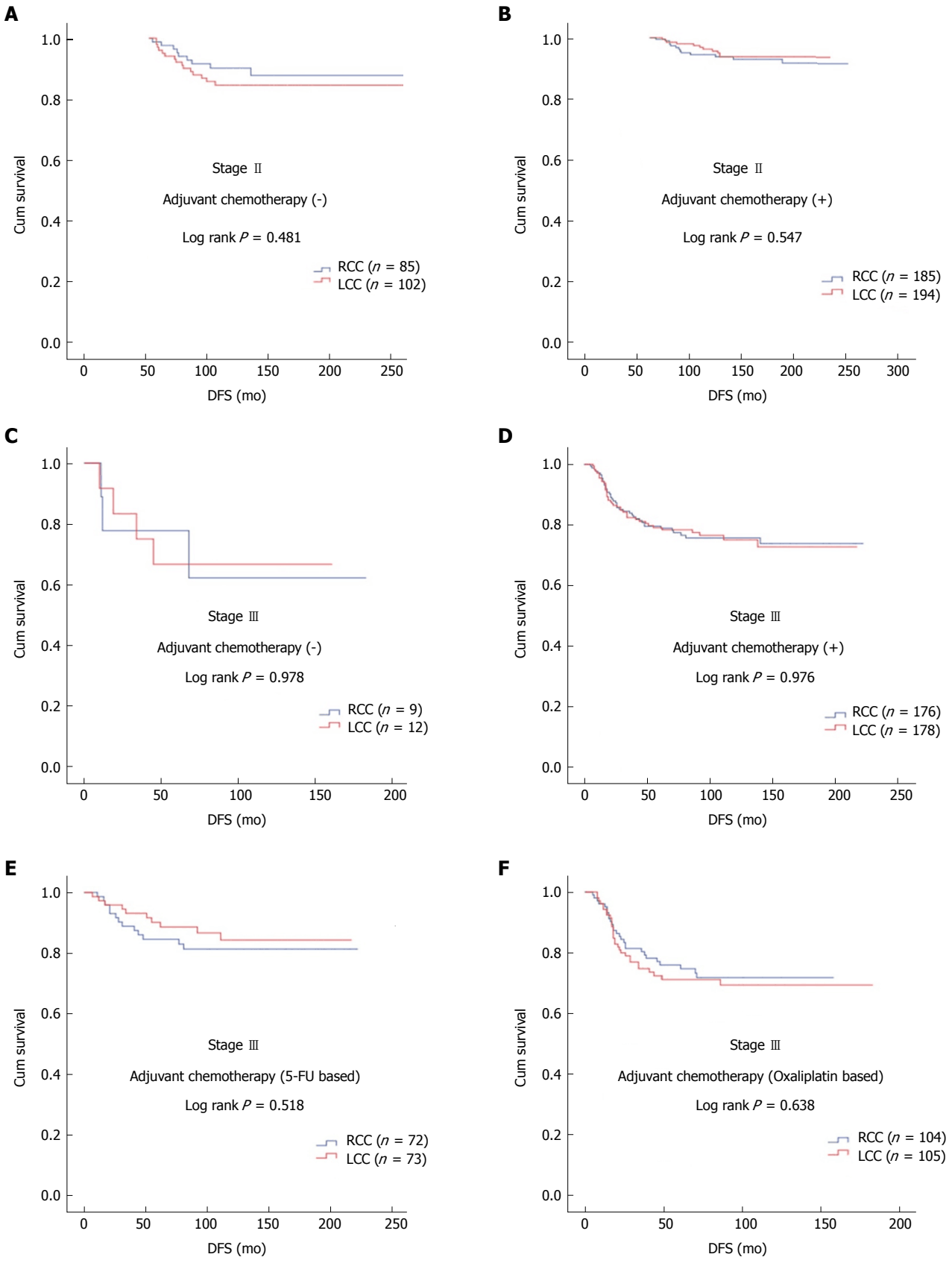

Figure 1 Disease free survival by primary tumor localization in Kaplan-Meier analysis. A: Stage Ⅱ patients not receiving adjuvant therapy; B: Stage Ⅱ patients receiving adjuvant therapy; C: Stage Ⅲ patients not receiving adjuvant therapy; D: Stage Ⅲ patients receiving adjuvant therapy; E: Stage Ⅲ patients receiving adjuvant 5-fluorouracil based therapy; F: Stage Ⅲ patients receiving adjuvant oxaliplatin based therapy. 5-FU: 5-Fluorouracil; DFS: Disease free survival; LCC: Left colon cancer; *n*: Number of patients; RCC: Right colon cancer.

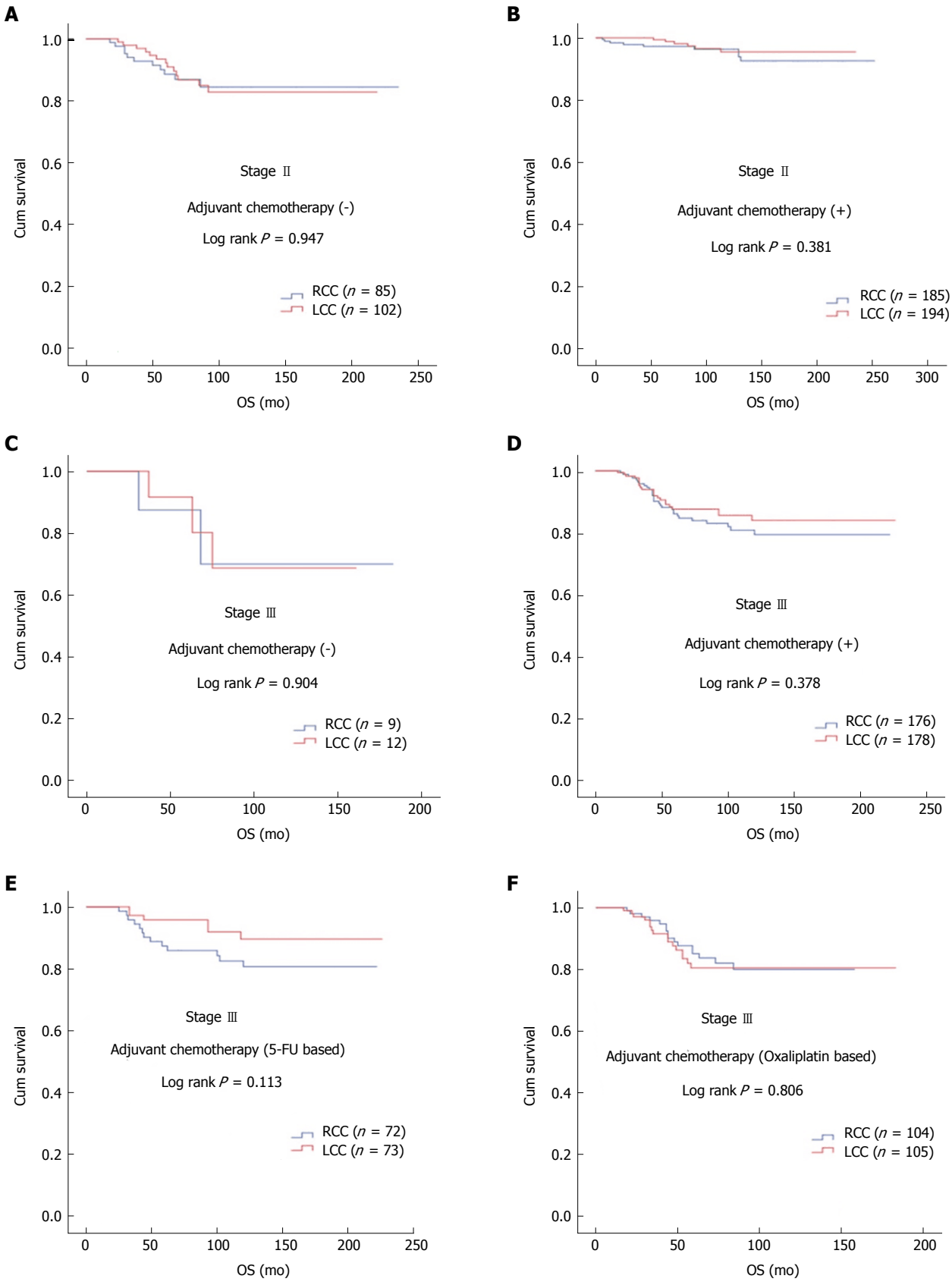

Figure 2 Overall survival by primary tumor localization in Kaplan-Meier analysis. A: Stage Ⅱ patients not receiving adjuvant therapy; B: Stage Ⅱ patients receiving adjuvant therapy; C: Stage Ⅲ patients not receiving adjuvant therapy; D: Stage Ⅲ patients receiving adjuvant therapy; E: Stage Ⅲ patients receiving adjuvant 5-fluorouracil based therapy; F: Stage Ⅲ patients receiving adjuvant oxaliplatin based therapy. 5-FU: 5-Fluorouracil; LCC: Left colon cancer; *n*: Number of patients; OS: Overall survival; RCC: Right colon cancer.

Table 3 Factors affecting disease free survival

		Univariate analysis				Multivariate analysis			
		HR	95%CI		*P*	HR	95%CI		*P*
Age (yr)	< 65	1				1			
	⩾ 65	1.779	1.268	2.496	0.001	1.88	1.305	2.708	0.001
Gender	Male	1							
	Female	0.96	0.686	1.343	0.812				
Family history	No	1							
	Yes	1.195	0.489	2.919	0.696				
Smoking status	No	1							
	Yes	0.908	0.641	1.287	0.587				
Alcohol using status	No	1							
	Yes	0.372	0.118	1.167	0.09				
Mode of surgery	Elective	1				1			
	Emergent	1.796	1.22	2.646	0.003	1.718	1.131	2.611	0.011
DM	No	1							
	Yes	0.973	0.549	1.724	0.925				
HT	No	1							
	Yes	1.541	0.967	2.224	0.067				
Histology	Adenocarcinoma	1							
	Mucinous adenocarcinoma	1.207	0.793	1.839	0.38				
Tumor grade	Well and moderately	1							
	Poorly	1.574	0.889	2.787	0.119				
Tumor location	RCC	1							
	LCC	0.997	0.714	1.392	0.984				
Tumor stage	Ⅱ	1				1			
	Ⅲ	2.99	2.109	4.238	< 0.001	2.281	1.485	3.505	< 0.001
pT stage	T1 + 2	1			< 0.001				
	T2	1.912	0.999	3.662	0.05				
	T4	9.308	4.478	19.348	< 0.001				
Number of removed lymph nodes	⩾ 12	1				1			
	< 12	2.166	1.421	3.301	< 0.001	1.751	1.13	2.712	0.012
pN	N0	1			< 0.001				
	N1	2.779	1.908	4.047	< 0.001				
	N2	3.56	2.237	5.664	< 0.001				
PNI	Negative	1				1			
	Positive	3.953	2.801	5.578	< 0.001	2.277	1.549	3.347	< 0.001
LVI	Negative	1				1			
	Positive	3.372	2.382	4.774	< 0.001	1.825	1.221	2.728	0.003
Surgical margin	Negative	1							
	Positive	3.884	1.436	10.505	0.008				
Adjuvant treatment	No	1				1			
	Yes	0.591	0.346	0.954	0.041	0.514	0.323	0.82	0.005

DM: Diabetes mellitus; HT: Hypertension; Max: Maximum; Min: Minimum; LCC: Left colon cancer; LVI: Lymphovascular invasion; pN: Pathological lymph node stage; PNI: Perineural invasion; pT: Pathological tumor stage; RCC: Right colon cancer.

CC with a median duration of 66.7 mo, during which the 5-year DFS was significantly higher in LCC (88.3%) than in RCC (81.4%). In multivariate analysis, pT3-4, pN1-2, and histologic grades were reported to be prognostic factors for DFS[7]. Moritani *et al*[8] recruited 820 stage Ⅰ to Ⅲ patients with a median follow-up of 55.8 ± 34.9 mo. No statistically significant difference was reported between RCC and LCC in five-year DFS (RCC 88.6%, LCC 89.4%, $P = 0.231$)[8]. Another study had 4029 stage Ⅰ to Ⅲ patients, for which the median follow-up was five years. While three- and five-year DFS rates of patients with RCC were 79.8% and 76.7%, it was 82.0% and 77.6% for LCC, respectively, with no statistically significant difference ($P = 0.35$) [9].

Five, ten, and 15-year DFS were 87.5%, 84.0%, and 82.1% for RCC and 86.7%, 84.2%, and 83.4% for LCC, respectively. In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, DFS was similar in terms of primary tumor localization. Independent risk factors for recurrence included age ⩾ 65 years, presentation with ileus, advanced stage, dissected number of LNs < 12, and presence of PNI and LVI.

In the study by Aoyama *et al*[9], three and five-year median OS rates were 87.6% and 81.6% for RCC and 91.5% and 84.5% for LCC, where the difference was statistically significant ($P < 0.009$). Investigators have emphasized that this difference might originate from the fact that RCC patients were more likely to be older and to have poorly differentiated and mucinous histology[9]. A Far East study performed with 4426 RCC,

Table 4 Factors affecting overall survival

		Univariate analysis				Multivariate analysis			
		HR	95%CI		*P*	HR	95%CI		*P*
Age (yr)	< 65	1				1			
	⩾ 65	4.136	2.731	6.263	< 0.001	4.049	2.578	6.358	< 0.001
Gender	Male	1							
	Female	0.951	0.636	1.423	0.808				
Family history	No	1							
	Yes	0.306	0.043	2.196	0.239				
Smoking status	No	1							
	Yes	0.815	0.533	1.247	0.346				
Alcohol using status	No	1							
	Yes	0.348	0.086	1.411	0.139				
Mode of surgery	Elective	1							
	Emergent	1.342	0.812	2.219	0.252				
DM	No	1							
	Yes	1.683	0.953	2.972	0.073				
HT	No	1							
	Yes	3.067	2.035	4.623	< 0.001				
Histology	Adenocarcinoma	1							
	Mucinous adenocarcinoma	1.213	0.733	2.006	0.452				
Tumor grade	Well and moderately	1							
	Poorly	1.036	0.453	2.369	0.933				
Tumor location	RCC	1							
	LCC	0.807	0.539	1.208	0.297				
Tumor stage	Ⅱ	1				1			
	Ⅲ	2.363	1.57	3.557	< 0.001	1.723	1.037	2.863	0.036
pT stage	T1 + 2	1			< 0.001				
	T2	4.836	1.526	15.326	0.007				
	T4	21.34	6.162	73.897	< 0.001				
Number of removed lymph nodes	⩾ 12	1							
	< 12	1.402	0.897	2.192	0.138				
pN	N0	1			< 0.001				
	N1	2.122	1.353	3.327	0.001				
	N2	3.015	1.742	5.219	< 0.001				
PNI	Negative	1				1			
	Positive	3.653	2.4	5.562	< 0.001	2.198	1.374	3.517	0.001
LVI	Negative	1				1			
	Positive	3.735	2.445	5.707	< 0.001	2.523	1.543	4.127	< 0.001
Surgical margin	Negative	1							
	Positive	2.57	0.633	10.435	0.187				
Adjuvant treatment	No	1				1			
	Yes	0.587	0.379	0.91	0.017	0.517	0.311	0.86	0.011

DM: Diabetes mellitus; HT: Hypertension; LCC: Left colon cancer; LVI: Lymphovascular invasion; pN: Pathological lymph node stage; PNI: Perineural invasion; pT: Pathological tumor stage; RCC: Right colon cancer.

LCC and rectal cancer patients in all stages reported significantly longer DFS and OS in LCC than those in RCC in univariate analysis, yet survival failed to show significant difference by localization in multivariate analysis. The authors concluded that primary tumor localization was not an independent prognostic factor in Chinese patients with stage Ⅰ-Ⅲ colorectal cancer (CRC)[10]. Patel *et al*[6] recruited stage Ⅱ-Ⅲ CRC patients, 40% of which were RCC and 31% of which had rectal cancer. Merely 45% of stage Ⅲ CRC cases had received adjuvant therapy. No correlation was found between survival and tumor localization in patients receiving and not receiving adjuvant treatment[6].

Weis *et al*[12] reported no difference in 5-year mortality between RCC and LCC of any stage with stage Ⅰ to Ⅲ. Analysis by stage indicated lower mortality at stage Ⅱ of LCC than RCC and higher mortality at stage Ⅲ of LCC than RCC[12]. Warschkow *et al*[13] reported 5-year OS rate for patients with RCC as 65.1% (95%CI: 64.6-65.6) and LCC as 72.1% (95%CI: 71.5-72.6). The prognosis of RCC in stages Ⅰ and Ⅱ was reported as better overall. RCC and LCC had a similar prognosis at stage Ⅲ. In multivariate analysis, there was no difference between RCC and LCC in terms of 5-year OS[13]. In another study by Huang *et al*[14], with 1095 patients at all stages and at all sites including the rectum, only in stage 3 disease were right colon localized tumors worse for survival.

In our study, OS rates at five, ten, and 15 years were found as 91.2%, 87.1%, and 85.2% in RCC compared

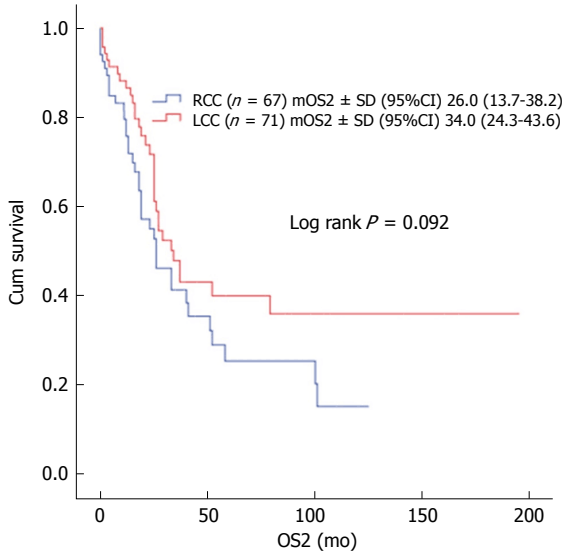

Figure 3 The overall survival effect of tumor localization after recurrence. LCC: Left colon cancer; OS2: Overall survival after recurrence; RCC: Right colon cancer; n: number of patients.

to 93.8%, 88.1%, 88.1% in LCC. There was no significant difference between stage 2 and stage 3 RCC and LCC patients without adjuvant treatment. Despite having a slightly higher mortality in RCC, especially in stage Ⅲ patients receiving 5-FU-based regimens, but this difference did not reach statistical significance in terms of primary tumor localization in stage Ⅱ and Ⅲ patients. Age ⩾ 65 years, advanced stage, PNI, and LVI were found to be the most statistically significant factors for mortality in multivariate analysis.

The relationship between tumor localization and prognosis in metastatic disease has been investigated, and studies reported worse prognosis of the right colon than the left colon[3,4,15]. In a study of 1947 patients with metastatic disease, the median OS was 14 mo (95%CI: 12.7-15.3 mo) in RCC and 20.5 mo (95%CI: 18.5-22.5) in LCC, and this difference was statistically significant ($P < 0.001$)[15]. In another study by Lee *et al*[16] using Australian CRC registry data, the post-recurrence survival in early stage patients was worse in right CC. In a study by Kerr *et al*[17], after recurrence, the median OS was 1.25 years and 2.25 years in RCC and LCC, respectively. In the subgroup analysis of 138 patients with recurrence in our study, median OS was 26 mo (95%CI: 13.7-38.2) in RCC and 34 mo (95%CI: 24.3-43.6) in LCC, where the difference did not reach statistical significance, possibly due to the small number of cases ($P = 0.092$).

It is known that in recent years, the incidence of CC at younger ages has increased[1]. Surveillance, Epidemiology, and End Results (SEER) trials usually involve elderly patients, and data on comorbidities and family history are not available in the SEER database[11,12]. It is not clear how much these parameters may have affected the analyses. In our study, patients from all age groups (19-94 years) were included, and the median age was lower than that in other studies. In addition, the duration of median follow-up in our study was 90 mo (6-252 mo), which was longer than that in all other studies[15-12,14-16]. Besides, our study only included stage Ⅱ and Ⅲ patients, unlike other studies[4,5,8,15-18]. In our study, family history and comorbidities were added to the analysis, where those receiving and not receiving adjuvant therapies were assessed separately.

The causes of the inconsistent relationship between mortality and tumor localization are most likely related to tumor biology. Microsatellite instability (MSI) and BRAF mutations are more likely to be found in RCC than in LCC. BRAF mutations have been reported to be associated with poor prognosis[13,18]. On the other hand, MSI was reported to have a positive effect on the prognosis of stage Ⅱ CRC[13]. Perhaps the most important limitation of our study is the absence of BRAF and MSI data of patients. It is not known how the MSI and BRAF situation affects the results of the study. In our study, the number of dissected LNs was lower than that in RCC, and the percentage of patients with < 12 dissected LN number were higher in LCC. This might have affected DFS and OS in LCC. In addition, our study did not analyze disease-specific survival; therefore, some of the mortal events might have occurred for non-cancer reasons during the long follow-up period.

In conclusion, tumor localization was not found to be associated with DFS or OS in stage Ⅱ and Ⅲ CC patients who were treated with or without adjuvant therapy. However, it was observed that OS was worse in RCC patients after recurrence. Further large and prospective studies also involving MSI and BRAF status are warranted.

ARTICLE HIGHLIGHTS

Research background

It is well known that metastatic right colon cancer (RCC) is more aggressive than left colon cancer (LCC). However, the effects of tumor location on the decision of adjuvant therapy and survival are not clearly known in early stage disease.

Research motivation

In recent trials, prognosis data of early stage RCC and LCC are conflicting. The uncertainty of whether tumor localization is functioning as an important additional risk factor for patients and clinicians in locoregional disease is still present.

Research objectives

In our study, we examined the effect of tumor localization on survival in patients who received or did not receive adjuvant therapy for stage Ⅱ and Ⅲ colon cancer. We also investigated the effects of chemotherapy regimens in stage Ⅲ disease on survival in terms of tumor site.

Research methods

In the study, a total of 942 patients with stage Ⅱ-Ⅲ colon cancer, excluding rectal cancer, were included. Comorbidities (diabetes mellitus, hypertension),

family histories, adjuvant therapy status and chemotherapy regimens were added to the analysis. The tumors from the caecum to the splenic flexure were defined as RCC and those from the splenic flexure to the sigmoid colon as LCC.

Research results

There was no difference for age and gender in the groups. Mucinous adenocarcinoma rate and the number of removed lymph nodes was higher in the RCC group. Recurrence and mortality risk was lower in patients with adjuvant treatment for all stages. In patients with stage Ⅱ and Ⅲ disease with or without adjuvant therapy, disease free survival and overall survival were similar in terms of primary tumor localization. In stage Ⅲ disease, there was no statistically significant difference for disease free survival and overall survival in patients receiving 5-Fluorouracil (commonly known as 5-FU)-based or oxaliplatin-based regimens according to tumor location. After recurrence, RCC was more aggressive.

Research conclusions

In conclusion, our study showed no association of tumor localization with either disease free survival or overall survival in patients with stage Ⅱ or Ⅲ colon cancer managed with or without adjuvant therapy. However, after recurrence, RCC was more aggressive.

