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Localization of mesenteric lymph node metastases in relation to the level of arterial ligation in rectal cancer surgery

Catarina Tiselius [a, c, *], Csaba Kindler [b], Andreas Rosenblad [c, d], Kenneth Smedh [a, c]

[a] Department of Surgery, Västmanland Hospital Västerås, Västerås, Sweden
[b] Department of Pathology, Västmanland Hospital Västerås, Västerås, Sweden
[c] Centre for Clinical Research Västerås, Uppsala University, Västmanland Hospital Västerås, Sweden
[d] Department of Statistics, Stockholm University, Sweden

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Introduction: For oncological reasons, central arterial ligation of the inferior mesenteric artery (IMA) is suggested in rectal cancer surgery although no conclusive evidence support this. We have therefore investigated the localization of lymph node metastases and compared central ligation of the IMA versus peripheral arterial ligation, in rectal cancer specimens.
Methods: This was a cross-sectional population-based study of consecutive recruited patients who underwent resection for rectal cancer in 2012–2015. Multiple linear regression analysis was used to explore the relationship between lymph node count and age, sex, body mass index, preoperative oncological treatment, type of surgery, tumour stage, and vessel and specimen length.
Results: 151 patients (54 women) were included, with median (range) age 70 (45–87) years. The median (range) number of lymph nodes retrieved was 25 (3–70), which was associated with body mass index, type of surgery and vessel length. Vessel length, median (range) 9.6 (5–14) and 9.2 (5–15) cm for reported central and peripheral arterial ligation, respectively, was associated with body mass index. In 39 of 42 samples, metastatic lymph nodes were located in the mesorectum, and 13 of 42 samples also had metastatic lymph nodes in the sigmoid mesentery. None were found around the ligated artery.
Conclusion: To recruit all metastatic lymph nodes in rectal cancer surgery, it is important to include the sigmoid mesentery in the specimen, but not to perform a central ligation of the IMA compared with ligation of the SRA close to the left colic artery (LCA).

Introduction

Lymph node (LN) status is one of the main prognostic factors in non-metastatic colorectal cancer and is used to identify the need for adjuvant therapy. The number of LNs retrieved is considered crucial; thus, the surgical technique is also of major importance [1–3]. Based on data from studies of colon cancer [4], the current guidelines recommend that at least 12 LNs should be examined in colorectal cancer.

LN yield has been shown to correlate with several factors such as age, tumour location, surgical technique and neoadjuvant treatment [5]. Studies of rectal cancer have shown that chemoradiotherapy reduces the LN yield [6,7] and that the length of the resected specimen is associated with number of LNs harvested [8]. Stracci et al. [5] reported that, for specimen length less than 20 cm, there is a high risk of obtaining an inadequate LN yield.

The preferred surgical technique for operations for sigmoid or rectal cancer varies between institutions. Some prefer central/high ligation of the inferior mesenteric artery (IMA), whereas others prefer peripheral/low arterial ligation of the superior rectal artery (SRA) below the origin of the left colic artery (LCA) [9]. A better oncologic result in terms of retrieval of more LNs has been suggested for central ligation of the IMA. According to the Japanese Society for Colorectal Cancer, 5.1% of metastatic LNs are located around the IMA [10]. However, recurrence and survival data has been inconclusive [11–13].

To create a tension-free anastomosis, central ligation of the inferior mesenteric vessels is preferred [14]. The risks of an

* Corresponding author. Department of Surgery, Västmanland Hospital Västerås, S-721 89, Västerås, Sweden.
E-mail address: catarina.tiselius@regionvastmanland.se (C. Tiselius).

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anastomotic leak, impaired defecatory function or postoperative complications do not seem to differ between central versus peripheral ligation [15,16]. By contrast, peripheral ligation might decrease the risk of injury of the hypogastric plexus [17,18].

