TITLE: Oncological and clinical outcomes after conventional right hemicolectomy

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ABSTRACT

Purpose: Complete mesocolic excision (CME) has been proposed for better local control of colon cancer and to improve cancer-specific survival (CSS). However, CME may be associated with increased morbidity from bleeding during central vascular ligation. This study aimed to investigate the outcome of conventional right hemicolectomy, a traditional anatomical dissection along anatomical planes with radical excision of the central lymph nodes at the level of the origin of colic artery but without exposure of superior mesenteric vein and artery (SMV/SMA).

Method: This was a retrospective review of a cohort of all elective right hemicolectomies performed at a specialist tertiary unit during a five-year period (2011-2015).

Results: Five-hundred and nineteen patients (271 female, a median age of 73.0 years (interquartile range (IQR) 65.0-80.0)) were included (Stage I disease: 2.7%, stage II: 53.2%, stage III: 33.3%, stage IV: 10.8%). At the latest follow-up (a median 47 months (IQR 29-67)), local recurrence occurred in 34 patients (6.6%). Three-year overall survival was 74.4% and 3-year CSS was 85.9%. Subgroup analysis for stage I-III showed local recurrence in 6.0%, sole distant recurrence in 7.6% while 19 patients (4.1%) suffered concomitant local and distant recurrence. The anastomotic leak rate was 1.0% and perioperative bleeding occurred in 1.2%.

Conclusions: Oncological outcomes comparable to those of CME can be achieved by conventional surgery but with low rates of bleeding complications and anastomotic leakage. The proposed advantages of CME should be carefully considered and balanced against patients' co-morbidities and potential complications.

Keywords

conventional, right hemicolectomy, colon cancer, complication, complete mesocolic excision

Declarations

Funding: None

Conflicts of interest: Yasuko Maeda has received research grant from Medtronic, speaker honorarium from Astellas and consultant fee from Creo Medical.

Ethics approval: The study was approved by the responsible local audit committee and conducted according to applicable law as well as good clinical practice and the Declaration of Helsinki.

Consent to participate/Consent for publication: As per approval by the local audit committee, specific consent for participation/publication was not required due to use of anonymised data.

Availability of data and material The datasets generated analysed during the current study are subject to protection of patient confidentiality, thus not publicly available as per regulations set by the local audit committee.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Michaela Ramser, Allan Kwok and Yasuko Maeda. The first draft of the manuscript was written by all authors. All authors read and approved the final manuscript.

INTRODUCTION

Colorectal cancer is a leading cause of cancer-related death[1, 2]. Surgical excision and systematic lymphadenectomy following oncologic principles is the treatment of choice for resectable disease. The number of resected and examined lymph nodes (LNs) in the surgical specimen is essential for correct staging and has been shown to be an independent prognostic factor for improved survival[3, 4], with the removal and analysis of at least 12 LNs being recommended by national and international guidelines[5, 6].

Complete mesocolic excision (CME), sometimes referred to as right hemicolectomy with D3 lymphadenectomy, was first proposed by Hohenberger *et al.* in 2009 [7]. The rationale for CME originates from rectal cancer surgery, where an improvement in survival and recurrence was observed after the introduction of total mesorectal excision (TME) [8]. The main principles of CME include separating the mesocolic plane from the parietal plane and performing a central vascular ligation [9]. This technique has been proposed to confer lower rates of locoregional recurrence (LRR) and increased cancer-specific survival (CSS) [10, 11]. However, CME may be associated with increased morbidity from major vascular injury and higher re-operation rates [10, 12, 13]. There is ongoing conjecture on the optimal anatomical level of vascular ligation, the role of apical LN involvement and their impact on prognosis and survival [14, 15].

We aimed to review rates of LRR and perioperative complications in our current practice following conventional right hemicolectomy, a traditional anatomical dissection along anatomical planes with radical excision of the central lymph nodes at the level of the origin of colic artery but no exposure of superior mesenteric vein and artery (SMV/SMA) [16].

MATERIALS AND METHODS

Patient population

A prospectively-maintained database on all elective right hemicolectomies performed for colon cancer between January 2011 and December 2015 were reviewed retrospectively. Data collection was completed by March 2019 to ensure a minimum of 3-year follow-up.

Collected data included demographic information (age, sex), operative details (open vs. laparoscopic approach, American Society of Anesthesiologists (ASA) status), histopathological results (TNM stage, number of harvested LNs, number of positive nodes), administration of adjuvant chemotherapy and post-operative complications (including Clavien-Dindo grading [17]. Neuroendocrine tumours and appendiceal cancers were excluded.