Research perspectives

Further large and prospective studies also involving microsatellite instability and BRAF status are needed to determine the effectiveness of tumor location on decision of adjuvant therapy in patients with stage Ⅱ-Ⅲ colon cancer.

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P- Reviewer: Alkan A, Aykan NF, Shu X, Sunakawa Y
S- Editor: Wang JL **L- Editor**: Filipodia **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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

World J Gastrointest Oncol 2018 November 15; 10(11): 421-430

DOI: 10.4251/wjgo.v10.i11.421

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer

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Author contributions: Kang H and Park JY led the study design; the study was supervised by Park JY. Kang H, Jo JH, Lee HS, Chung MJ, Bang S, Park SW, Song SY, and Park JY were contributed to the collection and assembly of data; Kang H did the data analysis; all authors interpreted the analyzed data; Kang H and Park JY wrote the manuscript; all authors reviewed every version of the manuscript and approved the final manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board of Yonsei University Health System (Approval number: 4-2017-0757) and carried out in accordance with the Declaration of Helsinki.

Informed consent statement: The institutional review board waived the need for consent for this study due to its retrospective design.

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

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: August 6, 2018
Peer-review started: August 7, 2018
First decision: August 31, 2018
Revised: September 7, 2018
Accepted: October 10, 2018
Article in press: October 10, 2018
Published online: November 15, 2018

Abstract

AIM

To directly compare the efficacy and toxicity of standard-dose FOLFIRINOX (sFOLFIRINOX) and modified-dose FOLFIRINOX (mFOLFIRINOX, 75% of standard-dose) for pancreatic cancer.

METHODS

One hundred and thirty pancreatic cancer patients who received sFOLFIRINOX (n = 88) or mFOLFIRINOX (n = 42) as their first-line chemotherapy from January 2013 to July 2017 were retrospectively reviewed. For efficacy analysis, the objective response rate (ORR),

disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were evaluated and compared using Pearson's chi-square test, Kaplan-Meier plot and log-rank test. The adverse events (AEs) were evaluated, and severe (⩾ grade 3) AEs rates of the two groups were compared for toxicity analysis.

RESULTS

The mFOLFIRINOX group included more female patients (30.7% *vs* 57.1%; *P* = 0.004) and older patients [age (median), 57 *vs* 63.5; *P* = 0.018] than the sFOLFIRINOX group. In the efficacy analysis, the ORR and DCR were not significantly different between the two groups (ORR: 39.8% *vs* 35.7%; *P* = 0.656; DCR: 80.7% *vs* 83.3%; *P* = 0.716). The median PFS and OS were also not different between the groups (PFS: 8.7 mo *vs* 8.1 mo, *P* = 0.272; OS: 13.9 mo *vs* 13.7 mo, *P* = 0.476). In the safety analysis with severe AEs, the rates of neutropenia (83.0% *vs* 66.7%; *P* = 0.044), anorexia (48.9% *vs* 28.6%; *P* = 0.029) and diarrhea (13.6% *vs* 0.0%; *P* = 0.009) were markedly lower in the mFOLFIRINOX group.

CONCLUSION

mFOLFIRINOX showed comparable efficacy but better safety compared to sFOLFIRINOX. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy.

Key words: Dose modification; Adverse event; Pancreatic cancer; Adenocarcinoma; FOLFIRINOX; Chemotherapy

Core tip: Although the efficacy of FOLFIRINOX for pancreatic cancer has been well demonstrated, its relatively high toxicity rate is an important concern. We aimed to directly compare the efficacy and toxicity of standard-dose FOLFIRINOX and modified-dose FOLFIRINOX (mFOLFIRINOX, 75% of standard-dose) for pancreatic cancer. One hundred and thirty patients with pancreatic cancer (standard: 88 *vs* modified: 42) were reviewed retrospectively. Response rates, progression-free survival, and overall survival were not different between both groups. However, severe adverse events such as neutropenia, anorexia and diarrhea were significantly lower in the mFOLFIRINOX group. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy.

Kang H, Jo JH, Lee HS, Chung MJ, Bang S, Park SW, Song SY, Park JY. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. *World J Gastrointest Oncol* 2018; 10(11): 421-430 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/421.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.421

INTRODUCTION

Pancreatic cancer (PC) is the fourth-most common cause of cancer deaths estimated in the United States[1]. It is also reported as the fifth-most common cause of cancer-related deaths in South Korea[2]. Despite the introduction of several novel regimens, the five-year survival rate for all stages of PC remains around ten percent[1,2]. These statistics are based on the fact that < 20% of newly diagnosed PC cases are suitable candidates for surgical resection, while disseminated disease was noted in > 50% of new cases[1].

Ever since the survival benefit of gemcitabine in patients with advanced PC was reported, gemcitabine-based regimens have been primarily used for > twenty years[3-6]. Recently, a non-gemcitabine-based combination regimen comprising folinic acid (FA), 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) was introduced for metastatic PC (MPC). In the PRODIGE4/ACCORD11 randomized phase Ⅲ trial, FOLFIRINOX was associated with a significant survival benefit compared to gemcitabine monotherapy as the first-line therapy for patients with MPC[7]. Thereafter, several studies were conducted to determine the role of FOLFIRINOX in locally advanced PC (LAPC) or borderline resectable PC (BRPC), and meta-analysis reports showed promising improvements in median survivals and resection rates[8,9]. Consequently, FOLFIRINOX is recommended as a preferred front-line therapy for MPC in major up-to-date guidelines and on the list of options for BRPC or LAPC, although prospective randomized data are still lacking[10-12].

However, the relatively high toxicity of FOLFIRINOX is still a concern. In the PRODIGE4/ACCORD11 trial, FOLFIRINOX showed higher severe toxicity rates than gemcitabine, particularly for grade three or four neutropenia in 45.7% of patients[7]. The National Comprehensive Cancer Network guidelines for PC restrict FOLFIRINOX to patients with Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 or 1[12]. Owing to the high toxicity profile of FOLFIRINOX, several retrospective studies and phase Ⅱ trials using modified-dose FOLFIRINOX (mFOLFIRINOX) were performed with variable modification strategies. This research showed improved safety profiles and comparable efficacy[13-17]. Nevertheless, clinical feasibility or optimal strategy for dose-modification of FOLFIRINOX still remains unclear, since previous studies on mFOLFIRINOX indirectly compared their results to those of the PRODIGE4/ACCORD11 trial. Direct comparative study between standard-dose FOLFIRINOX (sFOLFIRINOX) and mFOLFIRINOX is still lacking. Therefore, in this study, we directly compared the therapeutic efficacy and safety of sFOLFIRINOX and mFOLFIRINOX as first-line

chemotherapies for PC.

MATERIALS AND METHODS

Patient selection

All patients diagnosed with PC who received FOLFIRINOX as their first-line chemotherapy in Severance Hospital from January 2013 to July 2017 were retrospectively reviewed. The inclusion criteria were as follows: (1) patients over 19 years of age; (2) histologically- or cytologically-proven pancreatic adenocarcinoma; and (3) at least one measurable lesion in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[18]. The exclusion criteria were as follows: (1) discontinued FOLFIRINOX for any reason before the first response evaluation; (2) dose adjustment in the first cycle other than 75% of the standard-dose; (3) did not start the first cycle of FOLFIRINOX in Severance Hospital; (4) diagnosed other active malignancy at the same time as PC diagnosis; (5) administered another agent in combination with FOLFIRINOX; and (6) regularly administered granulocyte colony stimulating factor (G-CSF) for primary prophylaxis. All patients who met the inclusion criteria and did not meet the exclusion criteria were identified. These patients were divided into sFOLFIRINOX and mFOLFIRINOX groups according to their starting dose of FOLFIRINOX.

Work-up and treatment

Pretreatment assessment was conducted for all patients. Appropriate imaging modalities were used for staging work-up, as needed. The specimen for histological or cytological confirmation of malignancy was obtained by endoscopic ultrasonography-guided fine needle aspiration, percutaneous biopsy, or exploratory laparotomy, as indicated. For each patient, the attending physician made a clinical decision on whether the first cycle should be initiated with sFOLFIRINOX or mFOLFIRINOX. sFOLFIRINOX comprised a 2 h intravenous infusion (IVF) of oxaliplatin 85 mg/m^2, followed by a 90 min IVF of irinotecan 180 mg/m^2. FA 400 mg/m^2 IVF was performed over 2 h after termination of irinotecan infusion. This was followed by a 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 IVF for 46 h. Patients who received a standard dose at the first cycle were grouped as sFOLFIRINOX. Patients who started with a 75% of standard-dose based on the decision of the attending physician were grouped as mFOLFIRINOX. All patients were regularly administered 0.25 mg of palonosetron 30 min before oxaliplatin infusion for emesis prophylaxis. G-CSF was not used for primary prophylaxis of neutropenia, and was administered when grade three or four neutropenia or neutropenic fever occurred. FOLFIRINOX was repeated every 2 wk until evidence of progressive disease (PD), significant deterioration of patient condition, or patient unwillingness. Dose reduction or delay was at the treating physician's discretion and fully considered if the patient did not appear to tolerate the dosage of the previous cycle.

Assessment of treatment efficacy

Primary endpoints of this study were objective response rate (ORR) and disease control rate (DCR). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). Treatment response was evaluated after every four cycles using computed tomography or magnetic resonance image. All imaging modalities were conducted and reviewed in compliance with the institutional standard protocols. According to the RECIST, responses were reported by a professional radiologist, and the final assessment was independently made by each attending physician. The best treatment response of each patient was recorded. The ORR included the rate of complete response (CR) and partial response (PR), while DCR was defined as a sum of ORR and the rate of stable disease (SD). For survival analysis, the patient's survival status, date of death, and date of last follow-up were recorded. The cut-off date of both survival and follow-up data was February 6, 2018. PFS was defined from the date of initiation of FOLFIRINOX to PD or death. The patients who survived and remained without PD were censored at the date of the last follow-up. Patients who missed a follow-up without PD and with < a 6-mo follow-up period were censored at 6 mo from treatment initiation, even if deaths were confirmed after that. If a treatment switch occurred without PD, such as curative resection, irreversible electroporation, or another chemotherapeutic regimen, the date of switching treatment was considered as the censoring point. OS was always defined from the date of initiation of FOLFIRINOX to death. Patients whose deaths were not confirmed were censored at the date of the last follow-up.

Assessment of adverse events

Treatment-related AE was also included in the secondary endpoints of this study. During the period of chemotherapy, treatment-related adverse events (AEs) were monitored and recorded by the attending physicians at each visit. All of the patients' medical records on AEs were reviewed. The assessment of AEs was carried out in conformity with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[19]. AEs leading to dose-reduction or dose-delay were recorded separately.

Statistical analysis

For comparing the variables of both groups, Mann-Whitney test was used for continuous variables and Pearson's χ^2 test or Fisher's exact test were used for categorical variables. For the analysis of survival data, the Kaplan-Meier method was used to estimate the median survival with a 95% confidence interval (CI) and the log-rank test was used for comparison. A

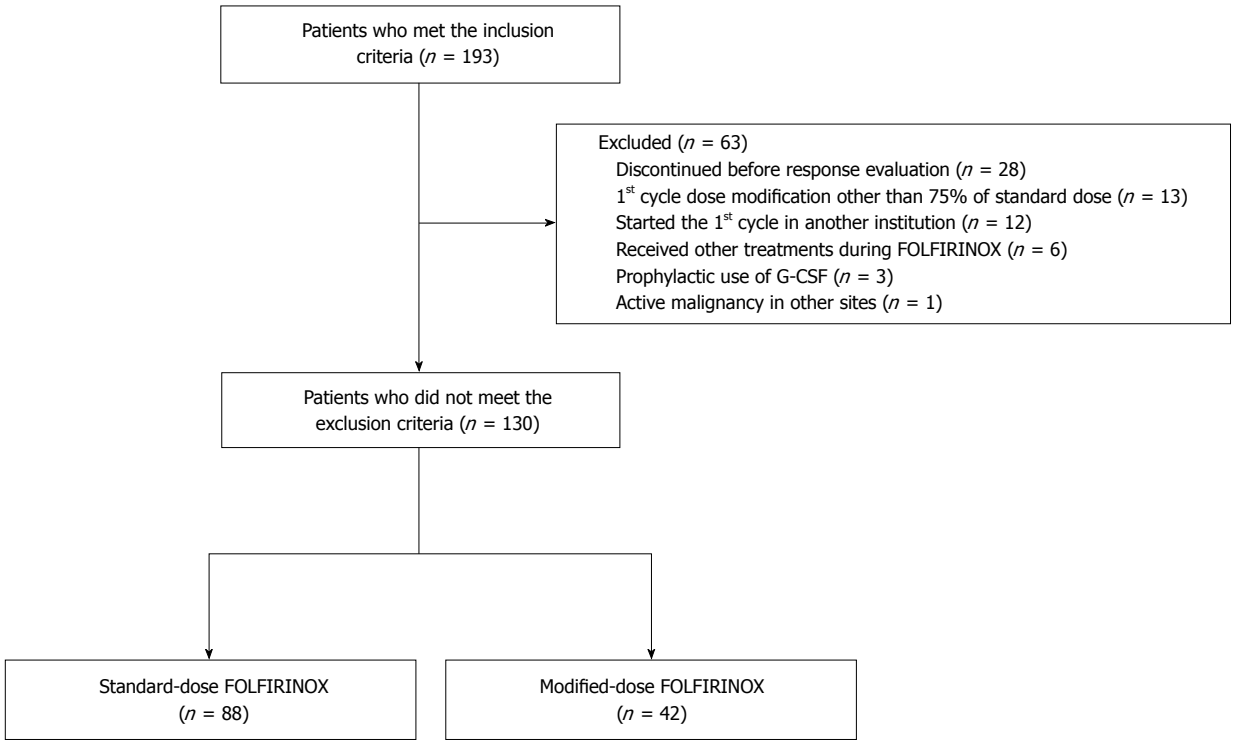

Figure 1 Flow chart of patient selection. G-CSF: granulocyte colony stimulating factor.

Cox proportional-hazards model was used to estimate the adjusted hazard ratios (HR). *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS (version 23.0, IBM Corp., Armonk, NY, United States).

RESULTS

Patients and pretreatment characteristics

In total, 130 patients were included in the final analysis based on the inclusion and exclusion criteria. Of the 130 patients, 88 were assigned to the sFOLFIRINOX group and 42 patients were assigned to the mFOLFIRINOX group. The detailed flow chart of patient selection is shown in Figure 1. When comparing the pretreatment characteristics, the mFOLFIRINOX group included more female patients (30.7% *vs* 57.1%; *P* = 0.004) and older patients [age (median), 57 *vs* 63.5; *P* = 0.018] than the sFOLFIRINOX group (Table 1). Other characteristics did not differ between the two groups.

Treatment characteristics

The treatment characteristics are summarized in Table 2. The number of cycles administered and treatment duration were not different between the two groups. The median relative dose intensities (RDIs) of each of the four agents were significantly higher in the sFOLFIRINOX group than in the mFOLFIRINOX group. The proportion of patients who experienced dose-reduction after the first cycle was larger in the sFOLFIRINOX group than in the mFOLFIRINOX group (70.5% *vs* 38.1%; *P* < 0.001); however, the rate of dose delay was not different between the two groups. Dose reduction due to neutropenia was higher in the sFOLFIRINOX group (60.2% *vs* 21.4%; *P* < 0.001), and, therefore, more patients were administered G-CSF (81.8% *vs* 64.3%; *P* = 0.028) and more G-CSF administrations were performed during the treatment period [3.5 times (range: 0-24) *vs* 2 times (range: 0-12); *P* = 0.043] than in the mFOLFIRINOX group.

Treatment responses and survivals

The ORR and DCR (primary end-points of this study) were not different between the two groups (Table 3). The median duration of follow-up was 10.3 mo in the sFOLFIRINOX group and 11.1 mo in the mFOLFIRINOX group (*P* = 0.181). The estimated median PFS of both groups were not different [sFOLFIRINOX: 8.7 mo (95%CI: 6.4-11.0) *vs* mFOLFIRINOX: 8.1 mo (95%CI: 6.7-9.6), *P* = 0.272] (Figure 2A). The estimated median OS of the sFOLFIRINOX group was 13.9 mo (95%CI: 11.5-16.4), and it was not different from that of the mFOLFIRINOX group [13.7 mo (95%CI: 9.5-17.9), *P* = 0.476] (Figure 2B). Additionally, age and sex-adjusted HRs of the mFOLFIRINOX group to the sFOLFIRINOX group were not statistically significant [HR for disease progression or death, 1.36 (95%CI: 0.81-2.26), *P* = 0.242; HR for death, 0.94 (95%CI: 0.55-1.60), *P* = 0.813].

Treatment-related AEs

Severe (grade three or higher) treatment-related AEs

Table 1 Pretreatment characteristics

	sFOLFIRINOX (*n* = 88)	mFOLFIRINOX (*n* = 42)	*P* value
Sex, *n* (%)			
Male	61 (69.3)	18 (42.9)	0.004[1]
Female	27 (30.7)	24 (57.1)	
Age, yr			0.018[1]
Median (range)	57 (31-79)	63.5 (41-77)	
ECOG-PS, *n* (%)			
0	68 (77.3)	35 (83.3)	0.426
1	20 (22.7)	7 (16.7)	
Laboratory test results, median (range)			
Absolute neutrophil count, /μL	4200 (1610-11170)	4525 (2080-18930)	0.317
Hemoglobin, g/dL	12.3 (7.1-17.1)	12.1 (8.5-14.9)	0.36
Platelet count, $\times 10^3$/μL	218 (76-439)	245 (107-764)	0.247
Total bilirubin, mg/dL	0.7 (0.2-4.8)	0.5 (0.2-2.7)	0.144
Albumin, g/dL	3.9 (2.8-5.0)	3.9 (2.4-4.8)	0.797
Creatinine, mg/dL	0.67 (0.37-1.02)	0.70 (0.37-1.04)	0.516
Level of CA 19-9			
U/mL, median (range)	172.2 (0.6-20000.0)	455.5 (0.7-20000.0)	0.709
Normal, *n* (%)	17 (19.3)	11 (21.5)	
Elevated, < 59 × ULN, *n* (%)	53 (60.2)	19 (45.2)	0.274
Elevated, ⩾ 59 × ULN, *n* (%)	18 (20.5)	12 (28.6)	
Biliary drainage, *n* (%)			0.435
Presence	29 (33.0)	11 (26.2)	
Tumor location in pancreas, *n* (%)			
Head	40 (45.5)	16 (38.1)	0.657
Body and tail	44 (50.0)	23 (54.8)	
Recurrent	4 (4.5)	3 (7.1)	
Tumor size, cm			0.313
Median (range)	3.6 (1.3-7.7)	4.0 (1.3-8.0)	
Disease extent, *n* (%)			
Borderline resectable	17 (19.3)	6 (14.3)	0.243
Locally advanced	26 (29.5)	8 (19.0)	
Metastatic	45 (51.1)	28 (66.7)	
Stage, *n* (%)			
Ⅱ	24 (27.3)	8 (19.0)	0.248
Ⅲ	19 (21.6)	6 (14.3)	
Ⅳ	45 (51.1)	28 (66.7)	
Prior treatment, *n* (%)			
Naïve	75 (85.2)	33 (85.7)	0.941
Curative resection	4 (4.5)	4 (9.5)	0.272
CCRT	9 (10.2)	4 (9.5)	1.000

[1]Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; ECOG-PS: Eastern Cooperative Oncology Group performance status; ULN: Upper limit of normal range; CA: Carbohydrate antigen; CCRT: Concurrent chemoradiotherapy.

in the two groups are listed and compared in Table 4. Of the hematologic AEs, the rate of severe neutropenia was significantly lower in the mFOLFIRINOX group than in the sFOLFIRINOX group (83.0% *vs* 66.7%; *P* = 0.044). Other hematologic AE rates, including febrile neutropenia, were not different. Severe anorexia and diarrhea occurred less frequently in the mFOLFIRINOX group than in the sFOLFIRINOX group (48.9% *vs* 28.6%; *P* = 0.029; 13.6% *vs* 0.0%; *P* = 0.009; respectively). All other non-hematologic severe AEs tended to occur less frequently in the mFOLFIRINOX group, with the exception of lung infection.

DISCUSSION

In this study, we aimed to retrospectively compare the therapeutic efficacy and safety of sFOLFIRINOX and mFOLFIRINOX as first-line chemotherapies for PC. To the best of our knowledge, this is the first direct comparative study that evaluated the efficacy and safety of sFOLFIRINOX and mFOLFIRINOX within a single institution. We observed that the median cycle and median duration of FOLFIRINOX were not different in both groups. Although the median RDI of all four agents were significantly less in the mFOLFIRINOX group, the therapeutic parameters such as ORR, DCR, OS, and PFS were not different between the two groups. Regarding the treatment-related AE profiles, severe neutropenia, anorexia, and diarrhea were remarkably lower in the mFOLFIRINOX group than in the sFOLFIRINOX group. Therefore, our study supports dose modification from the initiation of treatment without compromising treatment efficacy, particularly in elderly and female patients, who tend to show more

Table 2 Treatment characteristics

	sFOLFIRINOX (*n* = 88)	mFOLFIRINOX (*n* = 42)	*P* value
Number of cycles administered, median (range)	9.5 (4-24)	12 (4-32)	0.421
Treatment duration, d, median (range)	126 (42-322)	154 (42-434)	0.595
RDI to sFOLFIRINOX, %, median (range)			
Oxaliplatin	85.3 (56.3-100)	75.0 (51.1-75.0)	< 0.001[1]
Irinotecan	85.0 (56.3-100)	75.0 (51.1-75.0)	< 0.001[1]
5-FU (bolus)	92.1 (21.4-100)	75.0 (51.1-75.0)	< 0.001[1]
5-FU (infusion)	94.1 (56.3-100)	75.0 (51.1-75.0)	< 0.001[1]
Patients with ⩾ 1 dose reduction, *n* (%)	62 (70.5)	16 (38.1)	< 0.001[1]
Cause of dose reduction (> 5%), *n* (%)			
Neutropenia	53 (60.2)	9 (21.4)	< 0.001[1]
Febrile neutropenia	10 (11.4)	4 (9.5)	1.000
Patients with ⩾ 1 dose delay, *n* (%)	55 (62.5)	22 (52.4)	0.272
Cause of dose delay (> 5%), *n* (%)			
Neutropenia	16 (18.2)	5 (11.9)	0.363
Febrile neutropenia	16 (18.2)	5 (11.9)	0.363
Fatigue	7 (8.0)	8 (19.0)	0.081
No. of G-CSF administered, median (range)	3.5 (0-24)	2 (0-12)	0.043[1]
Patients received G-CSF, *n* (%)	72 (81.8)	27 (64.3)	0.028[1]

[1]Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; RDI: Relative dose intensity; 5-FU: 5-Fluorouracil; G-CSF: Granulocyte colony-stimulating factor.

Table 3 Response evaluation *n* (%)

	sFOLFIRINOX (*n* = 88)	mFOLFIRINOX (*n* = 42)	*P* value
CR	1 (1.1)	1 (2.4)	
PR	34 (38.6)	14 (33.3)	
SD	36 (40.9)	20 (47.6)	
PD	17 (19.3)	7 (16.7)	
Objective response[a]	35 (39.8)	15 (35.7)	0.656
Disease control[b]	71 (80.7)	35 (83.3)	0.716

[a]Objective response includes CR and PR; [b]Disease control includes CR, PR, and SD. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

concern about treatment-related toxicities.