Compared with colon cancer, less is known about the distribution of LNs in rectal cancer [19–21]. The primary aim of the present study was to investigate the anatomical location of mesenteric LN metastases in specimens from patients operated on for rectal cancer. A secondary aim was to elucidate the consequences of ligating centrally at the IMA or peripherally at the SRA in terms of harvesting metastatic LNs in patients operated on for rectal cancer.

Methods

Patients

In this cross-sectional study, all patients undergoing primary surgery for rectal cancer between 1 January 2012 and 31 December 2015 at Västmanland Hospital Västerås, Sweden, were consecutively enrolled. Västmanland Hospital Västerås, is a single institution serving 270 000 people in a well-defined geographical area with only one hospital treating rectal cancer. The cohort comprised the 228 patients who were registered with a rectal cancer diagnosis during this period. Rectal cancer was defined as a tumour with the distal margin located up to 15 cm from the anal verge. The patients represented a consecutive and unselected cohort. Sixty-one patients were excluded; of these, 14 patients received palliative chemoradiotherapy, 29 received a permanent stoma, seven had an endoscopically removed polyp cancer and 22 did not receive any treatment because of severe comorbidity. Fifteen patients had a complete pathological response after neoadjuvant treatment and were analysed separately. Specimens from 151 patients who were curatively operated on for rectal cancer were included (Fig. 1).

Information about patient background data such as age, sex, American Society of Anaesthesiology (ASA) physical status classification, body mass index (BMI), tumour distance from the anal verge, preoperative tumour stage, preoperative oncological treatment and type of surgery were collected from medical records and from the Swedish Colorectal Cancer Registry [22]. All patients were examined using a computed tomography (CT) scan of the chest and abdomen, magnetic resonance imaging (MRI) of the rectum and a colonoscopy or CT of the colon.

Neoadjuvant treatment and surgery

According to the preoperative staging of the tumour, patients with a less advanced tumour; rT1–rT3bN0, received no neoadjuvant treatment. Patients with a more advanced tumour (rT3 c/d N1/N2) received short-course radiation therapy (25 Gy) either with an immediate operation or delayed surgery after 6–8 weeks. Patients with an advanced tumour with growth or node metastases close to or outside the mesorectal fascia received neoadjuvant long-course radiotherapy (50 Gy) with concurrent chemotherapy if their comorbidity was not too high.

The tumour location was classified according to the distance from the anal verge. The surgical technique was standardized, and all the total mesorectal excision operations were performed by a few experienced surgeons. All operations were performed with an open technique. Most of the low tumours (less than 6 cm) underwent abdominoperineal excision (APE). Middle (6–10 cm) or higher (11–15 cm) tumours underwent anterior resection (AR) or Hartmann's procedure (HP).

The level of ligation of the IMA was either 1–2 cm from the aorta in central ligation or at the SRA close to the origin of the LCA in peripheral ligation. The choice of level of ligation was determined by the length of the colonic mesentery to get sufficient reach to construct a tension free anastomosis or an adequate colostomy.