Surgical technique

The surgical approaches were either laparoscopic or open. Right colon was mobilised either medial-to-lateral or lateral to medial. The embryonic plane was developed by dissecting beneath the ileocolic vessels. The ileocolic vascular pedicle was then ligated as high as possible, meaning that the plane above

the duodenum was prepared and the ileocolic vessels ligated near the origin from the SMA/SMV but without a specific exposure of the latter. Division of middle colic artery was determined by the position of cancer (Figure 1).

Definition of locoregional recurrence (LRR)

Locoregional recurrence was defined as recurrent cancer either in the colonic wall at or around the anastomosis, or in the territory of lymphatic drainage of the previously resected tumour, which has been confirmed clinically, radiologically or by pathological examination [3-5]. Disease recurrence in the peritoneum or other organs were considered distant metastases.

Statistical analysis

Continuous non-parametric data were reported using the median and interquartile range (IQR). Categorical values were analysed using the chi-squared and Fisher's exact tests accordingly. All '*p*-values' reported are two-sided, with $p<0.050$ being considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics Version 26 (Chicago, IL, USA).

This study did not require approval by the local ethics committee but an approval as an audit project was obtained.

RESULTS

In total, 519 patients (52.2% female, median age 73.0 years (IQR 65.0-80.0) underwent elective right hemicolectomy for cancer during the 5-year study period. Forty-six patients (8.9%) were ASA I, 281 were ASA II (54.1%), 158 (30.4%) were ASA III and 8 patients (1.5%) were ASA IV.

Two hundred and thirty-six colectomies (45.5%) were performed open, 261 (50.3%) were performed laparoscopically and 22 (4.2%) were converted from laparoscopic to open. The majority of patients (99.2%) underwent primary anastomosis and only 4 patients underwent creation of a stoma. Details of baseline patient characteristics and operative data are summarised in Table 1.

Histopathology

Using the 8th edition of AJCC Cancer Staging Manual [18], 2.7% of patients had stage I disease, 53.2% were stage II, 33.3% were stage III and 10.8% were stage IV.

The median number of total LNs examined in each patient was 18 (IQR 14-23). In 90.9% of patients ≥12 nodes were harvested and analysed in the operative specimen. Forty-three percent (223/519) of patients were found to have nodal disease. Of those with involved nodes, the median number of involved LN was 3 (IQR 1-5). Apical LN were identified in 502 patients with 92.3% found to be clear of disease. Of those with positive apical nodes (40/519), the median number of involved apical LNs was 1 (range 1-2) and in only one patient was the apical LN the only site of nodal disease. There was no significant difference in the proportion of patients from whom ≥12 LN were harvested between surgical approaches (90.3% in

the open group, 92.0% in the laparoscopic group, χ^2=0.650, p=0.420). In 38.9% (212/519) of patients there was evidence of tumour vascular invasion and in 16.6% (86/519) lymphatic invasion was reported.

An incomplete resection was reported in 32 patients (6.2%; R1 resection 5.0%, R2 resection 1.2%). Stage IV disease was strongly associated with higher rates of incomplete resection than stage I-III disease (χ^2=14.83, p<0.001, RR 3.76 (1.88 – 7.52)). Pathological features and staging data are summarised in Table 2.

Adjuvant therapy

Adjuvant chemotherapy was considered for patients with stage I and II disease with adverse tumour characteristics namely less than 12 lymph nodes analysed, T4 tumour, lymphovascular or perineural invasion, poorly differentiated histology or tumour perforation (n=1 and n=76, respectively), and all patients with stage III disease (n=173); therefore, 250 patients were potential candidates for adjuvant chemotherapy. The sole patient with stage I disease and extramural lymphatic invasion did not receive chemotherapy and only 30.3% (23/76) of eligible patients with stage II disease underwent adjuvant chemotherapy. The remainder of patients either declined (11.8%) or were deemed unsuitable for adjuvant chemotherapy by their oncologist or following multidisciplinary team discussion (57.9%). Additionally, 54.9% (95/173) of patients with stage III disease received adjuvant chemotherapy. Overall, only 47.2% of all eligible patients received adjuvant chemotherapy.

Follow-up, recurrence, mortality and survival

The median duration of follow-up was 47.0 months (IQR 29.0-67.0).