Currently, FOLFIRINOX is a universally-used first-line treatment for MPC[20,21], and it is also used for second-line or neoadjuvant treatment. Owing to its severe toxicities (grade ⩾ 3 neutropeniain 45.7% of patients; grade ⩾ 3 fatigue in 23.6% of patients) reported in the PRODIGE4/ACCORD11 trial[7], treatment-related AE is a major concern when using FOLFIRINOX.

To reduce FOLFIRINOX-related toxicities, several groups have conducted studies focused on dose modification of FOLFIRINOX from the first cycle. Most of the FOLFIRINOX dose-modifying studies compared their results with the PRODIGE4/ACCORD11 trial. Retrospective research conducted in the UK using a reduced dose of irinotecan and omitting a 5-FU bolus reported a markedly lower rate of severe neutropenia than that in the historical trial, with similar rates of other severe AEs[15]. In a US phase Ⅱ trial using reduced doses of irinotecan and 5-FU bolus, the rates of severe neutropenia and vomiting were significantly lower than the rates in the historical trial; however, other severe AEs were similar[17]. The toxicity of mFOLFIRINOX in this study was less severe than sFOLFIRINOX. In addition, compared with that of the historical trial, the rate of severe diarrhea was lower, but the rates of severe neutropenia, febrile neutropenia, anemia, and vomiting were still higher in the mFOLFIRINOX.

Regarding neutropenia, 77.8% of patients experienced severe neutropenia in a Japanese phase Ⅱ study of sFOLFIRINOX for chemotherapy-naïve MPC, which is similar to our study's findings[22]. In addition, most studies conducted in Asian countries reported severe neutropenia in > 65% of patients[23-26], which was more frequent than that in reports from western countries (11.0%-45.7%)[7,27-29]. These results suggest that Asians may be prone to severe FOLFIRINOX-related neutropenia, and dose adjustment is an option that should be considered when treating patients belonging to the Asian population. Unlike the present study, prophylactic G-CSF was routinely administered at every cycle in the aforementioned studies focusing on dose modification of FOLFIRINOX[13-17]. This distinction in therapeutic protocols should be considered when interpreting and comparing the rates of severe

Table 4 Adverse events (≥ Grade 3) *n* (%)

Event	sFOLFIRINOX (*n* = 88)	mFOLFIRINOX (*n* = 42)	*P* value
Hematologic			
Neutropenia	73 (83.0)	28 (66.7)	0.044[1]
Febrile neutropenia	24 (27.3)	9 (21.4)	0.474
Anemia	19 (21.6)	11 (26.2)	0.561
Thrombocytopenia	8 (9.1)	2 (4.8)	0.499
Non-hematologic			
Fatigue	33 (37.5)	14 (33.3)	0.644
Anorexia	43 (48.9)	12 (28.6)	0.029[1]
Nausea/Vomiting	53 (60.2)	19 (45.2)	0.108
Diarrhea	12 (13.6)	0 (0.0)	0.009[1]
Peripheral sensory neuropathy	12 (13.6)	2 (4.8)	0.224
Sepsis	5 (5.7)	0 (0.0)	0.174
Lung infection	3 (3.4)	4 (9.5)	0.212
Biliary tract infection	6 (6.8)	0 (0.0)	0.176

[1]Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX.

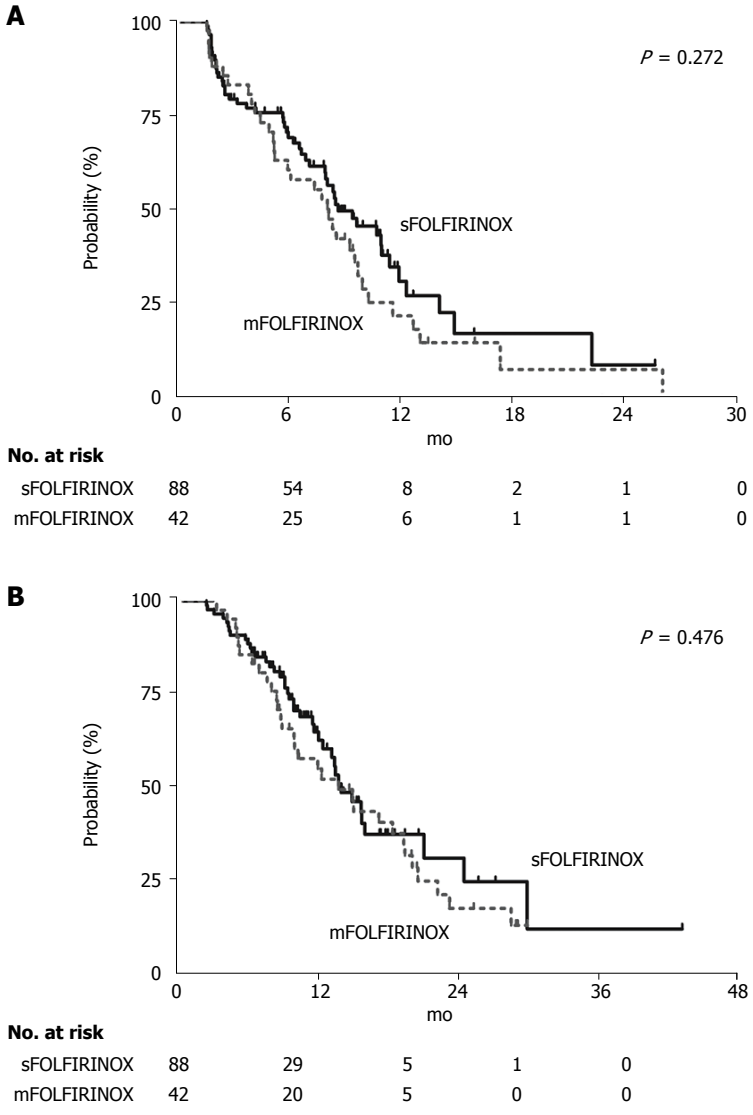

Figure 2 Survival analyses and comparisons. A: Progression-free survival; B: Overall survival, according to the treatment group. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX.

neutropenia and neutropenic fever associated with mFOLFIRINOX in our study with those of prior research (67.9% *vs* 0%-12%; 26.4% *vs* 0%-5.6%; respectively).

Regarding efficacy, previous studies using a modified form of FOLFIRINOX showed 17.2%-46.7% of ORR and 80%-100% of DCR, which were similar to those of the PRODIGE4/ACCORD11 trial[13,15,17]. Our modification of FOLFIRINOX with 75% of the standard-dose was able to markedly reduce toxicity, and the efficacy was comparable with that of sFOLFIRINOX or previous studies, including the PRODIGE4/ACCORD11 trial. This therefore suggests that, in our study population, dose modification to reduce toxicity is possible without compromising treatment efficacy.

There are certain limitations to this study. First, it has a retrospective study design. Although we selected patients based on strict exclusion criteria, the possibility of selection bias and information bias remains. Second, we included patients with BRPC and unresectable PC. When comparing the survival data with other trials, this characteristic of the patient population should be considered. Third, more females and older patients were included in the mFOLFIRINOX group. These differences may be attributed to the clinical characteristics of the patient, based on whether or not the attending physician decides to administer mFOLFIRINOX from the first cycle. These differences may affect the treatment outcome. A previous study reported that female gender could positively predict response to FOLFIRINOX in patients with advanced PC[30]. However, the prognostic significance of gender in PC remains controversial and warrants further evaluation[31]. Despite these limitations, this study is meaningful because it directly compares the two study groups, which underwent similar clinical practice within a single institution.

In conclusion, mFOLFIRINOX showed comparable efficacy to sFOLFIRINOX, with a better toxicity profile. Given the relatively high toxicity of sFOLFIRINOX, initiating FOLFIRINOX treatment, if clinically required, with 75% of the standard-dose can be an appropriate option to reduce toxicity concerns without compromising efficacy.

ARTICLE HIGHLIGHTS

Research background

Although FOLFIRINOX is one of the universally-used chemotherapies for pancreatic cancer, its relatively high rate of adverse events is still a major concern. Several studies suggest that dose-modified FOLFIRINOX (mFOLFIRINOX) can improve safety with comparable efficacy compared to the standard FOLFIRINOX (sFOLFIRINOX). However, clinical feasibility and the optimal strategy of mFOLFIRINOX remains unclear.

Research motivation

Previous studies on mFOLFIRINOX made conclusions based on comparing their results to the results of historical phase Ⅲ trials of FOLFIRINOX. To date, direct comparative studies between sFOLFIRINOX and mFOLFIRINOX for pancreatic cancer is lacking.

Research objectives

We directly compared the safety and efficacy of sFOLFIRINOX and mFOLFIRINOX in a single study. This could help clarify the clinical applicability of mFOLFIRINOX.

Research methods

The medical records of 130 pancreatic cancer patients [sFOLFIRINOX (n = 88), mFOLFIRINOX (n = 42)] were retrospectively reviewed. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were compared for efficacy analysis. Severe ($\geqslant$ grade three) adverse event (AE) rates of the two groups were compared for toxicity analysis.

Research results

Although the median relative dose intensities of each of the drugs were significantly lower in the mFOLFIRINOX group, the response rates and survival were not different between the two groups (ORR: 39.8% *vs* 35.7%, P = 0.656; DCR: 80.7% *vs* 83.3%, P = 0.716; PFS: 8.7 mo *vs* 8.1 mo, P = 0.272; OS: 13.9 mo *vs* 13.7 mo, P = 0.476). Severe AE rates, including neutropenia (83.0% *vs* 66.7%; P = 0.044), anorexia (48.9% *vs* 28.6%; P = 0.029), and diarrhea (13.6% *vs* 0.0%; P = 0.009), were significantly lower in the mFOLFIRINOX group.

Research conclusions

In this direct comparative restrospective study, mFOLFIRINOX showed comparable efficacy to sFOLFIRINOX, with a better toxicity profile. Given the relatively high toxicity of sFOLFIRINOX, initiating FOLFIRINOX treatment, if clinically required, with 75% of the standard-dose could be an appropriate option to reduce toxicity concerns without compromising efficacy.

Research perspectives

In the future, prospective comparative studies need to be conducted to determine the optimal dose modification of FOLFIRINOX and who will benefit from this strategy.

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P- Reviewer: Ouaissi M, Raffaniello R, Sawaki A **S- Editor**: Ma RY
L- Editor: Filipodia **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 November 15; 10(11): 431-438

DOI: 10.4251/wjgo.v10.i11.431

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

Effect of primary tumor side on survival outcomes in metastatic colorectal cancer patients after hepatic arterial infusion chemotherapy

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Author contributions: Li J and Zhu X designed the research; Zhang HY, Guo JH, Gao S, Zhang PJ and Chen H analyzed the data; Zhang HY wrote the paper; Wang XD, Yang RJ and Zhu X critically revised the manuscript for important intellectual content; Li J and Zhu X contributed equally to this work and should be considered co-first authors.

Supported by Capital Foundation of Medical Development (China), No. 2014-2-2154.

Institutional review board statement: This study has a statement on ethics approval by the Medical Ethics Committee of Beijing Tumor Hospital, which is a part of Beijing Cancer Hospital.

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

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

Data sharing statement: The datasets generated during the current study are not publicly available due to usage in another ongoing study, but are available from the corresponding author upon reasonable request.

Manuscript source: Unsolicited manuscript

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Received: August 7, 2018
Peer-review started: August 8, 2018
First decision: September 12, 2018
Revised: September 19, 2018
Accepted: October 12, 2018
Article in press: October 12, 2018

Published online: November 15, 2018 http://dx.doi.org/10.4251/wjgo.v10.i11.431

Abstract

AIM

To analyze the survival data between patients diagnosed with right-sided primary (RSP) tumors and patients diagnosed with left-sided primary (LSP) tumors after hepatic arterial infusion chemotherapy (HAIC) at our center.

METHODS

A retrospective analysis of pretreated metastatic colorectal cancer patients who received HAIC from May 2006 to August 2015 was conducted. A Cox proportional hazard regression analysis was used to assess the long-term survival outcomes. The mean and median age of patients was 61 years (range 27-85 years). There were 115 males and 53 females in our study.

RESULTS

One hundred sixty-eight patients were enrolled in this study. The overall response rate was 28.9% in LSP patients and 27.3% in RSP patients. The disease control rate was 76.3% in LSP patients and 69.7% in RSP patients. The median overall survival in response to HAIC was 16.3 mo in the LSP arm and 9.3 mo in the RSP arm (P = 0.164). The median progression-free survival was 5.7 mo in the LSP arm and 4.2 mo in the RSP arm (P = 0.851).

CONCLUSION

There was no significant difference in survival between LSP patients and RSP patients after HAIC. Further prospective studies are needed to confirm these findings.

Key words: Colorectal cancer; Hepatic arterial infusion chemotherapy; Primary tumor side; Local treatment; Hepatic metastasis

Core tip: Our study shows that the prognosis of left-sided colorectal cancer liver metastasis patients is superior to that of right-sided patients, but no significant difference in survival was found between left-sided primary and right-sided primary patients in response to treatment with hepatic arterial infusion chemotherapy.

Zhang HY, Guo JH, Gao S, Chen H, Wang XD, Zhang PJ, Liu P, Cao G, Xu HF, Zhu LZ, Yang RJ, Li J, Zhu X. Effect of primary tumor side on survival outcomes in metastatic colorectal cancer patients after hepatic arterial infusion chemotherapy. *World J Gastrointest Oncol* 2018; 10(11): 431-438 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/431.htm DOI:

INTRODUCTION

Colorectal cancer is the third leading cause of cancer death in both men and women in the Western world[1]. In China, the incidence of colorectal cancer is gradually increasing and has become the fourth most frequent cancer in women and the fifth in men[2]. Gene expression-based subtyping is now widely accepted as a predictive model of survival, including the mutually exclusive RAS and BRAF pathways, as well as the Wnt pathway[3,4]. In addition, increasing evidence indicates that patients with a left-sided primary (LSP) tumor have a survival advantage compared to those with a right-sided primary (RSP) tumor, indicating that primary location could be a predictive factor[5]. The distinguishing prognosis is ascribed to differences in biology, pathology, and epidemiology of colorectal cancer based on primary tumor location. LSP tumors arise from the hindgut at their embryological beginnings and are supplied by the inferior mesenteric artery, while RSP tumors arise from the midgut and are supplied by the superior mesenteric artery. There are also biological and molecular pathway variations between these two subtypes[6-9].

Due to the dissimilar genotype and phenotype of LSP and RSP tumors, the location of primary tumor has turned out to be predictive of outcome[10,11]. Subsequent studies have found that RSP patients have an inferior outcome in first-line chemotherapy[12], and targeted agents, such as anti-epidermal growth factor receptor (EGFR) monoclonal antibody and anti-vascular EGFR monoclonal antibody, show differential efficacy in RSP and LSP patients[5,13,14].

Metastasis occurs in approximately 50% of patients during disease[15]. Without efficient treatment, metastatic colorectal cancer (mCRC) patients who fail to respond to systemic chemotherapy only survive approximately 3.5 mo[16]. The survival benefit of third-line chemotherapies is 4.5-10.5 mo[17]. However, interventional treatments are potential choices for mCRC patients. Transarterial chemoembolization and hepatic arterial infusion chemotherapy (HAIC) can achieve a higher local response rate than systemic chemotherapy and remain effective when patients have failed to respond to previous chemotherapy[18,19]. Chemo-refractory patients treated with HAIC can survive 7.7-19 mo[20-23]. However, no studies have reported the relationship between the efficacy of HAIC and the primary tumor side. We gathered survival information on mCRC patients after HAIC in our center to clarify this issue.

MATERIALS AND METHODS

Study design and patient population

This was a retrospective analysis of the survival and

efficacy of HAIC in mCRC patients. The primary criteria for inclusion were as follows: Pathological diagnosis of adenocarcinoma of the colon or rectum, inoperable liver metastases or contraindications for liver resection, systemic chemotherapy failure (experienced at least first-line chemotherapy previously), treated with HAIC in our center, and received tumor assessment after HAIC. Subject demographic variables examined included age, sex, and survival or censored data. Tumor variables examined included location, gene status, histologic grade (well, moderate, or poor), and extrahepatic metastasis. Treatment variables examined included previous treatment, combined liver radiotherapy or radiofrequency ablation, and combined molecular targeted drugs.

RSP patients have a tumor site in the cecum, ascending colon, hepatic flexure, or transverse colon, while LSP patients present tumors in the splenic flexure, descending colon, sigmoid colon, or rectum. Disease evaluation was repeated every two cycles using computed tomography scans, and the Response Evaluation Criteria in Solid Tumors 1.1 criteria was applied. The primary end-point of this study was the overall survival (OS) difference between RSP and LSP patients. Secondary end-points were progression-free survival (PFS) and efficacy of several different chemotherapy regimens. Our retrospective study was in accordance with the ethical standards of the Beijing Cancer Hospital Ethics Committee.

Statistical analysis

OS was defined from the first day of HAIC until death from any cause. PFS was defined from the first day of HAIC until the first objective observation of disease progression or death from any cause. The SPSS software program (version 19; SPSS, Chicago, IL, United States) was used for analyses. The Graph Pad Prism 6 program (Graph Pad Software, Inc., La Jolla, CA, United States) was used to create charts. A Student's *t*-test was used to analyze continuous variables, which are reported as mean ± SD if normally distributed or as a median and range if skewed. A χ^2 test was used to analyze categorical variables, which are reported as a proportion (%) of the overall cohort. The Kaplan-Meier method was used to approximate PFS and OS, and the significance of survival differences between separate subgroups was assessed using the log-rank test. The Cox proportional hazards model was used to determine the univariate and multivariate hazards ratios for the study parameters. For all tests, a P-value < 0.05 was defined as statistically significant.

RESULTS

Patient characteristics

One hundred sixty-eight patients were included in this study between May 2006 and August 2015. The median age was 61 years (range 27-85 years), and the last follow up day was July 5, 2016. Median follow-up time was 17 mo. Among all patients included in this study, 138 patients died, 14 patients were lost during the follow-up period, and 16 patients were still alive. There were 135 LSP patients and 33 RSP patients. Extrahepatic metastases accounted for more than half of all patients (94/168). There were 17 *KRAS* mutation patients and 48 *KRAS* wild type patients among LSP tumors. There were eight *KRAS* mutation patients and seven *KRAS* wild type patients among RSP tumors. The baseline information of patients, disease, and treatment characteristics by primary tumor location are shown in Table 1. Eighty-nine (65.9%) LSP patients were previously administered first-line systemic chemotherapy, and 46 (34.1%) patients were given second-line or subsequent therapies. Twenty-four (72.7%) RSP patients received first-line systemic chemotherapy, and nine (27.3%) patients received second-line or subsequent lines of chemotherapy.

Patients were injected with 20-40 mg epirubicin hydrochloride after routine arteriography by artery catheter, and iodipin was injected when obvious blood supply was found in the arteriography. Chemotherapy agents administered through the catheter after chemoembolization included oxaliplatin (85 mg/m^2) or irinotecan (180 mg/m^2) over 4 h, followed by fluorouracil (2000 mg/m^2) administered over approximately 44 h and cisplatin/fluorouracil (200 mg /m^2) over 2-4 h *vs* peripheral vein, combined with/without bevacizumab (7.5 mg/kg) or cetuximab (250 mg/m^2). Treatments were repeated every three weeks. One hundred fifty-three patients received oxalipatin-based chemotherapy, and only 15 patients received irinotecan-based chemotherapy. With respect to targeted therapy, 27 (20%) LSP patients were treated with bevacizumab; while another 13 (9.6%) were treated with cetuximab. In RSP patients, there were only two patients treated with bevacizumab and three with cetuximab.

No significant differences were found between RSP and LSP patients in terms of age, sex, tumor variables, or treatment variables (Table 1).

Efficacy of HAIC

The overall response rate was 28.9% in LSP patients and 27.3% in RSP patients. There were 0.7% complete response (n = 1), 28.9% partial response (n = 39), 47.4% stable disease (n = 64), and 23% progressive disease (n = 31) in LSP patients. There were 27.3% partial response (n = 9), 42.4% stable disease (n = 14), and 30.3% progressive disease (n = 10) in RSP patients The disease control rate was 76.3% in LSP patients and 69.7% in RSP patients.

Progression-free survival time

Most of the patients (n = 84) who progressed did so due to liver metastasis, while a small number of patients (n = 45) progressed due to the progression

Table 1 Patient characteristics

Variable	Left side (n = 135)	Right side (n = 33)	P-value
Age, mean (range), years	60.5 (27-85)	63.8 (37-83)	0.392
Men, n (%)	95 (70.4)	20 (60.6)	0.279
Previous system treatment, n (%)			0.455
Only first line	89 (65.9)	24 (72.7)	
Second line or more	46 (34.1)	9 (27.3)	
Extrahepatic metastasis, n (%)	73 (54.1)	21 (63.6)	0.321
Primary tumor resected, n (%)			0.173
No surgery	22 (16.2)	10 (30.3)	
Palliative surgery	49 (36.3)	11 (33.3)	
Radical surgery	64 (47.4)	12 (36.4)	
Synchronous metastases, n (%)	103 (76.3)	26 (78.8)	0.761
Gene status, n (%)			0.127
KRAS mutation	17 (35.6)	8 (24.2)	
KRAS wild type	48 (12.6)	7 (21.2)	
Unknown	70 (51.9)	18 (54.5)	
Targeted therapy, n (%)			
Bevacizumab treated	27 (14.8)	2 (6.1)	0.21
Cetuximab treated	13 (9.6)	3 (9.1)	
Other local treatment, n (%)	31 (23)	4 (12.1)	0.169
Repeated times of HAIC, n (%)			0.554
2	29 (21.5)	10 (30.3)	
3-4	43 (21.9)	10 (30.3)	
> 6	63 (46.7)	13 (39.4)	

HAIC: Hepatic arterial infusion chemotherapy.

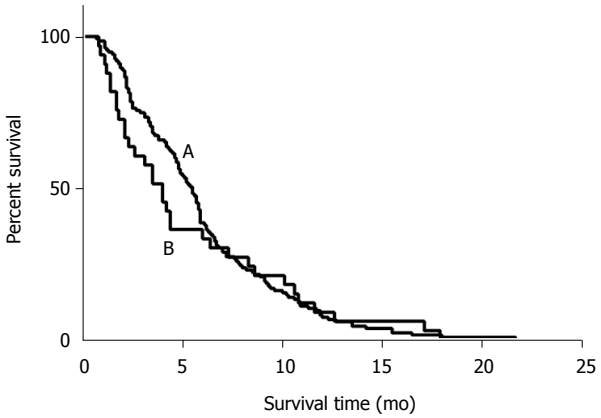

Figure 1 Overall survival data of patients who received hepatic arterial infusion chemotherapy treatment (n = 168). The median survival time of left-sided colorectal cancer liver metastasis patients was 16.3 mo (curve A). The median survival time of right-sided colorectal cancer liver metastasis patients was 9.3 mo (curve B).

of extrahepatic metastasis, and another 23 patients exhibited both liver and extrahepatic metastasis progression. Median PFS of all included patients was 5.5 mo (95%CI: 4.9-6.0 mo). The median PFS was 5.7 mo (95%CI: 5.3-6.1 mo) in LPS patients and 4.2 mo (95%CI: 3.2-5.1 mo) in RSP patients, and no significant difference was observed between these two groups (P = 0.851) (Table 2 and Figure 1).