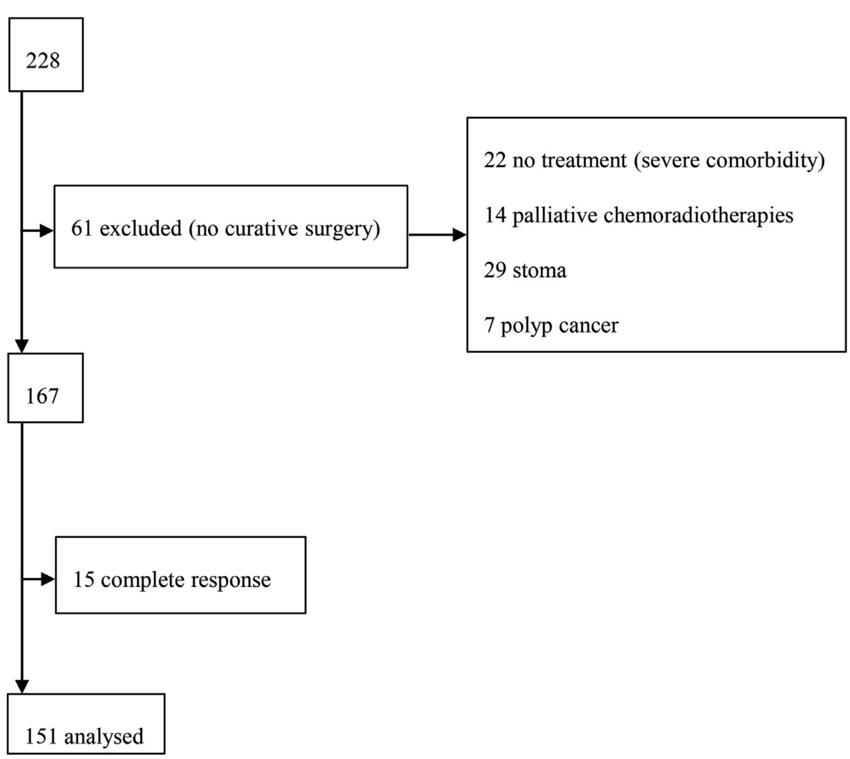

Fig. 1. CONSORT flow diagram of the number of patients diagnosed with rectal cancer 2012–2015 in Västmanland County, Sweden.

Analysis of pathology

Resected specimens were pinned to a board and fixed in 4 per cent buffered formalin for 12–48 h. Two experienced, similar trained, gastrointestinal pathologists examined all gross and microscopic pathological findings. They were unaware of the surgeons' reported location of the arterial ligation of the vessel. The specimens were divided into three sections according to a specific protocol (Fig. 2). The mesorectal fat (Fig. 2A), mesenteric fat from the sigmoid colon (Fig. 2B) and the fat within 3 cm of the IMA or proximal SRA (Fig. 2C) were analysed separately for LN retrieval, as shown in Fig. 2. The length of the artery was measured from the ligation to the bowel wall.

The LNs were dissected through manual palpation. Fat-clearing technique was used to retrieve them. All LNs were stained with hematoxylin and eosin and were examined for the presence of tumour metastases under light microscopy. Each specimen was cut in parallel sections about 5 mm thick. Each dissected LN was cut in 2–3 sections for analysis.

Tumours were assessed for histological type, pT stage, pN stage, tumour differentiation, lymphatic vessel invasion, venous invasion and perineural invasion. The histological diagnoses were based on the World Health Organization's TNM Classification of Malignant Tumours (7th edition) criteria [23].

Ethics

The study was approved by the Regional Ethics Committee of Uppsala University (Dnr 2013/099). The study is registered with ClinicalTrials.gov: NCT03314961.

Statistical analyses

Categorical data are presented as frequencies and percentages, n (%), when appropriate, while continuous data are presented as mean and standard deviation (SD), supplemented with median (range). Tests of differences between categorical variables were performed using Pearson's χ^2 test or Fisher's exact test. Multiple linear regression analysis was used to examine associations between patient age, sex, BMI, neoadjuvant treatment or type of resection, vessel length and specimen length (independent variables) on the one hand and the number of LNs (dependent variable) on the other hand. For all analyses, a *P*-value <0·05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24 (IBM, Amonk, NY, USA).

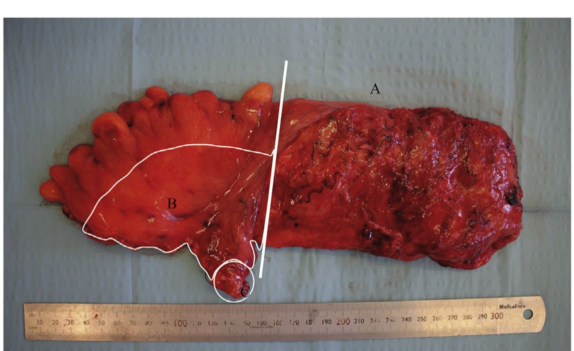

Fig. 2. Rectal specimen divided in three sections: (A) the mesorectum, (B) the sigmoid mesentery and (C) the area around the inferior mesenteric arterial ligation.