Thirty-four patients (6.6%) were diagnosed with LRR (without distant metastases) at the latest follow-up (Figure 1). A further 26 (5.0%) patients had distant metastases in addition to LRR. Fifty-four patients (10.4%) had distant metastasis without evidence of LRR. No patients with stage I disease had LRR; LRR without distant metastases was detected in 9/276 (3.3%) of patients with stage II disease and 13/173 (7.5%) of those with stage III disease.

Thirty-day mortality was 2.3%. Median OS was 47 months from the date of surgery (IQR 29-67). Three-year OS was 74.4% (386/519) and 3-year CSS was 85.9% (446/519). Three-year overall recurrence rate was 20.0% (104/519). Of patients who experienced any recurrence, median time from surgery to recurrence was 12.5 months (IQR 7.1-23.0) and median time from recurrence to death was 8.9 months (IQR 3.6-17.6). Data on follow-up, recurrence, mortality and survival are summarised in Figure 2 and Table 3.

Post-operative complications

One or more post-operative complications was experienced in 7.9% of patients. Clavien-Dindo (CD) Grade I complications occurred in 0.4% of patients, CD Grade II in 3.1% and CD Grade III in 2.5% (Grade IIIa 1.3%; Grade IIIb 1.2%). CD Grade IV complications occurred in 0.4% of patients and overall

mortality was 2.3% (CD Grade V). The cumulative incidence of CD Grade I-V complications was therefore 8.7%.

Subgroup analysis of patients with stage I-III colon cancer

Overall, 89.2% (463/519) of patients were diagnosed with a stage I-III colon cancer. Baseline characteristics were similar to the full study population. No significant differences between the full study population and the stage I-III subset were seen with respect to nodal yield, nodal involvement, lymphovascular invasion, tumour size, nearest longitudinal margin, or completeness of resection (Table 2).

Overall LRR for stage I-III colon cancer was 6.0% (28/463). Sole distant recurrence occurred in 7.6% while 4.1% of patients suffered simultaneous locoregional and distant recurrence.

There was no significant difference noted in 3-year LRR (p=0.665) or 3-year recurrence (p=0.082) when patients with stage IV disease were excluded. For patients with stage I-III disease, median time from surgery to recurrence was 13.4 months (IQR 7.1-23.3) and median time from recurrence to death was 9.0 months (IQR 4.1-20.4) and 3-year OS and 3-year CSS (80.8% and 91.8%, p=0.017 and p=0.004 respectively) were improved as stage IV disease were excluded.

DISCUSSION

Meticulous anatomical dissection and lymphadenectomy are the key components of sound oncologic resection. However, the necessity of the extent of resection (in particular the supposed advantage of the central vascular ligation after Kocherisation the duodenum) has been questioned as it might be associated with considerable complications such as catastrophic bleeding or major vessel injury [19].

The involvement of central nodes without disease elsewhere is uncommon [15]. One Japanese study reported metastatic central nodal disease in only 3% of patients after right hemicolectomy with D3 lymphadenectomy [20]. In our group 7.7% (40/519) of patients were found to have metastasis in the apical LN but in only one patient was the apical node the only site of nodal disease in the surgical specimen. The multicentre randomised COLD trial found no patient with D3 LNs as the only site of nodal disease but showed that 30-day morbidity, ICU admission rates and hospital re-admission rates were increased following D3 lymphadenectomy whilst there was no difference in the mean LN yield [21]. It may therefore be prudent to adopt a tailored approach with respect to central vascular ligation whereby it is performed only in selected cases after careful consideration [22, 23]. The question remains whether a more extensive resection yielding a larger mesenteric surface area and a potentially higher number of LN should remain the goal of colonic resection.

The improved survival rates cited in early publications on CME may not be solely attributable to surgical technique but also to the simultaneous introduction and utilisation of adjuvant chemotherapy for node-positive colon cancer [24]. The data was presented as overall and stage 1-3, as stage 4 has metastasis and we did not feel this group will be influenced by the surgical technical difference.

Overall data is shown as summary of the cohort data, then stage 1-3 to show whether this group was impacted by our D2 resection compared to outcome reported in literature. Decisions regarding adjuvant chemotherapy will not usually be influenced solely by apical LN status but other factors such as adverse features of tumour (eg. extramural lymphovascular invasion), patients' frailty and preference as well. In our study, the proportion of patients with any extramural lymphovascular invasion was around 40% (overall 42.4%, stage I-III 38.4%).