The median PFS of LSP patients was 5.5 mo in liver progression (n = 67, 54%), 4.7 mo in extrahepatic progression (n = 39, 31%), and 6.7 mo in both liver and extrahepatic progression groups (n = 18, 15%) (P = 0.155). The median PFS of RSP patients was 4.0 mo in liver progression (n = 16, 57%), 4.4 mo in extrahepatic progression (n = 7, 25%), and 4.4 mo in both liver and extrahepatic progression groups (n = 5, 18%) (P = 0.986).

LSP patients who had only first-line systemic chemotherapy exhibited a median PFS of 5.9 mo, and those who received second or more lines of treatment exhibited a median PFS of 4.6 mo (P = 0.001). RSP patients who had only first-line systemic chemotherapy exhibited a median PFS of 4.4 mo, and those who received second or more lines of treatment exhibited a median PFS of 2.3 mo (P = 0.018).

OVERALL SURVIVAL TIME

There were 112 out of 135 LSP patients and 26 out of 33 RSP patients who died during the follow-up period. The median OS from the diagnosis of CRC was 31.4 mo in LSP patients and 22.2 mo in RSP patients (P = 0.186). The OS after HAIC was 16.3 mo in LSP patients and 9.3 mo in RSP patients (P = 0.164) (Figure 2).

The median OS after HAIC in patients treated with HAIC and bevacizumab was 22 mo, and patients treated with HAIC and cetuximab or HAIC only exhibited a median OS of 15.4 mo (P = 0.162). LSP patients treated with HAIC and bevacizumab had a median OS of 24.5 mo and 15.4 mo in the cetuximab arm (P = 0.053). No significant difference was observed between the bevacizumab and cetuximab arms. Only two RSP patients were treated with bevacizumab, and their OS was 9.3 mo and 13 mo. The three RSP patients treated

Table 2 Analyses of survival outcomes by primary tumor location

Subgroup	OS events *n* (%)	Median OS, mo (95%CI)		Hazard ratio (95%CI)	*P*-value	PFS events *n* (%)	Median PFS, mo (95%CI)		Hazard ratio (95%CI)	*P*-value
		Left-sided	Right-sided				Left-sided	Right-sided		
All eligible patients (*n* = 168)	138 (82.1)	16.3 (13.5-19.0)	9.3 (3.4-15.1)	0.74 (0.48-1.13)	0.164	151 (89.9)	5.7 (5.3-6.1)	4.2 (3.2-5.1)	0.96 (0.64-1.50)	0.851
KRAS wild type (*n* = 55)	44 (76.4)	17.6 (12.3-22.9)	15.4 (6.0-24.7)	0.85 (0.33-2.19)	0.74	51 (92.7)	5.1 (4.2-5.9)	4.0 (2.7-5.3)	0.76 (0.32-1.81)	0.529
KRAS mutation (*n* = 25)	18 (72)	10.9 (0-34.6)	9.0 (2.4-15.5)	0.77 (0.29-2.02)	0.6	22 (88)	4.8 (2.9-6.6)	2.1 (0-5.0)	0.97 (0.36-2.58)	0.956
KRAS unknown (*n* = 88)	78 (88.6)	16.1 (14.1-18.1)	9.3 (6.9-11.7)	0.69 (0.38-1.24)	0.218	78 (88.6)	6.2 (5.1-7.3)	6.0 (3.3-8.7)	0.75 (0.42-1.33)	0.324
Bevacizumab (*n* = 29)	21 (72.4)	24.5 (16.6-32.3)	9.3 (-)	0.30 (0.06-1.43)	0.11	27 (93.1)	6.2 (4.9-7.4)	4.0 (-)	0.45 (0.10-2.01)	0.285
Cetuximab (*n* = 16)	12 (75)	16.5 (9.0-23.9)	8.2 (-)	0.21 (0.03-1.29)	0.065	15 (93.8)	3.6 (0.89-6.3)	4.0 (-)	0.42 (0.08-2.06)	0.269

OS: Overall survival; PFS: Progression-free survival.

with cetuximab exhibited an OS of 2.6 mo, 3.8 mo, and 8.2 mo.

The median OS in *KRAS* wild type patients (*n* = 55) was 16.6 mo, 13 mo in patients with *KRAS* mutation (*n* = 25), and 15.6 mo in *KRAS* status unknown patients (*n* = 88). In *KRAS* wild type patients, ten were treated with cetuximab and six with bevacizumab. The median OS of these two group were 11.5 mo and 22 mo, respectively (*P* = 0.087) (Table 2). Among all 48 LSP *KRAS* wild type patients, nine were treated with bevacizumab and eleven with cetuximab. The median OS of these two different treatments was 28.1 mo and 21.1 mo, respectively (*P* = 0.444). There were only seven KRAS wild type patients in the RSP group.

LSP patients who progressed by liver metastases had a median OS of 18.8 mo, progression of extrahepatic metastasis was 14.6 mo, and progression of both liver and extrahepatic metastasis was 13.7 mo (*P* = 0.771). RSP patients who progressed by liver metastases exhibited a median OS of 8.6 mo, progression of extrahepatic metastasis was 10.1 mo, and progression of both liver and extrahepatic metastasis was 9.3 mo (*P* = 0.885). No significant difference was observed in survival between liver metastasis only and extrahepatic metastases patients (*P* = 0.493).

A prognostic factor analysis showed that different infusion agents resulted in differential survival. OXA-based infusion chemotherapy (*n* = 153) resulted in a median OS of 15.8 mo, while CPT-11-based chemotherapy (*n* = 15) reached 22.8 mo (*P* = 0.518). Neither LSP nor RSP patients experienced a significant difference in this treatment variable. Among all factors considered, primary tumor histology, radiofrequency ablation or liver radiotherapy, normal serum CA19-9 levels, and response to HAIC were protective factors associated with OS (Table 3).

DISCUSSION

Differences in survival resulting from differences in biological behavior were examined in LSP and RSP patients. In our study, we analyzed the survival data between patients with LSP tumors and those with RSP tumors after HAIC in mCRC in our center. When comparing PFS between LSP and RSP patients, no obvious advantages were found in LSP patients; however, a trend did exist. These results suggest that combined hepatic arterial infusion (HAI) does not change survival in patients with liver metastasis from either LSP or RSP colorectal cancer, which is inconsistent with the survival data for mCRC patients who undergo hepatic metastasis resection. Patients treated with hepatic metastasis surgery exhibit an OS similar to LSP and RSP patients after liver metastasis. However, this result was based on retrospective analysis, and patient selection bias was likely to have influenced the outcome. We cannot conclude that local treatment of liver metastasis reverses the worse prognosis in RSP patients.

In systemic chemotherapy, one of the most important prognostic factors is the use of molecular targeted drugs, especially with respect to differences between anti-EGFR and anti-vascular endothelial growth factor monoclonal antibodies. However, an interesting phenomenon was found in our study wherein the OS of LSP patients was significantly better in those treated with bevacizumab than in those treated with cetuximab, and the OS of RSP patients exhibited the same trend. This phenomenon is completely opposite to data concerning systemic chemotherapy in both LSP and RSP patients. Possible reasons for these discrepancies include the following: The optimal dose of bevacizumab and cetuximab in HAI treatment has not been clearly verified; only a few cases were treated with cetuximab; only *KRAS* genotyping was performed

Table 3 Univariate analysis of predictive factor of survival after first hepatic arterial infusion chemotherapy

Variable	MST (mo)	Univariate analysis		*P*-value
		HR	95%CI	
Primary tumor site (right/left)	9.3 *vs* 16.3	1.353	0.881-2.079	0.167
Age (> 60/< 60 yr)	16 *vs* 15.5	1.026	0.731-1.440	0.88
Gender (male/female)	16.5 *vs* 13	0.744	0.520-1.063	0.104
Histology (poor/well to moderate)	10.3 *vs* 15.9	1.706	1.003-2.904	0.049*
Serum CA19-9 (≥ 37U/mL/< 37 U/mL)#	12.5 *vs* 21.2	2.108	1.444-3.076	< 0.001*
Serum CA72-4 (≥ 6.7 U/mL/< 6.7 U/mL)#	13 *vs* 20.8	1.605	1.114-2.311	0.011*
Serum CEA (≥ 5U/mL/< 5 U/mL)#	14.6 *vs* 21.1	1.428	0.867-2.351	0.162
Extrahepatic metastasis (present/absent)	15.8 *vs* 15.8	1.172	0.825-1.667	0.376
Time to liver metastasis (synchronous/ metachronous)	14.8 *vs* 16.5	1.125	0.802-1.580	0.495
Other local treatment (combined/uncombined)	21.1 *vs* 14.6	0.651	0.426-0.995	0.047*
Response to HAIC				< 0.001*
PR	21.9	0.234	0.146-0.375	< 0.001*
SD	16.1	0.285	0.185-0.439	< 0.001*
PD	7.5	1	1	NA
Infusion agents (OXA/CPT-11)	15.8 *vs* 22.8	1.225	0.660-2.273	0.52
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MST: Median survival time; HR: Hazard ratio; HAIC: Hepatic arterial infusion chemotherapy; PR: Partial response; SD: Stable disease; PD: Progressive disease.

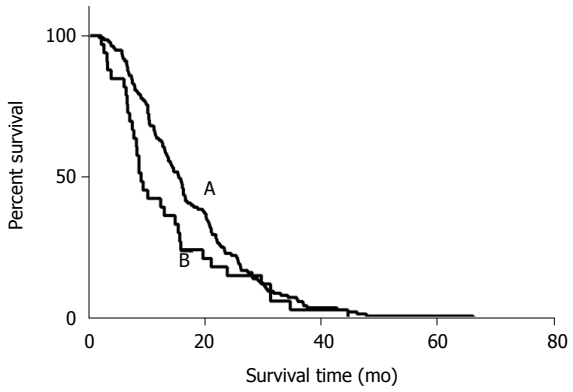

Figure 2 Progression-free survival data of patients who received hepatic arterial infusion chemotherapy treatment (*n* = 168). The median PFS of left sided colorectal cancer liver metastasis patients was 5.7 mo (curve A). The median PFS of right sided colorectal cancer liver metastasis patients was 4.2 mo (curve B).

instead of testing all RAS genes; and HAI treatment was not a first-line treatment in our study. Another study reported that RAS gene mutations might be influenced by previous treatment. However, in LSP patients, bevacizumab treatment showed an obvious advantage compared with cetuximab, and this advantage could even be observed in RAS wild-type patients. This demonstrates that in HAIC treatment, especially in left-sided colorectal cancer liver metastasis, bevacizumab is superior to cetuximab.

In comparison with cytotoxic agents, irinotecan seems superior to oxaliplatin in OS after HAI treatment. However, in first-line treatment of all patients, the vast majority received oxaliplatin-based systemic chemotherapy, so the data could support the conclusion that irinotecan is superior to oxaliplatin in HAI treatment. However, it is worth noting that, as a second-line or subsequent treatment, HAIC obtained close to 30% objective remission rates in both LSP and RSP patients when most patients had previously received oxalipatin. The overall response rate observed in this study was obviously superior to second-line systemic chemotherapy and was similar to systemic therapy treatment using FOLFOX and bevacizumab (E3200)[24], suggesting that HAIC treatment might be superior to systemic cytotoxic chemotherapy in second-line conversion therapy for mCRC.

In conclusion, for HAIC treatment of mCRC, the survival of patients with left colon cancer remains better than that of right colon cancer patients. Subgroup analysis showed that bevacizumab might be superior to cetuximab, especially in left-sided colorectal cancer liver metastasis. However, further study is needed on the optimal dosage and mode of administration of molecular targeted drugs for HAIC treatment. Both oxaliplatin and irinotecan achieve considerable objective remission rates.

ARTICLE HIGHLIGHTS

Research background

Previous studies have shown that left-sided colorectal cancer has a better survival prognosis than right-sided colorectal cancer. However, whether this prognosis difference is also present in liver metastasis colorectal cancer (CRC) patients treated with hepatic arterial infusion chemotherapy (HAIC) is still unknown.

Research motivation

Our study attempted to analyze for the first time, whether there would be a difference in survival and overall response rate in liver metastasis CRC patients

treated with HAIC.

Research objectives

To analyze the overall survival and overall response rate difference of patients with liver metastasis of left-sided or right-sided colorectal cancer after HAIC.

Research methods

A retrospective analysis of liver metastasis CRC patients from May 2006 to August 2015 was conducted. Cox proportional hazard regression analysis was used to assess long-term survival outcomes.

Research results

Overall response rate was 28.9% in left-sided primary (LSP) patients, and 27.3% in right-sided primary (RSP) patients. Disease control rate was 76.3% in LSP patients and 69.7% in RSP patients. Median overall survival after HAIC was 16.3 mo in the LSP arm and 9.3 mo in the RSP arm (P = 0.164). Median progression-free survival was 5.7 mo in the LSP arm and 4.2 mo in the RSP arm (P = 0.851).

Research conclusions

The treatment response rate of HAIC in metastatic CRC patients is similar when compared by different primary tumor site. LSP patients seemed to have a superior survival compared to RSP patients when treated by HAIC but no significant difference was found.

Research perspectives

Further large sample size and multi-center prospective studies are needed to confirm the conclusion of this study.

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P- Reviewer: Park SJ, Masaki O, Ko E **S- Editor**: Dou Y
L- Editor: Filipodia **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 November 15; 10(11): 439-448

DOI: 10.4251/wjgo.v10.i11.439

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Prospective Study

Raman spectroscopy for the diagnosis of unlabeled and unstained histopathological tissue specimens

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Author contributions: Ikeda H and Ito H conceived and designed the study, collected clinical data, collected samples, performed the statistical analysis, and interpreted the data; Hikita M performed Raman spectroscopic analysis; Yamaguchi N, Uragami N, and Yokoyama N performed medical examinations and surgical operations; Hirota Y and Kushima M performed pathological examinations; Ajioka Y and Inoue H participated in the study design and coordination; all authors have read and approved the final paper.

Supported by the Japan Society for the Promotion of Science (JSPS), through two JSPS KAKENHI Grants-in-Aid for Scientific Research (C), No. JP26460688 and JP17K09022.

Institutional review board statement: The Institutional Review Board of Showa University approved the study.

Clinical trial registration statement: This prospective study is registered with University Hospital Medical Information Network in Japan, UMIN000017045.

Informed consent statement: We obtained the written consent from the participant before executing this study.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: There is no additional data available.

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

Manuscript source: Invited manuscript

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Received: July 20, 2018
Peer-review started: July 20, 2018
First decision: August 31, 2018
Revised: September 6, 2018

Accepted: October 17, 2018
Article in press: October 17, 2018
Published online: November 15, 2018

Ikeda H, Ito H, Hikita M, Yamaguchi N, Uragami U, Yokoyama N, Hirota Y, Kushima M, Ajioka Y, Inoue H. Raman spectroscopy for the diagnosis of unlabeled and unstained histopathological tissue specimens. *World J Gastrointest Oncol* 2018; 10(11): 439-448 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/439.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.439

Abstract

AIM

To investigate the possibility of diagnosing gastric cancer from an unstained pathological tissue using Raman spectroscopy, and to compare the findings to those obtained with conventional histopathology.

METHODS

We produced two consecutive tissue specimens from areas with and without cancer lesions in the surgically resected stomach of a patient with gastric cancer. One of the two tissue specimens was stained with hematoxylin and eosin and used as a reference for laser irradiation positioning by the spectroscopic method. The other specimen was left unstained and used for Raman spectroscopy analysis.

RESULTS

A significant Raman scattering spectrum could be obtained at all measurement points. Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, are associated with the nucleotides adenine and cytosine, respectively. The Raman scattering spectrum intensity ratios of 782 cm^{-1}/620 cm^{-1}, 782 cm^{-1}/756 cm^{-1}, 782 cm^{-1}/1250 cm^{-1}, and 782 cm^{-1}/1263 cm^{-1} in the gastric adenocarcinoma tissue were significantly higher than those in the normal stomach tissue.

CONCLUSION

The results of this preliminary experiment suggest the feasibility of our spectroscopic method as a diagnostic tool for gastric cancer using unstained pathological specimens.

Key words: Label-free analysis; Raman spectroscopy; Histopathological examination; Gastric cancer

Core tip: We investigated the possibility of diagnosing gastric cancer from an unstained pathological tissue using Raman spectroscopy, and the findings were compared to those obtained with conventional histopathology. We analyzed unstained gastric pathological specimens by Raman spectroscopy. The Raman scattering spectrum intensity ratios of 782 cm^{-1}/620 cm^{-1}, 782 cm^{-1}/756 cm^{-1}, 782 cm^{-1}/1250 cm^{-1}, and 782 cm^{-1}/1263 cm^{-1} in the gastric adenocarcinoma tissue were significantly higher than those in the normal stomach tissue. The results of this preliminary experiment suggest the feasibility of our spectroscopic method as a diagnostic tool for gastric cancer using unstained pathological specimens.

INTRODUCTION

Histopathologic diagnosis represents the ultimate diagnostic method for many cancers[1]. The histopathological diagnosis method involves microscopic observation of a formalin-fixed specimen for a morphological diagnosis. Although chemical tissue staining is generally performed, such as hematoxylin and eosin staining, immunohistochemical (IHC) tissue staining using an antigen-antibody reaction may also be performed on pathological tissue specimens to obtain more detailed information on the cells and tissues[2,3]. Despite its advantage for improving diagnostic accuracy in carcinomas[4,5], IHC is a longer process than general chemical tissue staining, and the antigen-antibody reaction requires precise conditions; thus, preparation of IHC specimens demands a relatively high level of professional skill.

Raman scattering spectroscopy is a non-destructive method for determining the types and components that make up a given substance[6], allowing for qualitative evaluation without requiring direct contact with the substance through irradiation and subsequent evaluation of the reflected scattered light (*e.g.*, laser). The Raman scattering intensity is correlated with the target substance[7], and this method can be used to evaluate substances in any state, *i.e.*, gas[8], liquid[9], or solid state[10]. Besides its simplicity and minimally invasive non-destructive nature, Raman spectroscopy enables the evaluation of substances without staining or labeling for an antigen-antibody reaction, and thus has potential for use in unstained pathological tissue specimens. Moreover, since Raman scattering spectroscopy is also suitable for evaluation of living bodies[11], evaluation of both the collected tissue as well as the living body might be possible with this approach[12].

To date, Raman scattering spectroscopy has been used to analyze biological tissue specimens such as the brain[13], thyroid gland[14], mammary gland[15], liver[16], and kidney[17]; however, its clinical significance has not yet been clarified.

As a preliminary examination of the potential of Raman scattering spectroscopy for diagnosis, we evaluated this method in an unstained stomach tissue specimen, and compared the findings with those of conventional histopathology.

MATERIALS AND METHODS

Patient and clinical sample

The Institutional Review Board of Showa University

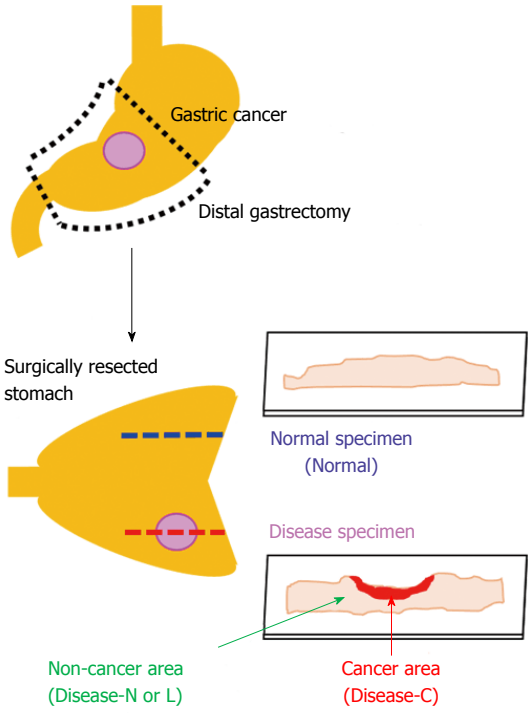

Figure 1 Two consecutive tissue specimens from areas with and without stomach cancer lesions. Each tissue specimen was sliced to a 3-μm thickness with a microtome and attached to a 1-mm-thick low-autofluorescence slide (SUPER FROST, Matsunami Glass Ind., Ltd, Tokyo, Japan). A thin cover glass (NEO microscope cover glass, Matsunami Glass Ind., Ltd., Tokyo, Japan) was placed on the tissue. Sections were deparaffinized by sequential immersion in xylene, ethanol, and water. One of the two tissue specimens was stained with hematoxylin and eosin and used as a reference for laser irradiation positioning by the spectroscopic method. Another tissue specimen was left unstained and used for analysis by Raman spectroscopy. We acquired the Raman spectrum of the cancer area (Disease-C), non-cancerous lymphocytes infiltration area (Disease-L), non-cancerous normal area (Disease-N) in the stomach cancer specimen, and normal stomach tissue specimen (Normal).

approved the study. This study was registered with the University Hospital Medical Information Network in Japan, number UMIN000017045.

We used the surgically resected stomach of a patient who provided informed consent for its use for this study after explaining the study protocol. The patient was a 61-year-old man diagnosed with early-stage gastric cancer of the mid-stomach, who underwent laparoscopic distal gastrectomy at Showa University Koto Toyosu Hospital in April 2015. The resected stomach was processed using general histopathological specimen preparation procedures. First, it was immersed in 20% neutral buffered formalin solution for 3 d for fixation, and subsequently dehydrated by immersion in 70% ethanol, 90% ethanol, and then 100% ethanol for 100 min each. Finally, the specimen was immersed in xylene three times for 2 h each, and embedded in paraffin.

We produced two consecutive tissue specimens from areas with and without stomach cancer lesions. Each tissue specimen was sliced to a thickness of 3 μm with a microtome and attached to a 1-mm-thick and low-autofluorescence slide (SUPER FROST, Matsunami Glass Ind., Ltd., Osaka, Japan). A thin cover glass (NEO microscope cover glass, Matsunami Glass Ind., Ltd., Tokyo, Japan) was placed onto the tissue specimen.

The sections were deparaffinized by sequential immersion in xylene, ethanol, and water. One of the two tissue specimens was stained with hematoxylin and eosin and used as a reference for laser irradiation positioning by the spectroscopic method. Another tissue specimen was left unstained and used for Raman spectroscopy analysis. We acquired the Raman spectrum of the cancer area (Disease-C), non-cancerous lymphocytes infiltration area (Disease-L), and non-cancerous normal area (Disease-N) in the stomach cancer specimen and normal stomach tissue specimen (Normal) (Figure 1).

Histopathological diagnosis

Two specialized pathologists at Showa University Koto Toyosu Hospital performed the histopathological diagnosis, which was determined to be type 0–IIc, 30 mm × 17 mm, well-differentiated adenocarcinoma, pT1bs (sm2), ly0, v0, pN0, Stage IA.

Spectroscopy

We used an inVia Raman microscope (Renishaw, Gloucestershire, United Kingdom), with a 100 × objective lens and a laser light source with a wavelength of 532 nm. We irradiated the tissue specimen with minimum power, and then gradually raised the laser output until it became visible within the field of view. The minimum visible laser output was 0.0002 mW. We adjusted the focus so that the beam diameter was minimized, based on visual observation. Spectra were digitized using standard spectroscopy software (WiRE 4; Renishaw, Gloucestershire, United Kingdom).