Results

The detailed demographic and clinical parameters for the patients operated on for rectal cancer in 2012–2015 are listed in Table 1. One hundred and six patients (70%) received neoadjuvant treatment. Seventy-eight (67%) received short-course and 27 (23%) received long-course radiotherapy along with chemotherapy. Of the 71 patients that received short-course radiotherapy (25 Gy), 22 had an operation immediately after (D), and 49 had an operation after 6–8 weeks (W). Thirty-four patients (22%) did not receive any pre-treatment and 11 (7%) had previously received radiotherapy. Eighty-five (56%) patients underwent a sphincter-preserving operation (AR), 49 (33%) underwent APE and 17 (11%) underwent HP. The median (range) specimen length was 30 (16–57) cm. The median (range) proximal and distal bowel resection lengths in relation to the tumour were 23 (7–49) cm and 4.5 (0.5–12) cm, respectively. The median tumour size (measured as tumour length) was 3.0 (1–10) cm and was not related to tumour stage.

Table 1
Demographic and clinical characteristics of the curative operated rectal cancer patients (n = 151).

Variable	Value
Age (years), mean (SD)	70 (9.8)
Gender, n (%)	
Male	96 (63.6)
Female	55 (36.4)
BMI (kg/m^2), mean (SD)	26·4 (4.7)
American Society of Anaesthesiology stage, n (%)	
1	13 (8.6)
2	84 (56)
3	53 (35)
4	1 (0·7)
Distance from the anal verge (cm), n (%)	
0–5	51 (33.8)
6–10	51 (33.8)
11–15	49 (32.5)
mean (SD)	7.9 (4.2)
Preoperative stage by MRI, n (%)	
1	25 (16.6)
2	51 (33.8)
3	63 (41.7)
4	10 (6.6)
X	2 (1.3)
Preoperative treatment, n (%)	
0	34 (22.5)
Radiotherapy (25 Gy)	22D + 49W = 71
Radiotherapy (50 Gy)	1
Chemoradiotherapy (25 Gy)	7
Chemoradiotherapy (50 Gy)	27
Previous radiotherapy	11
Pathological T stage, n (%)	
1	15 (10.0)
2	51 (33.8)
3	63 (41.7)
4	21 (13.9)
X	1(0.7)
Pathological N stage, n (%)	
0	96 (63.6)
1	45 (29.8)
2	10 (6.6)
X	1 (0.7)
Pathological M stage, n (%)	
0	141 (93.4)
1	9 (6.0)
P stage, n (%)	
1	13 (8.6)
2	79(52.3)
3	49 (32.5)
4	9 (6.0)
R1	1 (0.7)

D = operation immediately after radiotherapy, W = operation 6–8 weeks after radiotherapy.

The median (range) number of recruited LNs was 25 (3–70). The median (range) distribution of LNs was 13 (1–48) in the mesorectum (Figs. 2A), 12 (1–37) in the sigmoid mesentery (Figs. 2B) and 1 (0–10) around the central or peripheral arterial ligation (Fig. 2A). Rectal cancer specimens from 42 (28%) patients had metastatic LNs. In 39 (93%) of the specimens, metastatic LNs were located in the mesorectum. Thirteen of the 42 (31%) specimens also had metastatic LNs in the sigmoid mesentery. In three (7%) of the specimens, metastatic LNs were found only in the sigmoid mesentery. These patients had received neoadjuvant radiotherapy. None of the patients had metastatic growth in LNs close to the arterial ligation, regardless of ligation of the IMA or the SRA.

The cumulative percentages of metastatic LNs in relation to the total number of retrieved LNs are shown in Fig. 3. The diagram shows an almost linear relationship.