Despite this, only 64.8% of all eligible patients and only 54.9% of patients with stage III disease received chemotherapy. Some patients declined adjuvant chemotherapy and were deemed unfit at the point of oncological consultation. Currently there is no clear-cut objective measure of frailty and general fitness of patients for their suitability for adjuvant therapy, particularly after major oncological surgery. Additionally, the decision-making processes regarding adjuvant chemotherapy in our study population were based on individual discussions of the oncologist with the patient and his/her family, the details of which were not immediately available from patient records.

Despite the high rate of patients with lymphovascular invasion compared to a series by Bertelsen *et al.* [11] (17-23%) and similar incomplete resection rate (6%), our overall recurrence of 15.8% in stage I-III disease is not significantly worse compared to 13.5% reported by Sato *et al.* [24] from Japan where CME has been practiced since late 1990s and better compared to 18.0% reported by Bertelsen *et al.* [12]. Whilst surgery following oncological principle is essential, the ultimate outcome is influenced by other non-surgical factors as well and it is important to recognise this limitation and have a tailored approach.

There are a number limitations in this study. Although most of the cardinal data such as demographics, TNM stages, and histology were collected prospectively, other data were sought retrospectively for this study. For example, reasons for not receiving adjuvant therapy were sought by thoroughly reviewing medical records but they were not always explicit. This is one of the limitations of this retrospective study.

The fact that more than half of the eligible patients did not receive adjuvant chemotherapy may reinforce argument for those who advocate "extensive" surgery (i.e. CME), as it may be therapeutic. However the role of lymphadenectomy will be variable, it could be therapeutic if the excised lymph nodes are truly the furthest extent of the disease, yet it may simply be diagnostic if the involvement of apical nodes is part of an already extensive disease. Within the current diagnostic modalities available, it is not always possible to ascertain this preoperatively. The current study adds data to suggest we should be cognizant of the limitations in our knowledge of lymph node metastasis and that we should carefully weigh up risks and benefits individually with regards to the extent of surgery.

At our unit, we have not and currently do not perform CME, hence direct case-matching was not possible. Our results were compared against published CME and standard resection outcome in literature, and this is another limitation of cross-sectional cohort study with a single arm. A definitive evaluation of oncological outcome based on extent of lymphadenectomy will require long-term results of randomised controlled trials such as RELARC [25] or large prospective cohort studies such as T-REX study [16].

These studies are based in the part of world where obesity is less prevalent, which may have contributed to more favourable outcomes such as those reported by Ow *et al*. [26].

While CME is advocated and increasingly practiced, the current study shows a standardized approach to surgical oncology is still of value and can produce short and long-term results that are comparable to CME. Whether all patients will need CME or whether subgroups of patients are better served with a standard oncologic resection remains a subject for critical debate.