Spectroscopic measurements

The conditions for laser output and laser irradiation time were established on a marginal part of an unstained tissue specimen that included both gastric cancer lesion and non-lesion areas. To prevent tissue degeneration, we reduced the laser power as much as possible while maintaining detection of the Raman spectrum. Optimal measurement conditions were determined to be a laser output of 1.7 mW and an irradiation time of 10 s.

We measured the tissue specimens at regular intervals from the mucous membrane to the submucosal layer. In principle, intersection points of straight lines every 100 μm of both the length and width were used as the representative spectrum. We measured 121 points around one intersection point as far as a 10-μm square, and defined the mean value as a spectrum of the intersection point. From each obtained spectrum, we removed a spectrum only for glass by data processing. Furthermore, we similarly removed the spectrum of autologous fluorescence by the fifth-polynomial expression[18].

When a cell nucleus was observed, the field of view was fine-tuned to focus the laser on it. We measured 60

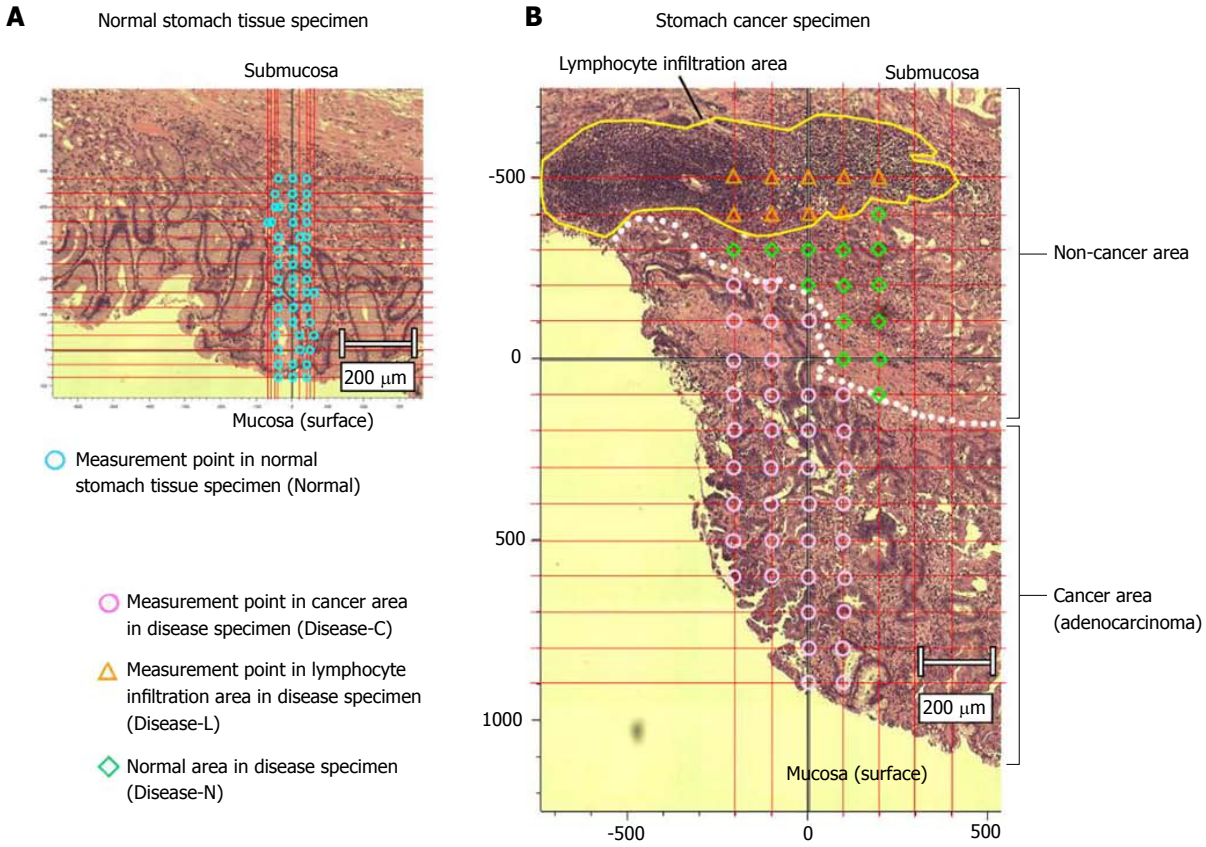

Figure 2 Measured points in the stomach cancer and normal tissue specimens. A: Normal stomach tissue specimen; B: Stomach cancer specimen. We established the conditions for laser output and laser irradiation time on a marginal part of an unstained tissue specimen that included both gastric cancer lesion and non-lesion areas. To prevent tissue degeneration, we reduced the laser power as much as possible, while maintaining detection of the Raman spectrum. Optimal measurement conditions were established as a laser output of 1.7 mW and an irradiation time of 10 s. We measured the tissue specimens at regular intervals from the mucous membrane to the submucosal layer.

and 48 points in the stomach cancer and normal tissue specimens, respectively. The 60 measured points in the stomach cancer specimen included 37 measured points in Disease-C and 23 measured points in the non-cancer area, nine of which were Disease-L and 14 were Disease-N (Figure 2).

Raman scattering spectrum intensity

We measured the Raman scattering spectrum intensities at 620 cm^{-1} (C-C twisting mode of phenylalanine)[19], 725 cm^{-1} (adenine)[19], 756 cm^{-1} (symmetric breathing of tryptophan)[19], 782 cm^{-1} (cytosine)[20], 1002 cm^{-1} (phenylalanine)[20], 1250 cm^{-1} (amide Ⅲβ-sheet)[21], and 1263 cm^{-1} (amide Ⅲα-Helix)[21], corresponding to the Raman scattering wavenumber of the organism constitution organic substance. We then calculated the ratio of the Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, associated with the nucleotides, to those of the others.

Statistical analysis

Statistical analyses were performed using JMP Pro 13.2.1 software (SAS Institute Inc., Cary, NC, United States). We statistically compared spectral intensity ratios among the four groups (Disease-C, Disease-N, Disease-L, and Normal) using a non-parametric Wilcoxon test. *P*-values less than 0.05 were considered statistically significant.

RESULTS

A significant Raman scattering spectrum could be obtained at all measurement points. Focusing on the intensity of the Raman scattering wavenumber 725 cm^{-1} derived from the nucleotide adenine, we found that all of the measured values for the ratios 725 cm^{-1}/620 cm^{-1}, 725 cm^{-1}/756 cm^{-1}, 725 cm^{-1}/1002 cm^{-1}, 725 cm^{-1}/1250 cm^{-1}, and 725 cm^{-1}/1263 cm^{-1} in the Disease-L tissue were significantly higher than those in the Disease-C, Disease-N, and Normal specimens, with no significant difference among these latter three groups (Figure 3). In the biaxial distribution, the distribution areas of the measured values of the Disease-C, Disease-N, and Normal specimens widely overlapped. Only the distribution area of the measurement value of Disease-L extended toward the higher value direction (Figure 4).

Similarly, focusing on the intensity of the Raman scattering wavenumber 782 cm^{-1} derived from the

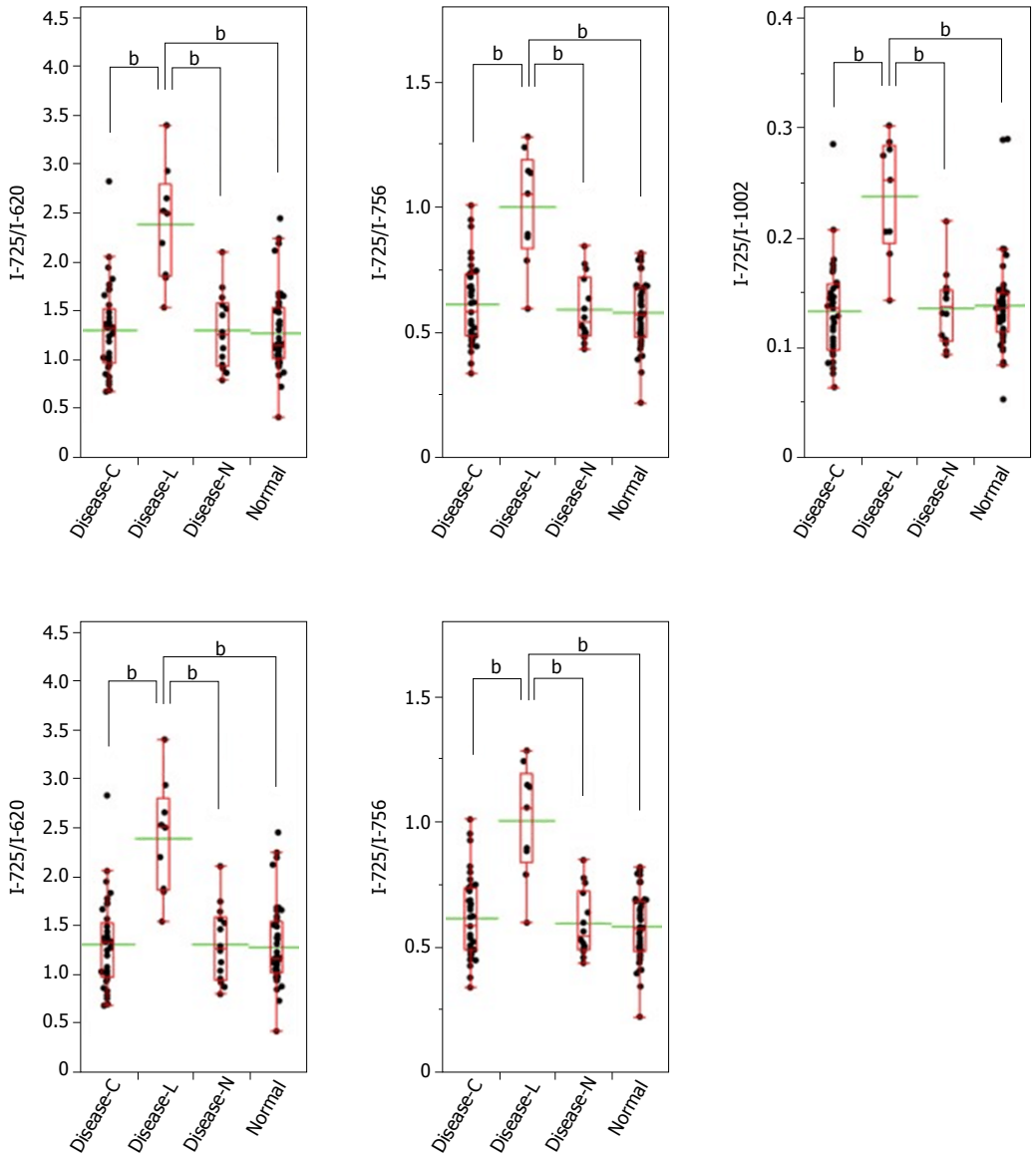

Figure 3 Raman scattering intensity ratio with intensity of wavenumber 725 cm^{-1} as the denominator. Dots indicate the ratio of Raman scattering intensity in each tissue specimen of the patient. The bottom and top of the red box represent the lower and upper quartiles, and the band across the box shows the median. The lower and upper bars at the ends of the whiskers show the lowest data point within the 1.5 interquartile range of the lower quartile, and the highest data point within the 1.5 interquartile range of the upper quartile, respectively. The green bar shows the average. $^{a}P < 0.05$, $^{b}P < 0.01$.

nucleotide cytosine, all of the measured values of 782 cm^{-1}/620 cm^{-1}, 782 cm^{-1}/756 cm^{-1}, 782 cm^{-1}/1002 cm^{-1}, 782 cm^{-1}/1250 cm^{-1}, and 782 cm^{-1}/1263 cm^{-1} in the Disease-L specimen were significantly higher than those of the other three groups. Moreover, the measured values of the 782 cm^{-1}/620 cm^{-1}, 782 cm^{-1}/756 cm^{-1}, 782 cm^{-1}/1250 cm^{-1}, and 782 cm^{-1}/1263 cm^{-1} ratios in the Disease-C specimen were significantly higher than those in the Normal specimen. There was no significant difference of the measured values between the Disease-C and Disease-N specimens, and between the Disease-N and Normal specimens (Figure 5). In the biaxial distribution, the distribution areas of measured values of Disease-N and Normal specimens widely overlapped. The distribution area of the measurement value of Disease-L extended toward the higher value direction, and the values for Disease-C were distributed in the middle of the range (Figure 6).

DISCUSSION

Gastrointestinal cancers such as esophageal cancer, stomach cancer, colon cancer, and rectal cancer are typically confirmed with an endoscope, and then tissues are collected for histopathological confirmation of the diagnosis, which requires histochemical or IHC staining. Although the procedure for general histochemical staining is relatively simple, the diagnostic capability is limited. By contrast, IHC can provide a more accurate histopathological diagnosis, but is relatively time-con-

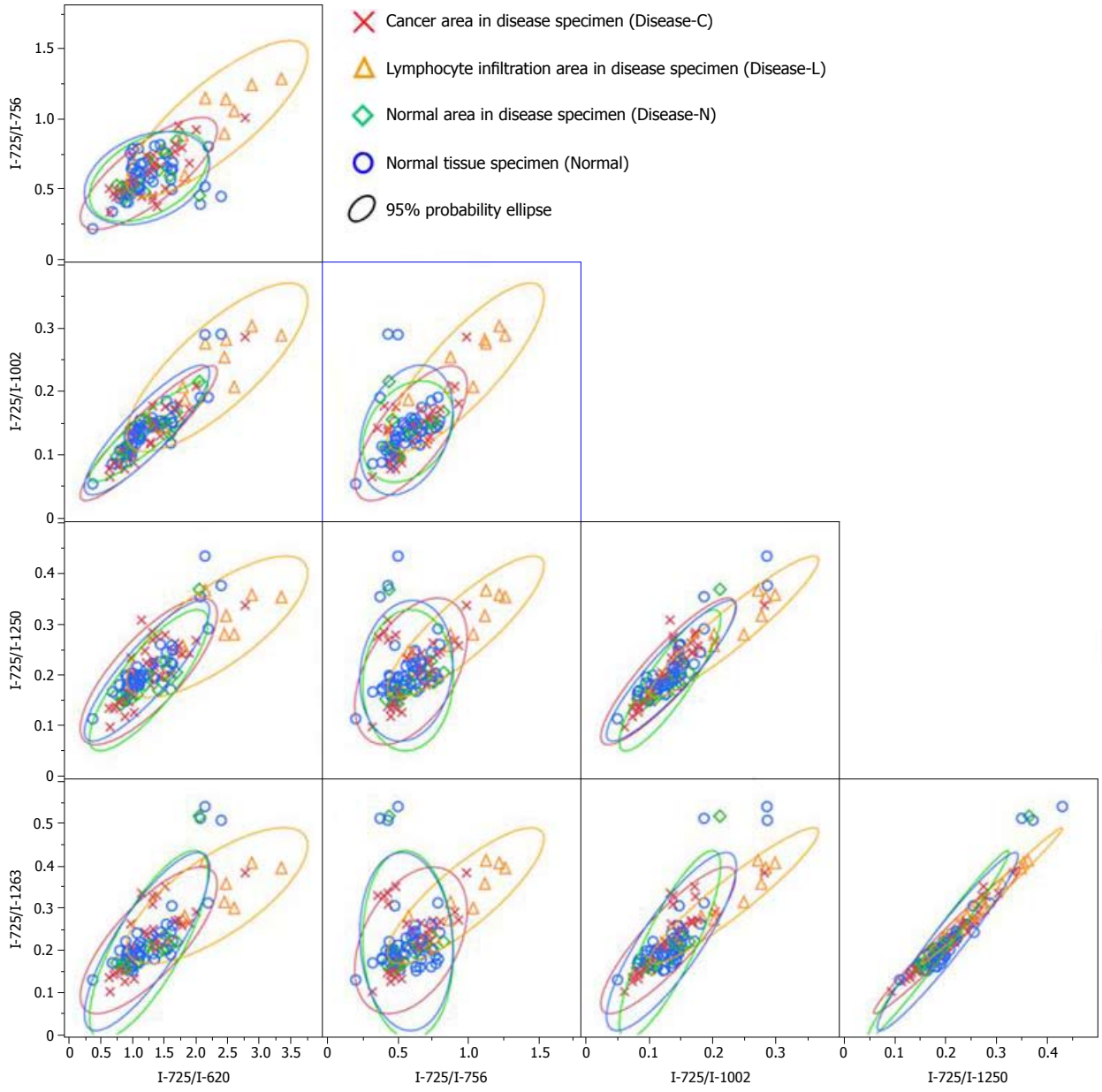

Figure 4 Biaxial distribution of the Raman scattering intensity ratio with the intensity of wavenumber 725 cm^{-1} as the denominator.

suming and requires specialized skills.

Raman scattering spectroscopy shows potential as a non-destructive method for live tissue evaluation, including the brain[22] and lung[23]; however, its potential utility for clinical in vivo evaluation has not yet been determined. Furthermore, although a few small-scale studies have been conducted on gastrointestinal tissue spectroscopy analysis[24–26], standard spectroscopy evaluation methods for living organisms have not yet been established. Here, we demonstrated that Raman scattering spectroscopy could be used to qualitatively evaluate unstained pathological tissue specimens since the cancer lymphocyte infiltration area in the gastric cancer tissue specimen (Disease-N) showed the most characteristic measurement value, followed by the cancer portion in the stomach cancer tissue specimen (Disease-C).

Based on comparison of the ratio of the Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, associated with the nucleotides adenine and cytosine, respectively, to those of the others, our results suggested that cytosine is present in the Disease-C region at a relatively high concentration, and both adenine and cytosine exist in the Disease-L region at a relatively high concentration in the stomach tissue. In addition, both adenine and cytosine were presumed to be present at higher concentrations in the Disease-L specimen compared to the Disease-C specimen.

Adenine and cytosine are bases that make up DNA. In tumor cells, the nuclear DNA amount is often in aneuploidy; thus, the cytosine concentration is theoretically expected to be high in tumor cells[27]. By

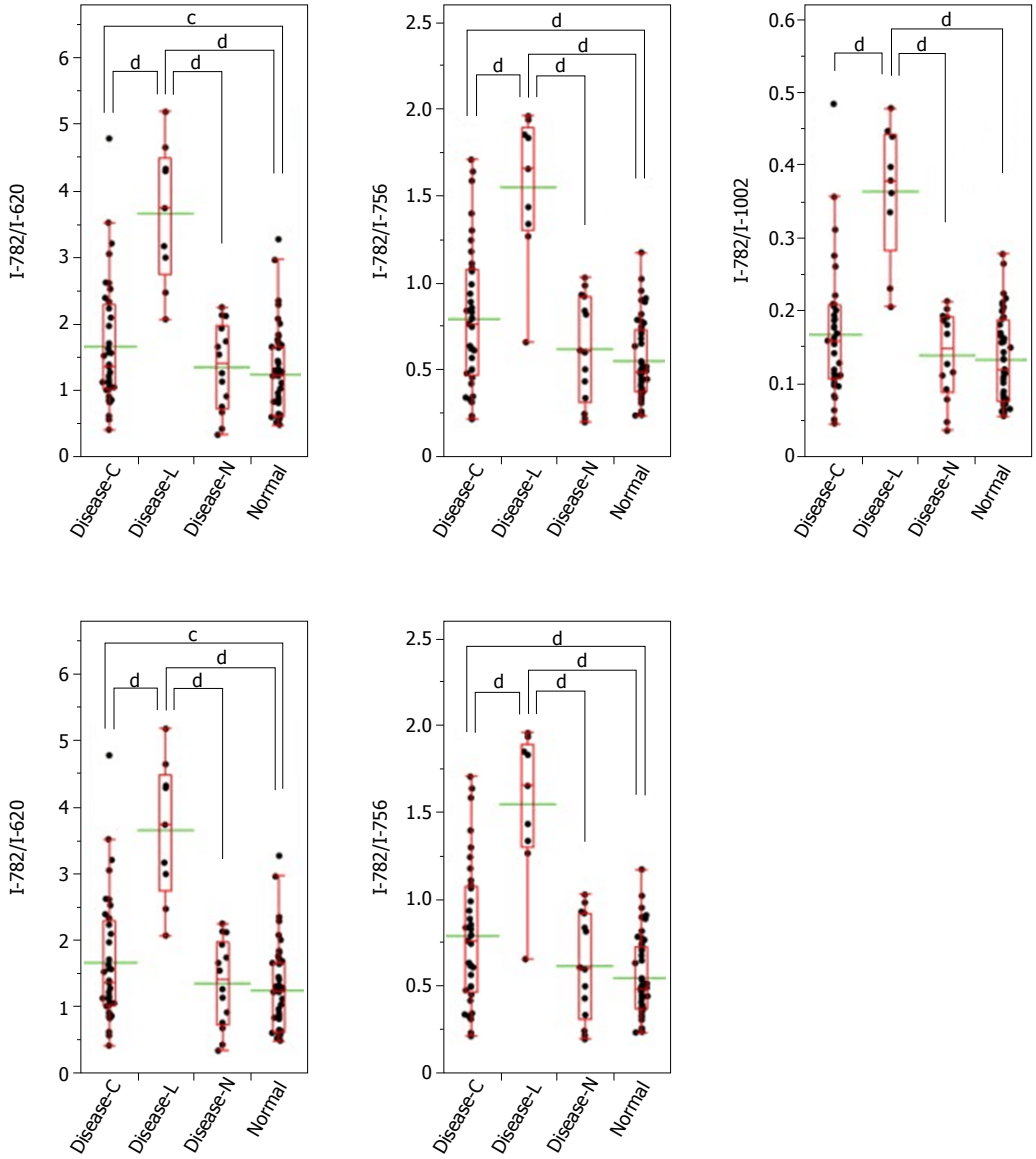

Figure 5 Raman scattering intensity ratio with the intensity of wavenumber 782 cm^{-1} as the denominator. Dots indicate the ratio of the Raman scattering intensity in each tissue specimen of the patient. The bottom and top of the red box represent the lower and upper quartiles, and the band across the box shows the median. The lower and upper bars at the ends of the whiskers show the lowest data point within the 1.5 interquartile range of the lower quartile, and the highest data point within the 1.5 interquartile range of the upper quartile, respectively. The green bar shows the average. $^{c}P < 0.05$, $^{d}P < 0.01$.

contrast, in lymphocytes, nuclear DNA is haploidal in many cases, and thus the amount of DNA in a given cell would not be expected to differ from that of a normal cell[27]. The clustered lymphocytes observed in the stomach cancer tissue specimens used in this study had a nucleus size equivalent to that of normal cells albeit a smaller cell size. Therefore, in the Disease-L region, it is likely that the focal point of the laser struck the cell nucleus, so that the Raman scattering intensities of 725 cm^{-1} and 782 cm^{-1}, derived from adenine and cytosine, were more strongly measured. Lymphocyte infiltration in tissues suggests the presence of inflammation or an immune response. Given the significant relationship between malignancies and lymphocyte infiltration[28,29], confirmation of lymphocyte infiltration may help to detect any abnormalities, including malignant disease.