Twenty (13.2%) specimens had tumour deposits, 11 of which were without positive LNs. Lymph vessel, venous and nerve invasion was detected in 58 (38.4%), 56 (37.1%) and 23 (15.2%) specimens, respectively.

Table 2 shows that there were no significant differences in arterial vessel length or mean LN number between patients who received ligation of the IMA and those who received ligation of the SRA. Of the patients operated on with AR, APE and HP, 87% (74/85), 49% (24/49) and 65% (11/17) were operated on with central ligation of the IMA.

Multiple regression analysis (Table 3) showed that the total number of LNs was positively associated with vessel length and BMI, and negatively associated with an operation of type APE. Age, sex, neoadjuvant treatment and specimen length was not significantly related to the number of total recruited LNs. However, specimen length was positively associated with higher BMI and if the patient was operated on by APE. Vessel length was positively associated with higher BMI but not with the type of surgery.

In the 15 patients who exhibited a complete pathological tumour response (yT0), one patient had metastases in two of five LNs in the mesorectum (Fig. 2C) and in one of eight LNs in the mesosigmoid mesentery (Fig. 2B).

Discussion

This study shows that most of the metastatic LNs were located in the mesorectum and about one-third in the sigmoid mesentery. None of these LNs were located around the arterial ligation irrespective of whether central ligation of the IMA or ligation of the SRA was performed. Neither retrieval of metastatic LNs nor vessel length was associated with the type of arterial ligation, due to the proximity of the two types of ligatures to the LCA. Moreover, vessel length was associated with patient habitus rather than the site of arterial ligation. An almost linear relationship was found between the cumulative percentage of metastatic LNs in relation to the total number of retrieved LNs.

There is a golden standard that at least 12 LNs should be analysed in specimens of colorectal cancer [3,4,24]. In our study, the mean number was 28, and these LNs were equally distributed between the resected colon and rectum. Most of the metastatic LNs were located in the mesorectum. Importantly, one-third of the LN metastases were located in the sigmoid mesentery and, theoretically, these could have been missed by arterial ligation distally at SRA or at the sigmoid vessels. In three patients, the only positive LNs in the specimen were located in the sigmoid mesentery. These patients were radiologically staged as rT3–4N1. They received neoadjuvant radiotherapy, which may theoretically explain the node-negative response in the mesorectum since radiotherapy decreases the LN number [25–27]. Univariate analysis of our data showed that the total number of LNs was negatively associated with the neoadjuvant radiotherapy received (data not shown).

An interesting finding was that there was an almost linear relationship between the cumulative percentage of metastatic LNs and the total number of retrieved LNs. Cserni et al. [28] have shown that at least 90 per cent of the tumours that demonstrate metastases to regional LNs could be identified by examining 18 nodes. However, our findings are inconsistent with these earlier findings.

In our study, the mean proximal and distal specimen lengths to the tumour were 23 and 4.6 cm, respectively. According to Cserni et al. [28] only the bowel segment 3 cm proximal and distal from the tumour needs to be obtained in colorectal cancer surgery to retrieve 92 per cent of the LN metastases in the specimen. This has