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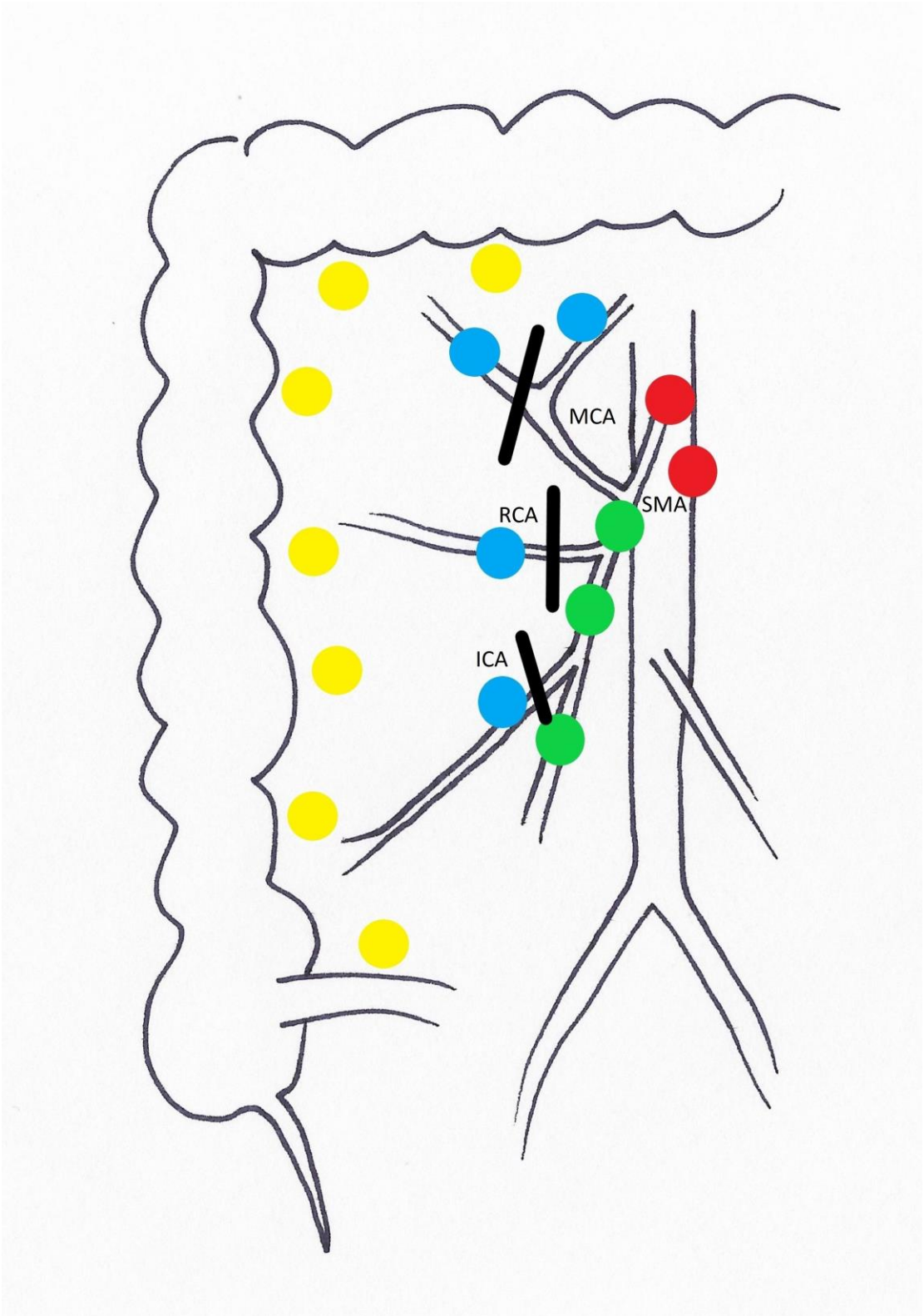
Figure 1. Schematic of standard oncologic resection



The embryonic plane was developed by dissecting beneath the ileocolic artery and vein (ICA/ICV). The ileocolic vascular pedicle was then ligated as high as possible, meaning that the plane above the duodenum was prepared and the ileocolic vessels ligated near the origin from the SMA/SMV but without stripping of lymphoadipose tissue on the surface of the vessels. Division of middle colic artery (MCA) was determined by the position of cancer. For central ligation of the middle colic artery Fredet's plane was not opened nor was Henle's trunk specifically transected. Right colic artery (RCA),

if present, was ligated at the level of mesenteric dissection connecting the plan from the two arteries. Lymph node levels D1 (yellow) and D2 (blue) were included in the specimen. Lymph nodes of D3 level (green) were not stripped from SMA. Paraaortic lymph nodes (red) were not harvested.

Table 1. Baseline patient characteristics and operative data

		Overall **n (%)** **Median (IQR)** ***n*=519**	**Stage I-III** **n (%)** **Median (IQR)** ***n*=463**
Sex	Male	248 (47.8)	213 (46.0)
	Female	271 (52.2)	250 (54.0)
Age (years)		73.0 (65.0-80.0)	73.0 (65.0-80.0)
ASA Grade	I	46 (8.9)	41 (9.4)
	II	281 (54.1)	253 (57.9)
	III	158 (30.4)	137 (31.4)
	IV	8 (1.5)	6 (1.4)
Surgical technique	Laparoscopic	261 (50.3)	244 (52.7)
	Open	236 (45.5)	201 (43.4)
	Converted to open	22 (4.2)	18 (3.9)
Stoma creation	No	515 (99.2)	460 (99.4)
	Yes	4 (0.8)	3 (0.6)
Tumour perforation	No	498 (96.0)	445 (96.1)
	Yes	21 (4.0)	18 (3.9)
Obstructing tumour	No	475 (91.5)	433 (93.5)
	Yes	44 (8.5)	30 (6.5)