Limitations

Given the preliminary nature of the study, there are some limitations that should be mentioned. First, histopathological samples are intended for general histopathological diagnosis, but without staining, and they were not optimized for spectroscopy. For evaluation by spectroscopy, we need to consider conditions such as the thickness of the specimen and the material of the plate to which the specimen is attached. Second, the sample size was small, and we only focused on the stomach without assessment of other organs. Third, the data were obtained using a limited wavelength laser, and the focus position of the laser could not be precisely

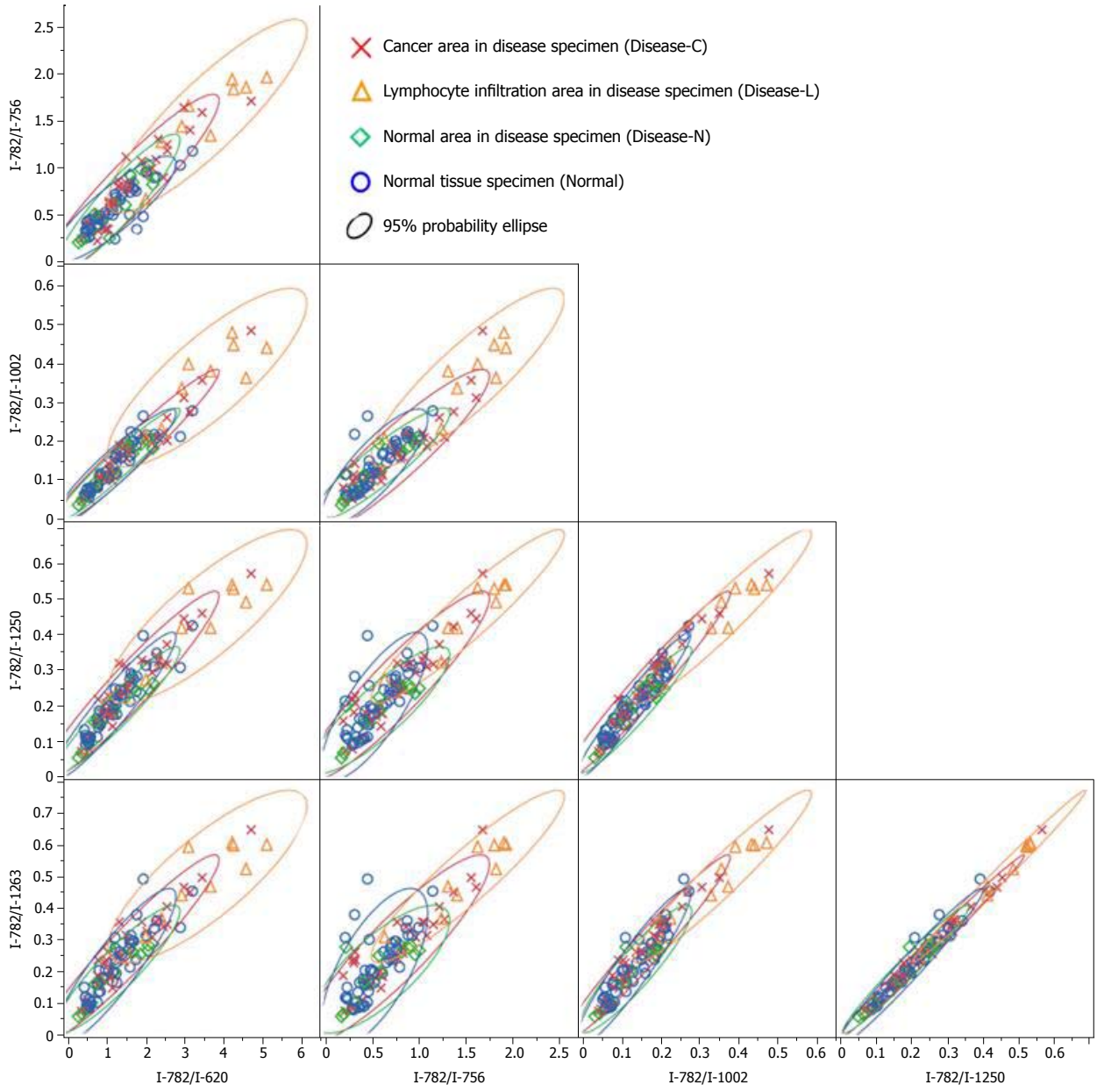

Figure 6 Biaxial distribution of the Raman scattering intensity ratio with intensity of wavenumber 782 cm^{-1} as the denominator.

controlled at a prescribed region of the cell. In particular, it has been suggested that lasers of longer wavelength such as 1064 nm are more suitable for analyzing samples with strong autofluorescence such as living tissue[30]. Therefore, other laser light sources should be tested in future studies, including long-wavelength lasers.

Therefore, for future experiments, we will optimize the analytical sample for spectroscopy by examining the tissue specimen, material, and thickness of the slide glass, and conduct measurements under more precise regulation. Moreover, we plan to expand the experiments for testing the effects of different wavelengths and in different organs.

Finally, toward realizing the ultimate goal of more accurate cancer diagnosis, it will be important to compare the results obtained from Raman scattering spectroscopy with the histopathological diagnosis as the present gold-standard, as well as with molecular biological findings obtained by next-generation sequencing and mass spectrometry (Figure 7).

Currently, Raman spectroscopy is an ancillary technique for adding qualitative information to histopathological morphological diagnosis. Further verification of our results and optimization of the technology as described above should help toward application of Raman spectroscopy as a diagnostic pathology technology without requiring staining or labeling. These advantages will help to more quickly and accurately diagnose cancer, and to realize early treatment initiation, with ultimate improvement of the treatment outcome. Moreover, such technology would allow for making a definitive diagnosis *in vivo* with-

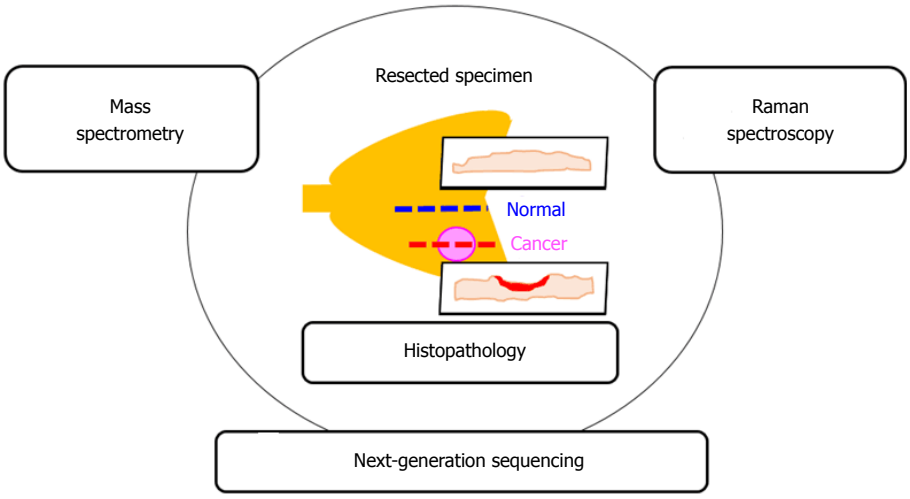

Figure 7 Schematic representation of potential histopathological diagnosis using Raman scattering spectroscopy, next-generation sequencing, and mass spectrometry for realizing a more accurate cancer diagnosis.

out invasive procedures of tissue collection and time-consuming histopathological diagnosis. Therefore, the biopsy step can be omitted to diagnose cancer quickly and less invasively.

ARTICLE HIGHLIGHTS

Research background

Histopathological evaluation is the gold-standard for cancer diagnosis. However, the diagnostic accuracy of histopathology staining is low, and the protocols for immunohistochemistry are complicated and time-consuming.

Research motivation

To achieve rapid, accurate and minimally invasive cancer diagnosis, a label-free and non-contact diagnostic technology is useful. Raman scattering spectroscopy has been used to analyze several types of biological tissue specimens; however, the clinical significance and diagnostic accuracy of this approach remain unclear. In addition, there are currently no standardized evaluation methods of gastrointestinal tissue spectroscopy analysis for living organisms.

Research objectives

We used the surgically resected stomach of a patient who underwent.

Research methods

The resected stomach was processed using general histopathological specimen preparation procedures. We produced two consecutive tissue specimens from areas with and without stomach cancer lesions. Each tissue specimen was sliced to a thickness of 3 μm and attached to a low-autofluorescence slide. One of the two tissue specimens was stained with hematoxylin and eosin and used as a reference for laser irradiation positioning by the spectroscopic method. Another tissue specimen was left unstained and used for Raman spectroscopy analysis by a laser light source with a wavelength of 532 nm.

Research results

Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, are associated with the nucleotides adenine and cytosine, respectively. The Raman scattering spectrum intensity ratios of 782 cm^{-1}/620 cm^{-1}, 782 cm^{-1}/756 cm^{-1}, 782 cm^{-1}/1250 cm^{-1}, and 782 cm^{-1}/1263 cm^{-1} in the gastric adenocarcinoma tissue were significantly higher than those in the normal stomach tissue. In addition, both adenine and cytosine were presumed to be present at higher concentrations in the non-cancerous lymphocytes infiltration area surrounding cancer compared to the cancer area in the gastric adenocarcinoma tissue specimen.

Research conclusions

This preliminary experiment suggests the feasibility of our spectroscopic method as a diagnostic tool for gastric cancer using unstained pathological specimens. The Molecular biological differences among cells in the resected stomach tissue can be detected by Raman spectroscopy. Adenine and cytosine may be influential substances for histopathological diagnosis by Raman spectroscopy. By focusing on adenine and cytosine, we were able to distinguish qualitative differences in the stomach tissue by Raman spectroscopy. Both adenine and cytosine were presumed to be present at higher concentration in the gastric adenocarcinoma tissue were significantly higher than those in the normal stomach tissue. We measured the Raman scattering spectrum intensities at 620 cm^{-1} (C-C twisting mode of phenylalanine), 725 cm^{-1} (adenine), 756 cm^{-1} (symmetric breathing of tryptophan), 782 cm^{-1} (cytosine), 1002 cm^{-1} (phenylalanine), 1250 cm^{-1} (amide IIIβ-sheet), and 1263 cm^{-1} (amide IIIα-Helix), corresponding to the Raman scattering wavenumber of the organism constitution organic substance. We then calculated the ratio of the Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, associated with the nucleotides, to those of the others. We compared the ratio of the Raman scattering spectrum intensities of 725 cm^{-1} and 782 cm^{-1}, associated with the nucleotides adenine and cytosine to qualitatively evaluate tissue. We found that Raman scattering spectrum intensities associated with the nucleotides adenine and cytosine were higher in adenocarcinoma than in normal tissue specimen of the stomach. In conclusion, we were able to distinguish qualitative differences in the stomach tissue by Raman spectroscopy.

Research perspectives

The Molecular biological differences among cells in the resected stomach tissue can be detected by Raman spectroscopy. In the future, we should raise the accuracy of estimation by Raman spectroscopy and to complete it as a technology that can obtain both high-precision morphological information and qualitative information.

ACKNOWLEDGMENTS

We are grateful to the clinical staff at Showa University Koto Toyosu Hospital.

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P- Reviewer: Jeong KY, Xu XY **S- Editor**: Ma RY **L- Editor**: A
E- Editor: Tan WW

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 November 15; 10(11): 449-464

DOI: 10.4251/wjgo.v10.i11.449

ISSN 1948-5204 (online)

META-ANALYSIS

Robotic total meso-rectal excision for rectal cancer: A systematic review following the publication of the ROLARR trial

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Conflict-of-interest statement: None to declare.

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

Manuscript source: Invited manuscript

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Received: April 16, 2018
Peer-review started: April 17, 2018
First decision: May 17, 2018
Revised: June 25, 2018
Accepted: June 28, 2018
Article in press: June 29, 2018
Published online: November 15, 2018

Abstract

AIM

To compare outcomes in patients undergoing rectal resection by robotic total meso-rectal excision (RTME) *vs* laparoscopic total meso-rectal excision (LTME).

METHODS

Standard medical electronic databases such as PubMed, MEDLINE, EMBASE and Scopus were searched to find relevant articles. The data retrieved from all types of included published comparative trials in patients undergoing RTME *vs* LTME was analysed using the principles of meta-analysis. The operative, post-operative and oncological outcomes were evaluated to assess the effectiveness of both techniques of TME. The summated outcome of continuous variables was expressed as standardized mean difference (SMD) and dichotomous data was presented in odds ratio (OR).

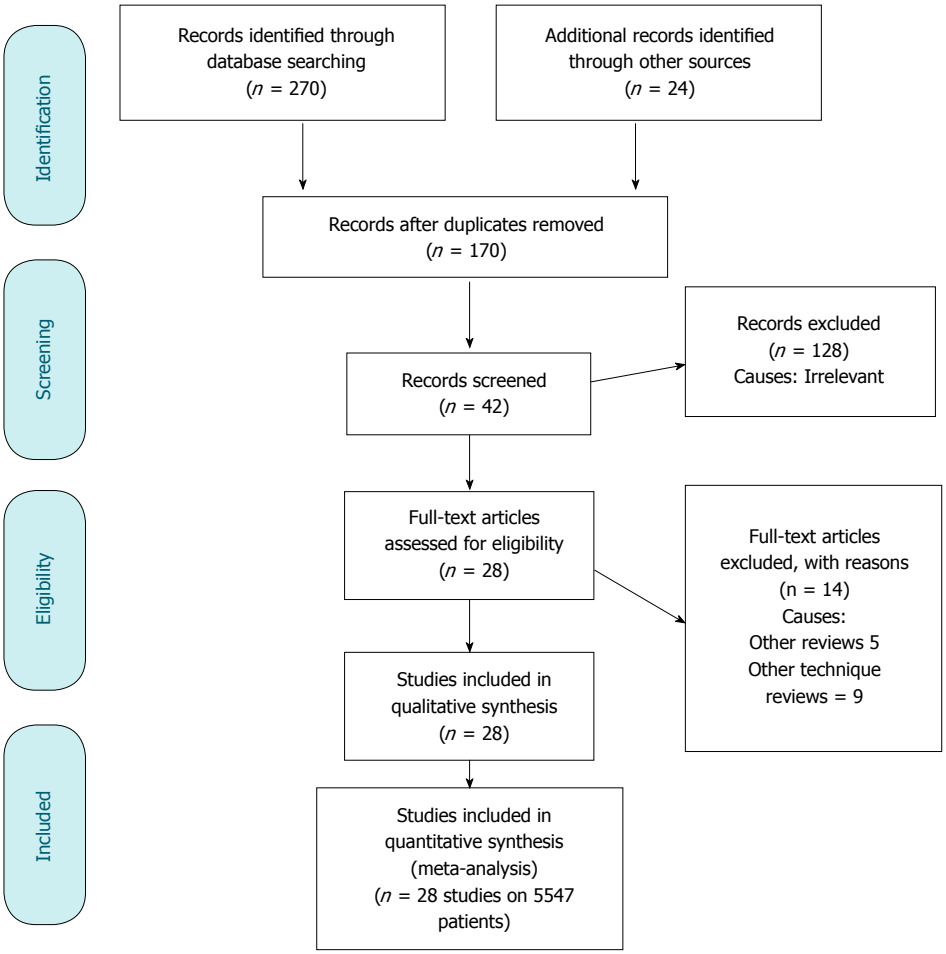

Figure 1 PRISMA flow diagram.

RESULTS

One RCT (ROLARR trial) and 27 other comparative studies reporting the non-oncological and oncological outcomes following RTME *vs* LTME were included in this review. In the random effects model analysis using the statistical software Review Manager 5.3, the RTME was associated with longer operation time (SMD, 0.46; 95%CI: 0.25, 0.67; z = 4.33; *P* = 0.0001), early passage of first flatus (*P* = 0.002), lower risk of conversion (*P* = 0.00001) and shorter hospitalization (*P* = 0.01). The statistical equivalence was seen between RTME and LTME for non-oncological variables like blood loss, morbidity, mortality and re-operation risk. The oncological variables such as recurrence (*P* = 0.96), number of harvested nodes (*P* = 0.49) and positive circumferential resection margin risk (*P* = 0.53) were also comparable in both groups. The length of distal resection margins was similar in both groups.

CONCLUSION

RTME is feasible and oncologically safe but failed to demonstrate any superiority over LTME for many surgical outcomes except early passage of flatus, lower risk of conversion and shorter hospitalization.

Key words: Diverticular disease; Colorectal resections; Multi-incision laparoscopic surgery; Colorectal cancer; Single incision laparoscopic surgery

Core tip: The findings of this meta-analysis of one RCT and 27 case control studies on 5547 patients are consistent with the recently published ROLARR trial validating the feasibility and oncological safety of robotic total meso-rectal excision (RTME). However, RTME failed to demonstrate any superiority over laparoscopic total meso-rectal excision except reduced conversion rate.

Jones K, Qassem MG, Sains P, Baig MK, Sajid MS. Robotic total meso-rectal excision for rectal cancer: A systematic review following the publication of the ROLARR trial. *World J Gastrointest Oncol* 2018; 10(11): 449-464 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i11/449.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i11.449

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Allemann 2016	291	67.7	20	313	67.7	40	3.4%	-0.32 [-0.86, 0.22]
Baek 2011	296	92.5	41	315	102.5	41	3.6%	-0.19 [-0.63, 0.24]
Baek 2012	285.2	69.1	154	219.7	71.2	150	4.0%	0.93 [0.69, 1.17]
Barnajian 2014	240	92.5	20	180	85	20	3.1%	0.66 [0.02, 1.30]
Bianchi 2010	240	62.5	25	237	93.75	25	3.3%	0.04 [-0.52, 0.59]
Cho 2015	361.6	91.9	278	272.4	83.8	278	4.1%	1.01 [0.84, 1.19]
Colombo 2016	274	78	60	228	76	60	3.8%	0.59 [0.23, 0.96]
D'Annibale 2013	270	18.75	50	280	22.5	50	3.7%	-0.48 [-0.88, -0.08]
Feroci 2016	342	233.4	53	192	233.4	58	3.8%	0.64 [0.26,1.02]
Foo 2015	271.5	66.5	164	229.2	60.7	137	4.0%	0.66 [0.43, 0.89]
Gorgun 2016	329	102.2	29	294	81.1	27	3.4%	0.37 [-0.16, 0.90]
Ielpo 2017	336	16	86	283	84	112	3.9%	0.82 [0.53, 1.12]
Jayne 2017	298.5	88.71	236	261	83.24	230	4.1%	0.44 [0.25, 0.62]
Kang 2013	309.7	115.2	165	277.8	81.9	165	4.1%	0.32 [0.10, 0.54]
Karim 2016	407	97	26	240	89	27	3.1%	1.77 [1.13, 2.41]
Kim JC 2016	189	52	533	127	35	486	4.2%	1.39 [1.25, 1.52]
Kim YS 2016	441	90.2	33	277	83.2	66	3.5%	1.90 [1.40, 2.40]
Kwak 2011	270	21	60	228	19.25	59	3.6%	2.07 [1.62,2.52]
Lim 2017	365.2	108.4	74	311.6	79.8	64	3.8%	0.55 [0.21, 0.90]
Park 2011	232.6	52.4	52	158.1	49.2	123	3.8%	1.48 [1.12, 1.84]
Popescu 2010	208	130	38	182	120	84	3.7%	0.21 [-0.17, 0.59]
Ramji 2016	407	174.1	26	240	174.1	27	3.3%	0.95 [0.37, 1.52]
Serin 2015	182	20	14	140	52.4	65	3.2%	0.86 [0.26, 1.45]
Silva-Velazco 2017	288	95.3	66	239	95.3	118	3.9%	0.51 [0.21, 0.82]
Valverde 2017	215	53	65	226	66	65	3.8%	-0.18 [-0.53, 0.16]
Yamaguchi 2016	232.9	72	203	227.6	62.6	239	4.1%	0.08 [-0.11, 0.27]
Zhang 2017	217	57.8	30	187	23.1	32	3.4%	0.68 [0.17, 1.19]
Total (95%CI)			**2601**			**2848**	**100.0%**	**0.65 [0.43, 0.87]**

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 367.50$, df = 26 ($P < 0.00001$); $I^2 = 93\%$

Test for overall effect: Z = 5.74 ($P < 0.00001$)

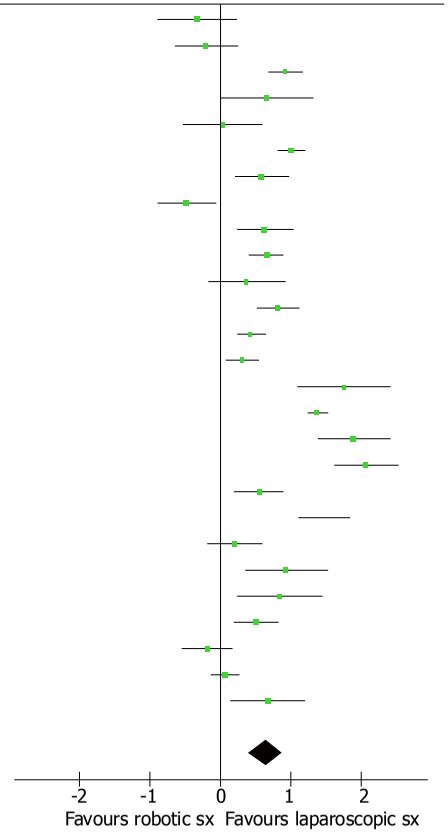

Figure 2 Forest plot for duration of operation following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

INTRODUCTION

Colorectal cancer has higher prevalence rate in the developed world and almost one third of cancers are diagnosed in the rectum[1-4]. Total mesorectal excision (TME) performed either by open or laparoscopic technique is an accepted gold standard treatment of rectal cancer worldwide. Laparoscopic TME (LTME) has apparent advantages and considered a preferred mode of surgery due to less tissue trauma[5-11]. Due to precision in dissection, stable base unit and better visualization in difficult areas like lower pelvis, the robotic TME (RTME) is also considered a possible alternative to LTME[12,13]. RTME may potentially offer same advantages which LTME offers as reported in some studies. There have been several previous systematic reviews[14-21] on LTME *vs* RTME; however, none since the ROLARR trial, a multi-centre randomised controlled trial

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	1	20	8	40	2.3%	0.21 [0.02, 1.82]
Baek 2011	3	41	9	41	5.5%	0.28 [0.07, 1.13]
Barnajian 2014	0	20	2	20	1.1%	0.18 [0.01, 4.01]
Bianchi 2010	0	25	1	25	1.0%	0.32 [0.01, 8.25]
Cho 2015	1	278	2	278	1.8%	0.50 [0.04, 5.53]
Colombo 2016	2	60	3	60	3.2%	0.66 [0.11, 4.07]
D'Annibale 2013	0	50	6	50	1.3%	0.07 [0.00, 1.24]
Feroci 2016	2	53	1	58	1.8%	2.24 [0.20, 25.39]
Foo 2015	3	164	4	137	4.6%	0.62 [0.14, 2.82]
Gorgun 2016	1	29	5	27	2.2%	0.16 [0.02, 1.44]
Ielpo 2017	4	86	13	112	7.9%	0.37 [0.12, 1.18]
Jayne 2017	19	236	28	230	28.3%	0.63 [0.34, 1.17]
Kang 2013	1	165	3	165	2.1%	0.33 [0.03, 3.20]
Karim 2016	3	26	10	27	5.2%	0.22 [0.05, 0.93]
Kim JC 2016	1	533	25	486	2.7%	0.03 [0.00, 0.26]
Kim YS 2016	2	33	0	66	1.1%	10.56 [0.49, 226.44]
Kwak 2011	0	60	2	59	1.1%	0.19 [0.01, 4.04]
Lim 2017	1	74	4	64	2.2%	0.21 [0.02, 1.89]
Park 2011	0	52	0	123		Not estimable
Ramji 2016	3	26	10	27	5.2%	0.22 [0.05, 0.93]
Serin 2015	0	14	2	65	1.1%	0.88 [0.04, 19.24]
Silva-Velazco 2017	6	66	18	118	11.1%	0.56 [0.21, 1.48]
Valverde 2017	3	65	11	65	6.0%	0.24 [0.06, 0.90]
Yamaguchi 2016	0	203	2	239	1.2%	0.23 [0.01, 4.89]
Total (95%CI)		**2379**		**2582**	**100.0%**	**0.40 [0.29, 0.55]**
Total evevts	56		169			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 21.68, df = 22 (P = 0.48); I^2 = 0%

Test for overall effect: Z = 5.51 (P < 0.00001)

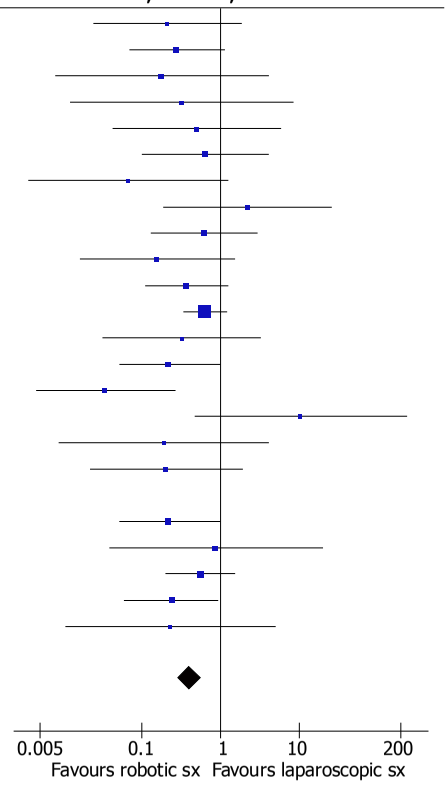

Figure 3 Forest plot for conversion following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

comparing RTME to LTME, has published its results. In addition, several new comparative studies have also been reported which require combined statistical evaluation to generate up to date and better evidence.