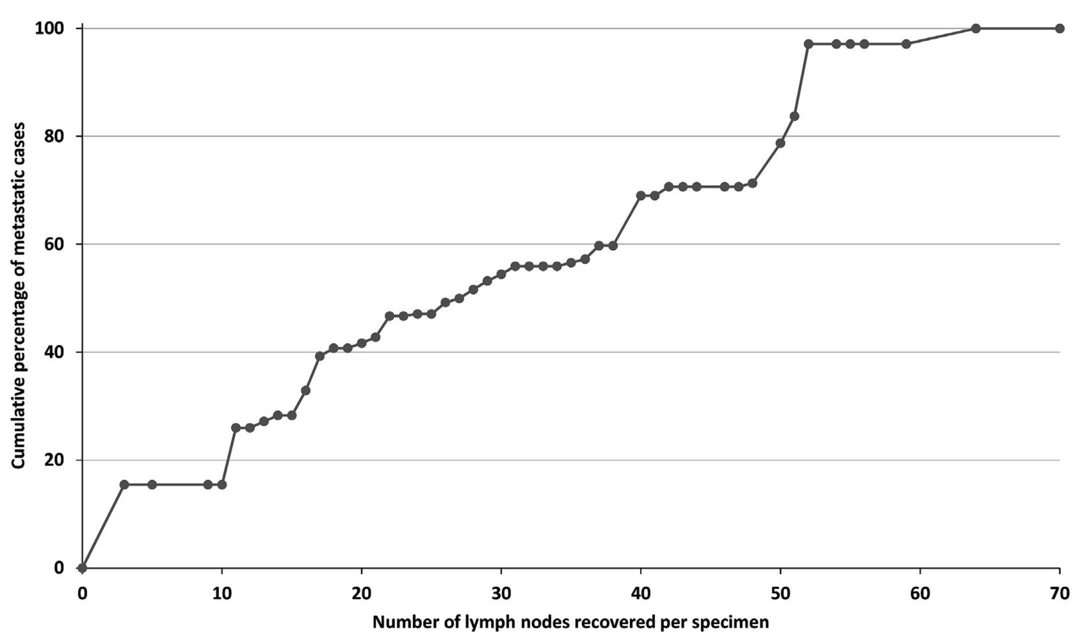

Fig. 3. Cumulative percentage of metastatic lymph node rectal cancer specimens in relation to total number of retrieved lymph nodes.

Table 2
Specimen and vessel lengths and number of lymph nodes in central ligation of the IMA and peripheral arterial ligation of the SRA in rectal cancer specimens.

Variable	Total	Central ligation	Peripheral ligation	*P*-value
Specimen length (cm)				
Mean (SD)	30.7 (6.6)			
Median (range)	30 (16–57)			
Level of ligation, n (%)	151 (100)	109 (72.2)	42 (27.8)	
Vessel length (cm)				
Mean (SD)	9.5 (2.2)	9.6 (2.2)	9.2 (2.1)	0.544
Median (range)	9 (5–15)			
n	144	105	39	
Number of lymph nodes				
Mean (SD)	28.0 (12.7)	28·9 (12.7)	25.6 (13.2)	0.153
Median (range)	25 (15–70)			

Table 3
Multiple linear regression analyses of the relationships between age, sex, BMI, neoadjuvant treatment and type of surgery on the one hand and vessel length, specimen length, and total number of lymph nodes on the other hand.

	Vessel length		Specimen length		Total number of lymph nodes	
Variable	β (95 per cent CI)	*P*-value	β (95 per cent CI)	*P*-value	β (95 per cent CI)	*P*-value
Age	−0·02 (0.06–0.02)	0.35	0.02 (−0.08 to 0.13)	0·67	0.09 (−0.14 to 0.31)	0.45
Gender	0·54 (−0·21 to 1.28)	0.16	0.86 (−1.15 to 2.88)	0·40	0.89 (−3.34 to 5.12)	0.68
BMI	0·10 (0.02–0.17)	0.018	0.46 (0.25–0.66)	<0·001	0.65 (0.18–1.12)	0·.07
Radiotherapy					−1.10 (−5.69 to 3.49)	0.64
Chemotherapy					−2.10 (−7.48 to 2.28)	0.29
Operation type						
AR	Reference		Reference		Reference	
HR	−0.21 (−1.49 to 1.07)	0.74	−0.21 (3.29–3.71)	0·90	−1·94 (−8.23 to 6.15)	0.78
APE	0.06 (0.75–0.87)	0.89	4.17 (2.00–6.34)	<0·001	−6·18 (−11.0 to −1.33)	0.001
Specimen length			N/A		0·26 (−0.088 to 0.62)	0.14
Vessel length	N/A				0.97 (0.01–1.93)	0.049

also been shown by others [29]. A recent study of rectal cancer specimens reported the distribution of LN metastases [21] as 53 per cent of the LN metastasis located above, 36 per cent located adjacent to and only 11 per cent located below the tumour. In that study, only eight of 90 LN metastases were located more than 5 cm above the tumour. The longest distance of a retrieved LN metastasis was 35 mm distal to the rectal tumour.