Table 2. Pathological features and staging

		Overall n (%) Median (IQR) *n*=519	Stage I-III n (%) Median (IQR) *n*=463
T-stage	T1	18 (3.5)	18 (3.9)
	T2	53 (10.2)	51 (11.0)
	T3	310 (59.7)	290 (62.6)
	T4	138 (26.6)	104 (22.5)
Lymph nodes examined		18 (14-23)	18 (15-23)
≥12 lymph nodes yielded	No	47 (9.1)	40 (8.6)
	Yes	472 (90.9)	423 (91.4)
Nodal involvement	No	296 (57.0)	286 (61.8)
	Yes	223 (43.0)	177 (38.2)
Number of LN involved (if node +ve disease)		3 (IQR 1-5)	2 (IQR 1-5)
Apical LN involved	No	479 (92.3)	436 (94.6)
	Yes	40 (7.7)	25 (5.4)
Staging (AJCC 8th edition)	I	14 (2.7)	14 (3.0)
	II	276 (53.2)	276 (59.6)
	III	173 (33.3)	173 (37.4)
	IV	56 (10.8)	(n/a)
Lymphatic invasion	No	433 (83.4)	392 (84.7)
	Yes	86 (16.6)	71 (15.3)
Vascular invasion	No	317 (61.1)	302 (65.2)
	Yes	202 (38.9)	161 (34.8)
Any lymphovascular invasion	No	299 (57.6)	285 (61.6)
	Yes	220 (42.4)	178 (38.4)
Tumour differentiation	Well	20 (3.9)	17 (3.7)
	Moderate	377 (72.6)	342 (73.9)
	Poor	122 (23.5)	104 (22.5)
Tumour size (mm)		42.0 (32.0-55.0)	40.0 (31.0-55.0)
Nearest longitudinal margin (mm)		50.0 (31.5-75.0)	50.0 (30.0-74.0)
Completeness of resection	R0	487 (93.8)	441 (95.2)
	R1	26 (5.0)	19 (4.1)
	R2	6 (1.2)	3 (0.6)

Table 3. Post-operative complications, recurrence rates and survival

		Overall n (%)	Stage I-III patients n (%)
Post-operative complication	No	478 (92.1)	430 (92.9)
	Yes	41 (7.9)	33 (7.1)
	Abscess	14 (2.7)	10 (2.2)
	PE	6 (1.2)	6 (1.3)
	Bleeding	6 (1.2)	4 (0.9)
	Leak	5 (1.0)	5 (1.1)
	Myocardial infarction	5 (1.0)	4 (0.9)
	Bowel ischaemia	2 (0.4)	2 (0.4)
	Gastric perforation	1 (0.2)	1 (0.2)
Post-operative complications (Clavien-Dindo grading)	I	2 (0.4)	1 (0.2)
	II	16 (3.1)	14 (3.0)
	III	13 (2.5)	9 (2.0)
	IV	2 (0.4)	2 (0.4)
	V	12 (2.3)	11 (2.4)
30-day mortality		12 (2.3)	11 (2.4)
Follow-up (months)		47.0 (29.0-67.0)	49.0 (37.0-69.0)
Recurrence	No	405 (78.0)	381 (82.3)
	Yes	114 (22.0)	82 (17.7)
	Locoregional only	34 (6.6)	28 (6.0)
	Distant only	54 (10.4)	35 (7.6)
	Locoregional + distant	26 (5.0)	19 (4.1)
Sites of distant Recurrence	Liver		38 (8.2)
	Peritoneal		40 (8.6)
	Lung		27 (5.8)
	Retroperitoneum		5 (1.1)
	Brain		2 (0.4)
	Ovary		3 (0.6)
3-year locoregional recurrence		29 (5.6)	23 (5.0)
3-year overall recurrence		104 (20.0)	73 (15.8)
3-year OS (%)		74.4	80.8
3-year CSS (%)		85.9	91.8