Our study is an up to date meta-analysis of studies comparing RTME *vs* LTME including recently published ROLARR trial to be able to distinguish the potential advantages or disadvantages that robotics may play in the treatment of rectal cancer.

MATERIALS AND METHODS

Study suitability standards

Following are features of individual publications needed to qualify for inclusion in this systematic review as depicted in the following PICOS style: (1) Participants: Adult

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Allemann 2016	58	76	20	219	421	40	4.1%	-0.46 [-1.00, 0.09]
Baek 2011	200	495	41	300	245.75	41	5.1%	-0.25 [-0.69, 0.18]
Baek 2012	167.8	26.1	154	126.2	267.7	150	7.1%	0.22[-0.01, 0.45]
Barnajian 2014	125	150	20	175	212.5	20	3.6%	-0.27 [-0.89, 0.36]
Cho 2015	179	236.5	278	147	295.3	278	7.7%	0.12 [-0.05, 0.29]
Colombo 2016	200	275	60	100	425	60	5.8%	0.28 [-0.08, 0.64]
Feroci 2016	60.8	138.3	53	47.4	138.3	58	5.7%	0.10 [-0.28, 0.47]
Gorgun 2016	434	612.4	29	339.4	271.9	27	4.3%	0.19 [-0.33, 0.72]
Ielpo 2017	43.2	117.6	86	30	68.4	112	6.6%	0.14 [-0.14, 0.42]
Kang 2013	133	192.3	165	140.1	216.4	165	7.2%	-0.03 [-0.25, 0.18]
Karim 2016	296	155	26	524	501	27	4.1%	-0.60 [-1.15, -0.05]
Kim YS 2016	232	180	33	205	163.8	66	5.2%	0.16 [-0.26, 0.58]
Popescu 2010	100	63.5	38	150	63.5	84	5.4%	-0.78 [-1.18, -0.39]
Ramji 2016	296	393.7	26	524	393.7	27	4.1%	-0.57 [-1.12, -0.02]
Silva-Velazco 2017	235	446.5	66	200	446.5	118	6.4%	0.08 [-0.22, 0.38]
Valverde 2017	143	180	65	92	112	65	5.9%	0.34 [-0.01, 0.68]
Yamaguchi 2016	15.4	26.1	203	39.1	85.1	239	7.5%	-0.36 [-0.55, -0.18]
Zhang 2017	100.3	43.7	30	150.3	68.2	32	4.3%	-0.86 [-1.38,-0.33]
Total (95%CI)			**1393**			**1609**	**100.0%**	**-0.10 [-0.26, 0.05]**

Heterogeneity: Tau^2 = 0.07; Chi^2 = 65.98, df = 17 (P < 0.00001); I^2 = 74%
Test for overall effect: Z = 1.27 (P = 0.20)

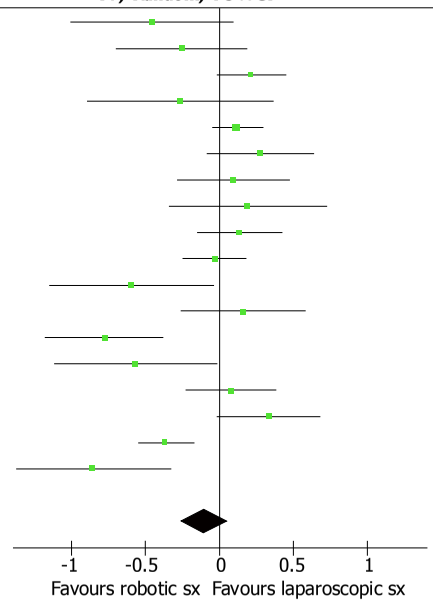

Figure 4 Forest plot for blood loss following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

patients with histologically proven and MDT recommended resectable rectal cancer; (2) Intervention (Exposure): RTME; (3) Control: Patients with rectal cancer undergoing TME or rectal resection by laparoscopic approach; (4) Outcomes: Length of stay, operation time, blood loss, post-operative complications, mortality, positive circumferential resection margins, length of distal resection margins, lymph node harvesting, surgical site infections, time till first flatus, conversion rate, tumour recurrence and re-operation rate; (5) Study design: No restrictions were placed in study design. However, published studies should have reported comparison between two arms, those are RTME *vs* LTME. No studies were excluded based on the year of publication, publication centre, age or gender of the participants or publication language.

Electronic resources for studies selection

Four databases: PubMed, Ovid EMBASE, SCOPUS, and Cochrane Library were searched to find target studies. Four trial registries: ClinicalTrials.gov, European Clinical Trials Register, ISRCTN Register, and the International Clinical Trials Registry were examined. The literature exploration was performed until March 2018.

Search terms

For PubMed, the search was run by means of using MeSH words and by utilizing advanced search choice. The MeSH words "rectal cancer", AND ("laparoscopic resection OR minimal invasive surgery resection OR robotic surgery resection OR total meso-rectal excision") were used. Furthermore, an advanced study exploration was done using

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Allemann 2016	0	0	0	0	0	0		Not estimable
Baek 2011	6.5	7.75	41	6.6	4.25	41	3.7%	-0.02 [-0.45, 0.42]
Baek 2012	11.1	7	154	10.8	8.6	150	5.6%	0.04 [-0.19, 0.26]
Barnajian 2014	6	6.75	20	7	7.75	20	2.5%	-0.13 [-0.76, 0.49]
Bianchi 2010	6.5	2.75	25	6	4	25	2.8%	0.14 [-0.41, 0.70]
Cho 2015	10.4	5.5	278	10.7	6.6	278	6.1%	-0.05 [-0.22, 0.12]
Colombo 2016	12	5.25	60	11	13.5	60	4.3%	0.10 [-0.26, 0.46]
D'Annibale 2013	8	1	50	10	1.5	50	3.6%	-1.56 [-2.01, -1.11]
Feroci 2016	6	20.6	53	8	20.6	58	4.2%	-0.10 [-0.47, 0.28]
Foo 2015	8	7.4	164	8.5	9.4	137	5.6%	-0.06 [-0.29, 0.17]
Gorgun 2016	6.4	4.2	29	8.4	4.4	27	3.0%	-0.46 [-0.99, 0.07]
Ielpo 2017	12.2	7.92	86	12.7	8.5	112	5.1%	-0.06 [-0.34, 0.22]
Jayne 2017	8	5.85	236	8.2	6.03	230	6.0%	-0.03 [-0.22, 0.15]
Kang 2013	10.8	5.5	165	13.5	9.2	165	5.7%	-0.36 [-0.57, -0.14]
Karim 2016	7	3.4	26	11.3	13.7	27	2.9%	-0.42 [-0.97, 0.12]
Kim JC 2016	6.6	2.9	533	6.2	1.8	486	6.5%	0.16 [0.04, 0.29]
Kim YS 2016	10.9	6.2	33	13.1	12.8	66	3.8%	-0.20 [-0.62, 0.22]
Park 2011	10.4	4.7	52	9.8	3.8	123	4.6%	0.15 [-0.18, 0.47]
Ramji 2016	7	3.4	26	11.3	13.7	27	2.9%	-0.42 [-0.97, 0.12]
Serin 2015	5	1.5	14	6	6.75	65	2.7%	-0.16 [-0.74, 0.42]
Silva-Velazco 2017	5	12.8	66	6	12.6	118	4.9%	-0.08 [-0.38, 0.22]
Valverde 2017	11	8	65	12	10	65	4.5%	-0.11 [-0.45, 0.23]
Yamaguchi 2016	7.3	2.3	203	9.3	6.7	239	5.9%	-0.39 [-0.58, -0.20]
Zhang 2017	13.6	1.3	30	13.8	1.8	32	3.2%	-0.13 [-0.62, 0.37]
Total (95%CI)			**2409**			**2601**	**100.0%**	**-0.15 [-0.27, -0.03]**

Heterogeneity: Tau^2 = 0.06; Chi^2 = 83.23, df = 22 (P < 0.00001); I^2 = 74%
Test for overall effect: Z = 2.46 (P = 0.01)

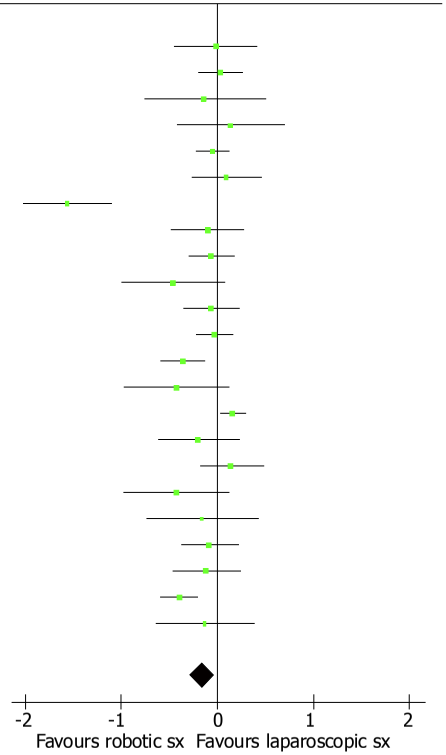

Figure 5 Forest plot for duration of hospital stay following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

the terms "rectal resection". Ovid, EMBASE and SCOPUS were searched with the same search terms as the PubMed advanced search. The Cochrane Library was searched using the term "rectal cancer". Trial registries were all examined using the word "rectal cancer".

Study selection

Two authors evaluated and studied initially titles and then abstracts, adding any curtained references into the Excel spreadsheet. The duplicate articles were excluded. Based upon the information given in the published abstracts, the initial decision of study inclusion or exclusion was made. The published article of the potentially includable studies was then evaluated. The conflicts about data, its accuracy and variability among extracting authors was sorted by agreement or by intercession of an experienced supervising consultant surgeon with had vast clinical and publication experience.

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Baek 2012	0	0	0	0	0	0		Not estimable
Barnajian 2014	0	0	0	0	0	0		Not estimable
Bianchi 2010	0	0	0	0	0	0		Not estimable
Cho 2015	0	0	0	0	0	0		Not estimable
Colombo 2016	3.2	1.9	29	4.3	2.3	27	32.8%	-0.52 [-1.05, 0.02]
Kang 2013	0	0	0	0	0	0		Not estimable
Karim 2016	0	0	0	0	0	0		Not estimable
Kim JC 2016	0	0	0	0	0	0		Not estimable
Kim YS 2016	0	0	0	0	0	0		Not estimable
Park 2011	0	0	0	0	0	0		Not estimable
Ramji 2016	2.6	1.5	26	2.9	1.5	27	32.0%	-0.20 [-0.74, 0.34]
Serin 2015	0	0	0	0	0	0		Not estimable
Zhang 2017	2.1	0.56	30	2.5	0.56	32	35.2%	-0.71 [-1.22, -0.19]
Total (95%CI)			**85**			**86**	**100.0%**	**-0.48 [-0.79, -0.18]**

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.81, df = 2 (P = 0.40); I^2 = 0%
Test for overall effect: Z = 3.09 (P = 0.002)

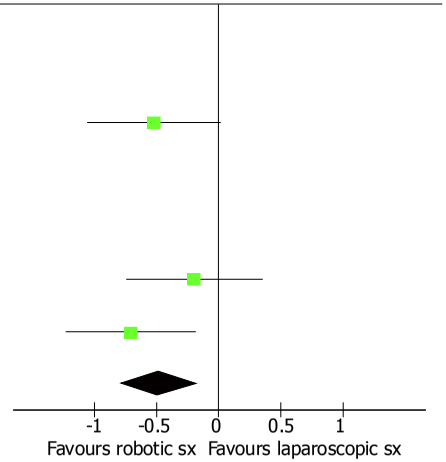

Figure 6 Forest plot for time to first flatus following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

Data collection process

Data was independently collected by two reviewers into the electronic data collection forms of the Microsoft Excel spread sheet. The data items were agreed by the authors prior to commencing study selection. The data pertaining to the analysable outcomes was extracted in addition to the study citation, ethics committee approval, study registration and study quality indicators for all types of comparative studies. Once each author had completed data extraction, the data files were electronically compared and discrepancies in data entry were investigated and resolved.

Statistical analysis

The comparative efficacy of robotic surgery and conventional laparoscopic surgery for rectal resection was directly matched and pooled for each outcome of interest if there were at least two studies for each comparison. The odds ratio (OR) was estimated and pooled across studies using a random-effect model. Heterogeneity was assessed using Cochrane Q test and I^2 statistic. The statistical analysis of the data was conducted according to the guidelines provided by the Cochrane Collaboration including the use of RevMan 5.3® statistical software, and the use of forest plots for the graphical display of the combined outcomes[22-28].

RESULTS

Characteristics of selected studies

A total of 294 studies were identified from Scopus and MEDLINE and other standard medical electronic databases. Among them, 1 RCT and 27 non-randomized comparative (both retrospective and prospective case control) studies[29-56] published until March 2018, were eligible for inclusion. The inclusion and exclusion pathway is

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	8	20	14	40	2.7%	1.24 [0.41, 3.74]
Baek 2011	9	41	11	41	3.1%	0.77 [0.28, 2.11]
Baek 2012	50	154	41	150	7.7%	1.28 [0.78, 2.09]
Barnajian 2014	8	20	2	20	1.3%	6.00 [1.08, 33.27]
Bianchi 2010	4	25	6	25	1.8%	0.60 [0.15, 2.47]
Cho 2015	72	278	66	278	9.4%	1.12 [0.76, 1.65]
Colombo 2016	17	60	12	60	4.1%	1.58 [0.68, 3.68]
D'Annibale 2013	10	50	18	50	3.7%	0.44 [0.18, 1.10]
Foo 2015	23	164	24	137	6.1%	0.77 [0.41, 1.43]
Gorgun 2016	24	29	26	27	0.8%	0.18 [0.02, 1.70]
Ielpo 2017	20	86	25	112	5.6%	1.05 [0.54, 2.06]
Jayne 2017	78	236	73	230	9.4%	1.06 [0.72, 1.57]
Kang 2013	34	165	46	165	7.5%	0.67 [0.40, 1.12]
Karim 2016	0	26	1	27	0.4%	0.33 [0.01, 8.56]
Kim JC 2016	65	533	63	486	9.7%	0.93 [0.64, 1.35]
Kim YS 2016	15	33	26	66	4.1%	1.28 [0.55, 2.98]
Kwak 2011	19	60	16	59	4.5%	1.25 [0.56, 2.75]
Park 2011	10	52	15	123	3.9%	1.71 [0.71, 4.12]
Serin 2015	2	14	16	65	1.4%	0.51 [0.10, 2.53]
Silva-Velazco 2017	26	66	52	118	6.2%	0.82 [0.45, 1.52]
Yamaguchi 2016	18	203	54	239	6.7%	0.33 [0.19, 0.59]
Total (95%CI)		**2315**		**2518**	**100.0%**	**0.92 [0.75, 1.12]**
Total evevts	512		607			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 32.93$, df = 20 ($P = 0.03$); $I^2 = 39\%$

Test for overall effect: Z = 0.83 ($P = 0.40$)

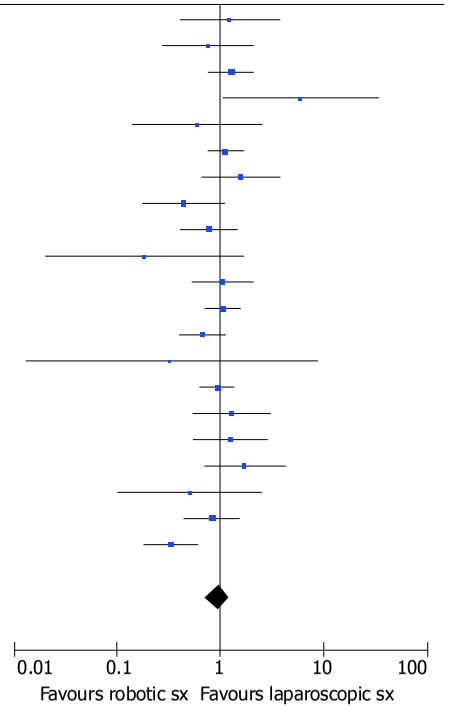

Figure 7 Forest plot for post-operative complications following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

described in PRISMA flow chart Figure 1.

Operative outcomes

All studies evaluated and reported the outcome of duration of operation. The duration of operation was longer (SMD, 0.20; 95%CI: -0.11, 0.52; z = 1.28; $P = 0.20$; Figure 2) in robotic surgery group, but with the clinical advantage of the reduced rate of conversion (OR, 0.40; 95%CI: 0.29, 0.55; z = 5.51; $P = 0.00001$; Figure 3) to open surgery. The reduced risk of conversion to laparotomy following RTME seems to be significantly advantageous in terms of the intensity of surgical trauma posed by laparotomy. There was similar risk of blood loss (SMD, 0.09; 95%CI: -0.14, 0.33; z = 0.76; $P = 0.45$; Figure 4) following both approaches of TME. Clinical and methodological heterogeneity [$Tau^2 = 0.31$, $\chi^2 = 367.50$, df = 26, ($P < 0.00001$); $I^2 = 93\%$] was noted in trials which was the basis for the random effects model analysis leading to the above outcomes.

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	0	20	0	40		Not estimable
Baek 2011	0	41	0	41		Not estimable
Barnajian 2014	0	20	0	20		Not estimable
Bianchi 2010	0	25	0	25		Not estimable
Cho 2015	0	278	1	278	7.6%	0.33 [0.01, 8.19]
Colombo 2016	4	60	6	60	44.8%	0.64 [0.17, 2.40]
D'Annibale 2013	0	50	0	50		Not estimable
Feroci 2016	0	53	0	58		Not estimable
Foo 2015	2	164	2	137	20.0%	0.83 [0.12, 5.99]
Ielpo 2017	0	86	0	112		Not estimable
Jayne 2017	2	236	2	239	20.1%	1.01 [0.14, 7.25]
Kang 2013	0	165	0	165		Not estimable
Karim 2016	0	26	0	27		Not estimable
Kim JC 2016	0	533	0	486		Not estimable
Kim YS 2016	0	33	0	66		Not estimable
Kwak 2011	0	60	0	59		Not estimable
Park 2011	0	52	0	123		Not estimable
Ramji 2016	0	26	0	27		Not estimable
Valverde 2017	0	65	1	65	7.5%	0.33 [0.01, 8.21]
Yamaguchi 2016	0	203	0	239		Not estimable
Zhang 2017	0	30	0	32		Not estimable
Total (95%CI)		**2226**		**2349**	**100.0%**	**0.67 [0.28, 1.62]**
Total evevts	8		12			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.59, df = 4 (P = 0.96); I^2 = 0%
Test for overall effect: Z = 0.89 (P = 0.38)

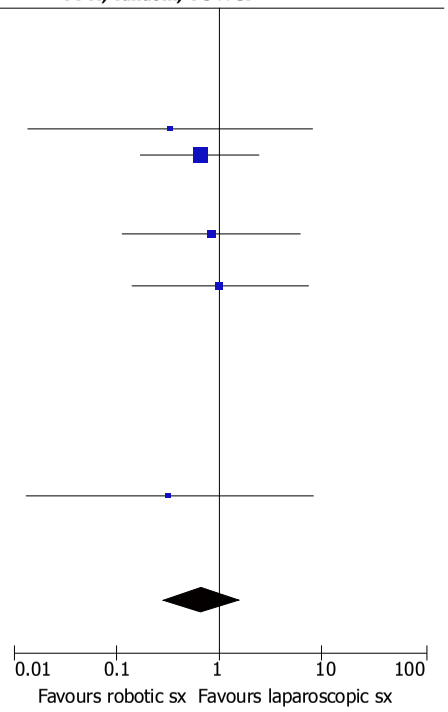

Figure 8 Forest plot for post-operative mortality following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

Post-operative outcomes

The in-hospital stay (SMD, -0.15; 95%CI: -0.27, -0.03; z = 2.46; P = 0.01; Figure 5) and time to first flatus (SMD, -0.48; 95%CI: -0.79, -0.18; z = 3.09; P = 0.002; Figure 6) in patients undergoing RTME were shorter compared to LTME group. However, the post-operative morbidity (OR, 0.92; 95%CI: 0.75, 01.12; z = 0.83; P = 0.40; Figure 7), post-operative mortality (OR, 0.67; 95%CI: 0.28, 1.62; z = 0.89; P = 0.38; Figure 8) and re-operation rate (OR, 0.76; 95%CI: 0.50, 1.16; z = 1.29; P = 0.20; Figure 9) were statistically similar in both groups.