In our study, the vessel length did not differ significantly between procedures using the central ligation of the IMA and peripheral ligation of the SRA, presumably because of the use of a standardized surgical technique with peripheral ligation performed close to the origin of the SRA. The vessel length was more closely related to patient factors such as height and body weight than to the type of arterial ligation. It could be argued that the ligature should be called peripheral at the location where the first sigmoid artery departs. If the SRA is ligated just proximal or distal to the origin of the sigmoid arteries, the ligature really could be called peripheral, in comparison with the present definition.

Prevot et al. [30] reported a significant correlation between the level assessed by the surgeon and the real level of ligation demonstrated by postoperative CT scans after sigmoidectomy for cancer in only 41 per cent of patients. The level was overestimated in 70 per cent of patients. These discrepancies indicate the need for careful interpretation of the risks of complications and survival based on the reported location of the anatomical arterial ligation.

Few studies have reported on the number and status of LNs retrieved around the area of ligation of the IMA. The definition of the area of tissue that should be included varies [9]. Langman et al. [21] investigated the size and distribution of LNs in rectal cancer specimens. In their study, the vascular pedicle was defined as a broad part of tissue around SRA, which was separated from the mesorectum containing 28% of the LNs in the specimen. Their study showed that 32% of the LNs were located in the sigmoid mesentery but LN metastases were discovered in only 0.3% of the patients. In our study, one-third of the LN metastases were also found in the sigmoid mesentery, probably because of the different pathological division of the mesentery.

In Japan, the surgical technique includes more extended LN dissection around the IMA with division of the vessel distal to the resected area close to the aorta. This procedure is not generally performed in Europe or in the USA.

In Europe, the choice between central and peripheral arterial vessel ligation has received much attention in the management of colorectal cancer surgery [18]. Only one randomized clinical trial on colon cancer has been published that focuses on this issue [31]. That study showed no differences in survival or early morbidity for resection of left-sided colon cancer. For rectal cancer, no convincing data have been reported on a survival benefit using central or peripheral arterial ligation [9,12,32,33].

The strength of this study is that it was a cross-sectional and population based with consecutive patients, and that surgery was standardized with TME, with selection of the site of ligature dependent of the anatomy. A few experienced surgeons were involved, and two similarly trained experienced gastrointestinal pathologists examined the specimens. Compared with other studies, more LNs were harvested by the pathologist, and the specimen length was sufficient, as mentioned earlier. The weaknesses of the study are that it was a single-centre study and the follow-up time is too short to analyse survival, although that was not the scope of the study. The number of LNs might have been larger around the ligation of the IMA with a more thorough resection of mesocolic fat around the aorta. By ligating the vessel centrally without extensive dissection close to the aorta, theoretically positive LNs may have been missed in our study. However, this procedure has considerable risks of harming the hypogastric nerves and causing a worse functional outcome.

Conclusion

This study showed that most LN metastases were located adjacent to the tumour in the mesorectum, but in one-third of patients, metastatic LNs were located in the sigmoid mesentery. Our findings suggest that, if the proximal bowel length is adequate for an anastomosis, peripheral ligation of the SRA close to the origin of the LCA seems oncologically safe in terms of retrieval of metastatic LNs. It might also have a functional advantage by reducing the risk of nerve damage. However, a very peripheral ligation of the SRA could cause metastatic LNs to be missed. Randomized controlled studies are needed to fully answer the question of which surgical approach is optimal for survival and functional outcome.

Conflict of interest

None.

Disclosures

None.

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