Figure 1:
3-year locoregional recurrence (%) by disease stage

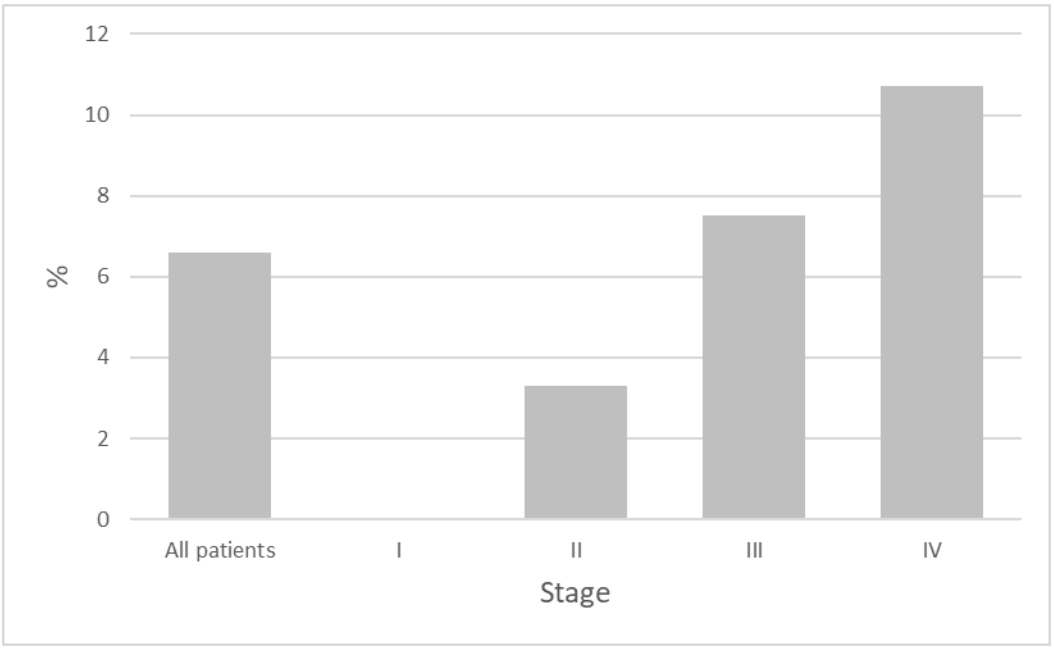


Figure 2:
3-year overall and cancer-specific survival (%) by disease stage

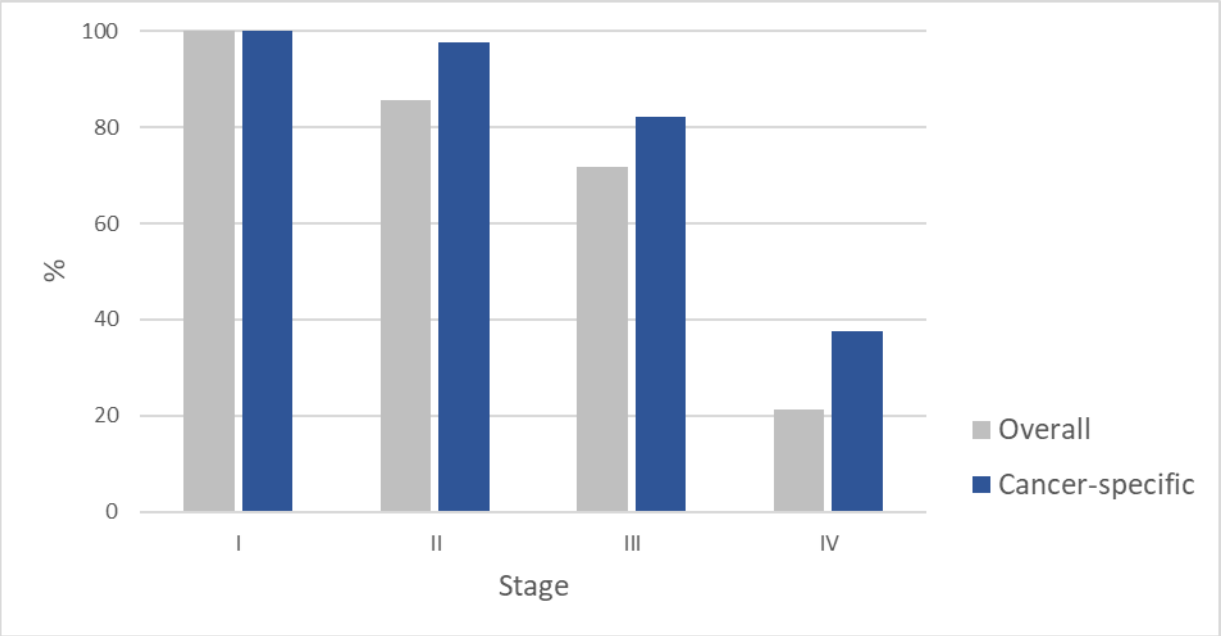


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Figure

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