Oncological outcomes

Oncological safety is one of the most important surgical outcomes for any new surgical intervention because positive circumferential resection margins are directly associated with overall survival and disease free survival in rectal cancer patients. The risk of positive circumferential resection margins (OR, 0.91; 95%CI: 0.68, 1.22; z = 0.62; P = 0.53; Figure 10), length of distal resection margins (SMD, 0.00; 95%CI: -0.11, 0.11; z = 0.04; P = 0.97; Figure 11), and lymph node yield (SMD, 0.04; 95%CI:

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	3	20	5	40	7.4%	1.24 [0.26, 5.79]
Bianchi 2010	0	25	2	25	1.9%	0.18 [0.01, 4.04]
Feroci 2016	3	54	8	58	9.2%	0.37 [0.09, 1.47]
Gorgun 2016	2	29	2	27	4.3%	0.93 [0.12, 7.08]
Kang 2013	15	165	25	165	38.2%	0.56 [0.28, 1.11]
Karim 2016	0	26	1	27	1.7%	0.33 [0.01, 8.56]
Kim YS 2016	1	33	2	66	3.0%	1.00 [0.09, 11.45]
Ramji 2016	0	26	1	27	1.7%	0.33 [0.01, 8.56]
Silva-Velazco 2017	4	66	11	118	12.6%	0.63 [0.19, 2.06]
Valverde 2017	15	65	8	65	20.1%	2.14 [0.84, 5.46]
Total (95%CI)		**509**		**618**	**100.0%**	**0.76 [0.50, 1.16]**
Total evevts	43		65			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.37, df = 9 (P = 0.50); I^2 = 0%

Test for overall effect: Z = 1.29 (P = 0.20)

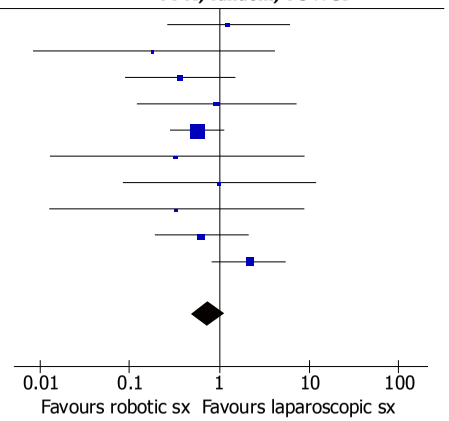

Figure 9 Forest plot for re-operation rate following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

-0.07, 0.14; z = 0.69; P = 0.49; Figure 12) were statistically similar in both groups. Therefore, the risk of local and distant recurrence (OR, 1.10; 95%CI: 0.87, 1.39; z = 0.79; P = 0.43; Figure 13) was also found to be similar in both groups.

DISCUSSION

Colorectal cancer is the third most common cancer diagnosis internationally. The highest incidence of colorectal cancer is reported the Europe, North America and Australia[1]. The highest incidence of colorectal cancer is in the anatomical area of rectum. In 2015 in the United Kingdom out of 41599 people diagnosed with colorectal cancer, 27% of these were located in the rectum. The incidence is slightly higher in men making up 32% of all colorectal cancer diagnoses compared to 23% for women[2]. With the introduction of the total meso-rectal excision (TME), developed in 1989 by Professor Heald, survival rates and the rates of local recurrence have significantly improved[3,4]. A TME is defined as an en bloc resection of the rectal tumour with endo-pelvic fascia to excise circumferential margins[5]. The decision to undertake a TME is influenced by several factors including distance of the cancer from the anal verge, degree of invasion into the pelvic walls, presence of metastases to regional lymph nodes, the patient's co-morbidities and the ability to withstand trans-abdominal surgery[6]. LTME has risen to become the gold standard for rectal cancer suitable for surgical resection[7]. Many trials including the COLOR Ⅱ trial established that it gave similar oncological outcomes compared to an open approach[8,9] and further studies showed it resulted in shorter length of stay, less pain and quicker resumption of normal diet[10,11]. The main reason behind these proven advantages of the laparoscopic TME is the reduced surgical trauma and tissue handling compared to open TME. As the use of robotics in surgery becomes more commonplace in gynaecological and urological procedures, the question arises on whether it has a place in colorectal surgery. Specifically, a TME demands precise dissection in an area that is difficult to visualise and access. These difficult aspects of a TME could be improved upon by robotics which offers a direct angle entry view, a stable retraction platform and more movement of instrument freedom[12,13]. Some studies have shown that robotic TME (RTME) results in shorter length of stay, whilst other studies have shown that there is no difference

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	2	20	2	40	2.1%	2.11 [0.27, 16.21]
Baek 2011	1	41	2	41	1.5%	0.49 [0.04, 5.60]
Bianchi 2010	0	25	1	25	0.8%	0.32 [0.01, 8.25]
Cho 2015	14	278	13	278	14.4%	1.08 [0.50, 2.34]
Colombo 2016	8	60	12	60	9.1%	0.62 [0.23, 1.63]
D'Annibale 2013	0	50	6	50	1.0%	0.07 [0.00, 1.24]
de Jesus 2016	9	59	4	39	5.5%	1.57 [0.45, 5.52]
Feroci 2016	0	53	1	58	0.8%	0.36 [0.01, 8.99]
Foo 2015	8	164	11	137	9.8%	0.59 [0.23, 1.50]
Gorgun 2016	2	29	2	27	2.1%	0.93 [0.12, 7.08]
Ielpo 2017	3	86	4	112	3.7%	0.98 [0.21, 4.48]
Jayne 2017	12	236	14	230	13.7%	0.83 [0.37, 1.83]
Kang 2013	7	165	11	165	9.1%	0.62 [0.23, 1.64]
Karim 2016	0	26	0	27		Not estimable
Kim JC 2016	8	533	5	486	6.8%	1.47 [0.48, 4.51]
Kim YS 2016	5	33	4	66	4.5%	2.77 [0.69, 11.10]
Kwak 2011	1	60	0	59	0.8%	3.00 [0.12, 75.14]
Park 2011	1	52	3	123	1.7%	0.78 [0.08, 7.72]
Ramji 2016	0	26	0	27		Not estimable
Serin 2015	1	14	3	65	1.6%	1.59 [0.15, 16.52]
Silva-Velazco 2017	5	66	4	118	4.7%	2.34 [0.60, 9.02]
Valverde 2017	4	65	7	65	5.3%	0.54 [0.15, 1.95]
Yamaguchi 2016	0	203	2	239	0.9%	0.23 [0.01, 4.89]
Total (95%CI)		**2344**		**2537**	**100.0%**	**0.91 [0.68, 1.22]**
Total evevts	91		111			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.00$, df = 20 ($P = 0.78$); $I^2 = 0\%$

Test for overall effect: Z = 0.62 ($P = 0.53$)

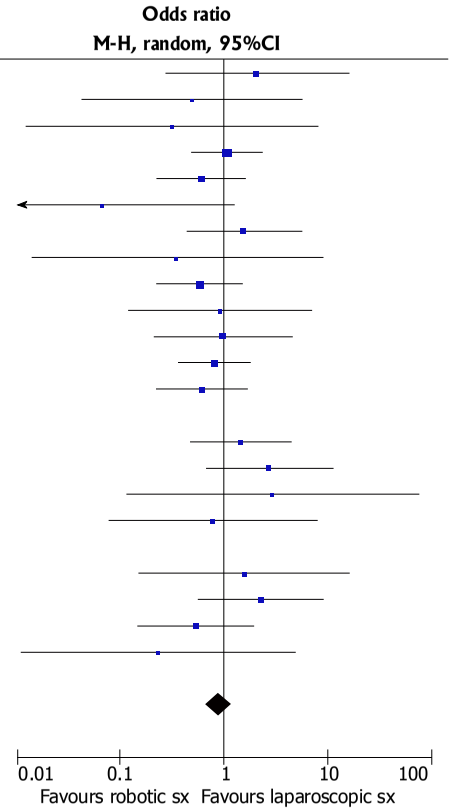

Figure 10 Forest plot for positive circumferential resection margins following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

in hospital stay, oncological outcomes or rates of converting procedures to open. There is an argument that in terms of cost, the use of robotics is more expensive than laparoscopic instruments and the learning curve for surgeons is longer and requires more cases than for a LTME.

Based upon the findings of this largest ever series on the role of robotic surgery in rectal cancer resection, the RTME is certainly a feasible technique and oncologically safe surgical intervention but failed to demonstrate any superiority over LTME for many surgical outcomes. Mere advantage of robotic surgery was noted in only three post-operative outcomes, that is early passage of flatus, lower risk of conversion and shorter hospitalization. It seems like these advantages may not truly reflect into the routine use of RTME in rectal cancer surgery and therefore, the examination of current 28 studies to date did not designate a major value of RTME over LTME. Demonstration of this conclusion has already been reported in previously published meta-analyses[14-21,57].

These findings needs further evaluation on the background of recently published ROLARR[42] trial. Among operative outcomes, current study indicates similar blood loss and longer duration of operation and these both outcomes are concordant with the findings of ROLARR[42] trial. The risk of conversion to open surgery was found to be lower in RTME arm of current study. Similarly the risk of conversion was lower in RTME group (8.1%) compared to LTME group (12.2%) in the ROLARR[42] trial but statistically it

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Baek 2011	36	24	41	38	26.5	41	4.1%	-0.08 [-0.51, 0.35]
Barnajian 2014	20.5	11.25	20	21.5	13.5	20	2.5%	-0.08 [-0.70, 0.54]
Bianchi 2010	20	7.5	25	20	4.25	25	2.9%	0.00 [-0.55, 0.55]
Cho 2015	20	14	278	22	14	278	9.0%	-0.14 [-0.31, 0.02]
Colombo 2016	15	17.75	60	11	20	60	5.2%	0.21 [-0.15, 0.57]
D'Annibale 2013	30	11	50	30	16	50	4.7%	0.00 [-0.39, 0.39]
Feroci 2016	25	15.6	53	15	15.6	58	4.8%	0.64 [0.25, 1.02]
Foo 2015	31.3	15.9	164	33.4	15.2	137	7.7%	-0.13 [-0.36, 0.09]
Gorgun 2016	39	21	29	32	20	27	3.2%	0.34 [-0.19, 0.86]
Kang 2013	19	14	165	20	17	165	7.9%	-0.06 [-0.28, 0.15]
Karim 2016	29.6	20.5	26	35.4	19	27	3.0%	-0.29 [-0.83, 0.25]
Kim JC 2016	26.8	15.5	533	26.8	15.5	486	10.0%	0.00 [-0.12, 0.12]
Kim YS 2016	22	15	33	22	17	66	4.3%	0.00 [-0.42, 0.42]
Kwak 2011	22	3.75	60	20	5.6	59	5.1%	0.42 [0.05, 0.78]
Lim 2017	17	14	74	22	15	64	5.5%	-0.34 [-0.68, -0.01]
Park 2011	28	19	52	32	21	123	5.7%	-0.19 [-0.52, 0.13]
Ramji 2016	29.6	20.5	26	35.4	19	27	3.0%	-0.29 [-0.83, 0.25]
Serin 2015	27.5	13.75	14	15	15	65	2.7%	0.84 [0.24, 1.43]
Yamaguchi 2016	2.8	1.9	203	3.2	2.2	239	8.6%	-0.19 [-0.38, -0.01]
Total (95%CI)			**1906**			**2017**	**100.0%**	**-0.00 [-0.11, 0.11]**

Heterogeneity: Tau^2 = 0.03; Chi^2 = 41.25, df = 18 (P = 0.001); I^2 = 56%
Test for overall effect: Z = 0.04 (P = 0.97)

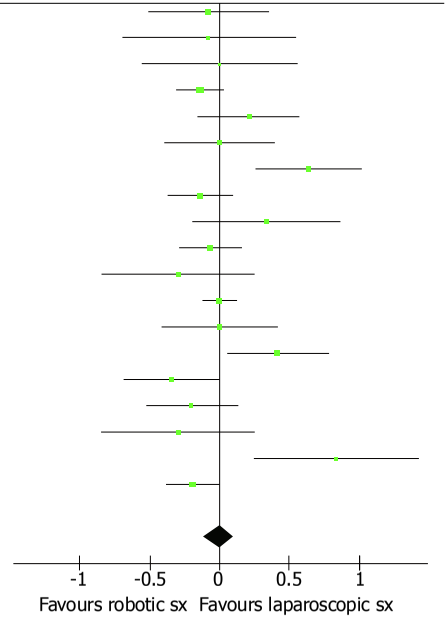

Figure 11 Forest plot for length of distal resection margin following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

failed to demonstrate any significance. The length of hospital stay was similar between both groups in the ROLARR[42] trial but current study shows significant reduction in the hospitalization time in patients undergoing RTME. Post-operative mortality, morbidity and re-operation rate were consistently similar in all included studies, current study and in the ROLARR[42] trial. The oncological outcomes such as positive circumferential resection margins, length of distal resection margins, lymph node yield and recurrence rate were also not different. The publication of the ROLARR[42] trials has answered several questions about the feasibility, safety and comparative equivalence of RTME and non-inferiority of LTME too. In addition, RTME seems to be relatively expensive[29,42,58,59] and less cost-effective procedure and therefore routine use of this approach may not be justified for TME.

Authors frankly accept the major limitations of this study and the most apparent is the combined analysis of an RCT[42] and 27 case control studies. Despite this limitation, the outcomes are almost matching with the conclusions of the only RCT[42] published on this subject. Other confounding factors which can potentially be influencing the final outcome are diverse inclusion and exclusion criteria among included studies; variable post-operative follow up duration; lack of an agreed follow up screening pathways; presence and absence of the use of neoadjuvant chemoradiotherapy in the recruited population; use of variable diagnostic pathways in included studies and variable experience of the operating surgeons especially in the RTME group. More RCTs are needed to consolidate the findings of ROLARR trial[42] and current study. Better outcomes and reduced cost may be anticipated in future trials due to the use of cost effective advanced technology and operating surgeons with extensive experience in robotic surgery. Until then the ROLARR trial and current study may provide the best possible evidence in this relatively innovative intervention for rectal cancer

Study or subgroup	Robitic surgery Mean	SD	Total	Laparosocpic surgery Mean	SD	Total	Weight	Std. Mean difference IV, Random, 95%CI
Allemann 2016	24	14	20	20	7	40	2.5%	0.40 [-0.14, 0.94]
Baek 2011	13.1	7.5	41	16.2	8.5	41	3.2%	-0.38 [-0.82, 0.05]
Barnajian 2014	14	4.75	20	11	3.5	20	2.0%	0.70 [0.06, 1.35]
Bianchi 2010	18	6.75	25	17	7.25	25	2.4%	0.14 [-0.41, 0.70]
Cho 2015	15	8.1	278	16.2	8.1	278	6.1%	-0.15 [-0.31, 0.02]
Colombo 2016	15	16.25	60	19	15.5	60	3.9%	-0.25 [-0.61, 0.11]
D'Annibale 2013	16.5	7.1	50	13.8	6.7	50	3.6%	0.39 [-0.01, 0.78]
de Jesus 2016	10	9.9	59	13	9.9	39	3.5%	-0.30 [-0.71, 0.11]
Feroci 2016	18	10.9	53	11	10.9	58	3.7%	0.64 [0.26, 1.02]
Gorgun 2016	25.5	14	29	21.8	9	27	2.6%	0.31 [-0.22, 0.84]
Ielpo 2017	9.2	4.5	86	9.7	6.8	112	4.8%	-0.08 [-0.37, 0.20]
Jayne 2017	23.2	11.97	236	24.1	12.9	230	5.9%	-0.07 [-0.25, 0.11]
Kang 2013	15	9.4	165	15.6	9.1	165	5.5%	-0.06 [-0.28, 0.15]
Karim 2016	16.7	6.8	26	16.8	7.7	27	2.5%	-0.01 [-0.55, 0.52]
Kim JC 2016	23.2	10	533	20.9	8.5	486	6.5%	0.25 [0.12, 0.37]
Kim YS 2016	22.3	11.7	33	21.6	11	66	3.4%	0.06 [-0.36, 0.48]
Kwak 2011	20	3.75	60	21	3.5	59	3.9%	-0.27 [-0.63, 0.09]
Lim 2017	11.6	6.9	74	14.7	6.5	64	4.1%	-0.46 [-0.80, -0.12]
Park 2011	19.4	10.2	52	15.9	10.1	123	4.3%	0.34 [0.02, 0.67]
Popescu 2010	11.37	3.4	38	11.07	3.4	84	3.7%	0.09 [-0.30, 0.47]
Ramji 2016	16.7	6.8	26	16.8	7.7	27	2.5%	-0.01 [-0.55, 0.52]
Serin 2015	32	9.75	14	23	15.75	65	2.3%	0.60 [0.01, 1.18]
Silva-Velazco 2017	22	14	66	24	14	118	4.5%	-0.14 [-0.44, 0.16]
Valverde 2017	17	9	65	19	10	65	4.1%	-0.21 [-0.55, 0.14]
Yamaguchi 2016	30	10.3	203	19.3	11.8	239	5.8%	0.06 [-0.12, 0.25]
Zhang 2017	15.2	0.56	30	13.9	4.9	32	2.8%	0.36 [-0.14, 0.86]
Total (95%CI)			**2342**			**2600**	**100.0%**	**0.04 [-0.07, 0.14]**

Heterogeneity: Tau^2 = 0.04; Chi^2 = 70.15, df = 25 (P < 0.00001); I^2 = 64%
Test for overall effect: Z = 0.69 (P = 0.49)

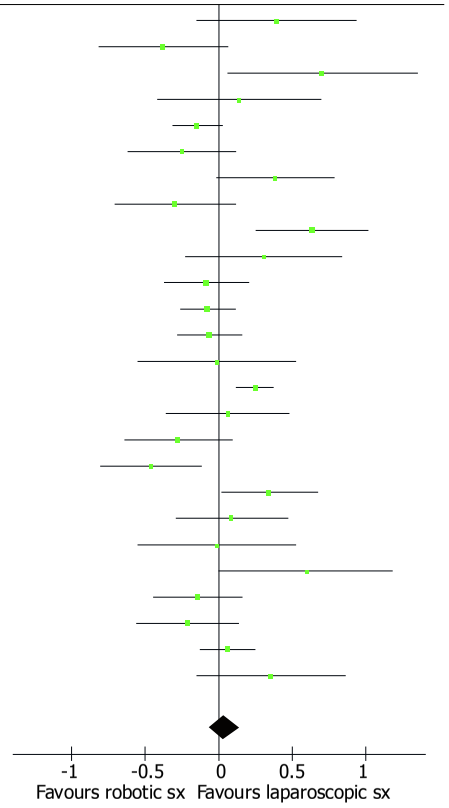

Figure 12 Forest plot for lymph node yield following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Standardized mean difference is shown with 95%CIs.

management.

ARTICLE HIGHLIGHTS

Research background

Robotic total meso-rectal excision (TME) is used at least for a decade to treat rectal cancer and the only evidence in favour of robotic TME was based on case control studies. Recently first ever RCT evaluating feasibility of robotic TME was published as ROLARR trial. This aims of this study was to strengthen the existing evidence on this technique which is mainly based upon the meta-analysis of case control studies and compare it with the results of ROLARR trial.

Study or subgroup	Robitic surgery Everts	Total	Laparosocpic surgery Events	Total	Weight	Odds ratio M-H, random, 95%CI
Allemann 2016	5	20	13	40	3.8%	0.69 [0.21, 2.32]
Cho 2015	49	278	53	278	29.7%	0.91 [0.59, 1.40]
Feroci 2016	1	53	3	58	1.0%	0.35 [0.04, 3.50]
Kim JC 2016	95	533	66	486	47.1%	1.38 [0.98, 1.94]
Kwak 2011	0	60	2	59	0.6%	0.19 [0.01, 4.04]
Lim 2017	16	74	14	64	8.3%	0.99 [0.44, 2.22]
Popescu 2010	2	38	5	84	1.9%	0.88 [0.16, 4.74]
Silva-Velazco 2017	10	66	16	118	7.5%	1.14 [0.48, 2.68]
Total (95%CI)		**1122**		**1187**	**100.0%**	**1.10 [0.87, 2.68]**
Total evevts	178		172			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.38, df = 7 (P = 0.61); I^2 = 0%

Test for overall effect: Z = 0.79 (P = 0.43)

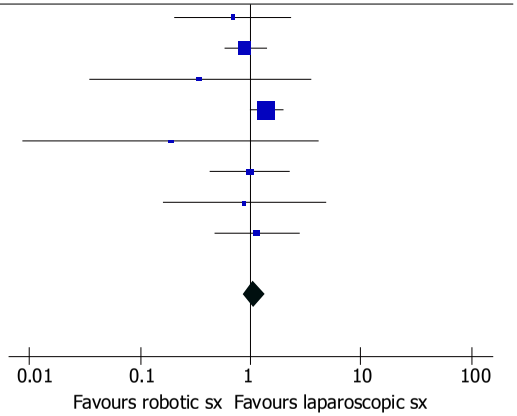

Figure 13 Forest plot for tumour recurrence following rectal resection by robotic surgery *vs* conventional laparoscopic surgery. Odds ratio is shown with 95%CIs.

Research motivation

Although robotic TME is being presented a way forward for rectal resection but its superiority over laparoscopic TME is not proven yet. Most of the evidence was based upon the systematic review of case-controlled studies, the publication of ROLARR trial is an attempt to answer this question. Comparison between the findings of ROLARR trial and systematic review of case-controlled trials can guide the surgeons in future about role of robotic TME.

Research objectives

The objective of this systematic review is to strengthen the existing evidence on the role of robotics for TME technique which is mainly based upon the meta-analysis of case control studies and compare it with the results of recently published ROLARR trial reporting robotic TME *vs* laparoscopic TME.

Research methods

Standard medical databases were searched. RCTs and all types of comparative studies reporting the effectiveness of robotic TME *vs* laparoscopic TME in the management of rectal cancer were retrieved and their data was extracted. The extracted data was analyzed using the principles of meta-analysis to generate higher level of evidence. RevMan 5.3 was used for statistical analysis and GradePro was used to generate summary of evidence.

Research results

One RCT (ROLARR trial) and 27 other comparative studies reporting the non-oncological and oncological outcomes following robotic TME *vs* laparoscopic TME were included in this review. In the random effects model analysis using the statistical software Review Manager 5.3, the RTME was associated with longer operation time (SMD, 0.46; 95%CI: 0.25, 0.67; z = 4.33; P = 0.0001), early passage of first flatus (P = 0.002), lower risk of conversion (P = 0.00001) and shorter hospitalization (P = 0.01). The statistical equivalence was seen between robotic TME and laparoscopic TME for non-oncological variables like blood loss, morbidity, mortality and re-operation risk. The oncological variables such as recurrence (P = 0.96), number of harvested nodes (P = 0.49) and positive circumferential resection margin risk (P = 0.53) were also comparable in both groups. The length of distal resection margins was similar in both groups.

Research conclusions

Robotic TME is feasible and oncologically safe but failed to demonstrate any superiority over laparoscopic TME for many surgical outcomes except early passage of flatus, lower risk of conversion, lower conversion to laparotomy rate and shorter hospitalization.

Research perspectives

Robotic TME failed to demonstrate superiority over laparoscopic TME. Laparoscopic TME may continuously be used to treat rectal cancer. More RCTs are needed to consolidate the findings of ROLARR trial [42] and current study. Better outcomes and reduced cost may be anticipated in future trials due to the use of cost effective advanced technology and operating surgeons with extensive experience in robotic surgery. Until then the ROLARR trial and current study may provide the best possible evidence in this relatively innovative intervention for rectal cancer management.

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P- Reviewer: Freha NA, Mastoraki A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Tan WW

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