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Should We Plan CME vs non-CME surgery in colon cancer based on preoperative CT? An observational cohort study

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Rezumat

Acuratețea CT-ului preoperator în stadializarea cancerului de colon și rolul în planificarea CME versus non-CME

Introducere: tratamentul chirurgcial specific în cancerul de colon câştigă popularitate în rândul chirurgilor colorectali. Mulți susțin adaptarea tehnicii chirurgicale pe baza stadializării CT preoperatorie, deoarece nu toți pacienții necesită excizie completă de mezocolon (CME) şi limfadenectomie D3. Aici ne propunem să evaluăm sensibilitatea şi specificitatea scanărilor CT preoperatorii în stadializarea ganglionilor şi să analizăm dacă recidivele locale ar fi putut fi influențate de stadializarea CT inadecvată.
Material şi Metode: acesta este un studiu retrospectiv, de cohortă, la pacienți cu cancer de colon în stadiul I-III urmăriți la spitalul nostru în perioada 2011-2019. Variabilele clinice şi patologice şi datele privind recurența locoregională (LRR) au fost extrase din dosarul electronic al pacientului, inclusiv datele imagistice efectuate ca parte a protocolului standard de urmărire oncologică.
Rezultate: acuratețea globală a scanării CT pentru a identifica starea ganglionară a fost de 56,9%, cu sensibilitatea şi specificitatea de 60,6% şi 52,5%. Suprastadializarea a avut loc la 95 de pacienți (22%) şi substadializarea la 92 (21%). Dintre pacienții substadializați, 8 (8,7%) au dezvoltat LRR nodală.
Concluzie: având în vedere că aproximativ unul din trei pacienți cu LRR ganglionară, au fost subdiagnosticați din punct de vedere al statusului ganglionar, prin evaluarea CT preoperatorie, deciziile terapeutice privind abordul chirurgical nu trebuie să fie ghidate de aceasta şi CME cu ligatură vasculară centrală (CVL) ar trebui să fie aplicată tuturor pacienților ca tehnică chirurgicală standardizată.

Cuvinte cheie: CT, CME, CVL, cancer de colon; limfadenectomie D3

ABSTRACT

Introduction: tumour specific surgery in colon cancer is gaining popularity among colorectal surgeons. Many advocate adapting surgical technique based on preoperative CT staging as not all patients require complete mesocolic excision (CME) and D3 lymphadenectomy. We aimed to assess the sensitivity and specificity of preoperative CT scans in nodal staging and analyse whether inadequate CT staging could have influenced local recurrences.

Material and Methods: a retrospective cohort study was conducted on patients with stage I-III colon cancer who were followed up at our hospital between 2011 and 2019. The clinical and pathological variables and data on locoregional recurrence (LRR) were extracted from the electronic patient file, including imaging data performed as part of the standard oncological follow-up protocol.

Results: the overall CT scan accuracy to identify the nodal status was 56.9% with sensitivity and specificity of 60.6% and 52.5%. Overstaging occurred in 95 patients (22%) and understaging in 92 (21%). Among understaged patients, 8 (8.7%) developed nodal LRR.

Conclusion: considering that roughly one in three patients with nodal LRR were underdiagnosed in terms of nodal status by the preoperative CT assessment, the therapeutic decisions regarding the surgical approach should not be guided by this and CME with central vascular ligation (CVL) should be applied to all patients as a standardized surgical technique.

Key words: CT, CME, CVL, colon cancer, D3 lymphadenectomy

Introduction

Local recurrences in colon cancer have seen a major decrease in the last decade due to standardised surgery and adjuvant regimens. Surgical technique significantly contributes to the better survival we see in our patients today, and we have CME to thank for the better outcomes. Adopting a clear plan and a set of values that surgeons must adhere to when performing oncological colon resections is now fundamental for any cancer centre. Starting from the Heald's concept of total mesorectal excision (TME) for rectal cancer (1, 2,3), Hohenberger applied the concept to colon cancer, and proposed CME with central vascular ligation (CVL) (4,5,6). Although sharp dissection following embryological planes is imperative for obtaining an intact surgical specimen, the benefit of central vascular ligation and extent of lymphadenectomy is still a matter of debate, especially when considering right colectomies.

In right colon cancer, there are differences in practice between East and West: Japanese are proponents of D3 lymphadenectomy while European centres recommend D2 lymphadenectomy as the standard surgical approach (7,8). The Japanese guidelines encourage adapting the type of lymphadenectomy according to the stage of the disease, with D2 dissection (removal of pericolic and intermediate nodes) for cT1 tumours and D3 dissection (removal of nodes at the root of the regional artery plus D2 node dissection) for cT2 to cT4 tumours and, or cN+ (9). Therefore, in Japan, D3 lymph node dissection has become the standard for stage II and III colon cancer (10,11,12)

For left sided colon cancer, there is still no consensus on high vs low ligation of the inferior mesenteric artery (IMA) as studies failed to

prove a clear survival benefit in patients with high ligation. Performing CME, CVL and D3 lymphadenectomy is more demanding from a technical point of view, requires better expertise and may be associated with a higher risk of significant vascular injury which can be challenging to control especially in a minimally invasive setting (13,14). Not all colorectal surgeons are comfortable with D3 lymphadenectomy. Hence, the recommendation refers to the cases that indicate CVL and D3 in institutions that regularly perform extensive surgery. Nevertheless, when is CME, CVL and D3 lymph node dissection indicated? The consensus is that cT3-4 and/or cN+ tumours should benefit from CME surgery. Thus, we solely rely on the preoperative CT to triage more advanced stage III, N+ cases, but CT interpretation can pose significant challenges to the radiologists compared to rectal cancer staging performed on MRI.

Herein, we aim to better understand the predictive role of CT in colon cancer staging, better stratify the indication of CME surgery and assess whether local recurrences in colon cancer may be attributable to preoperative CT understaging.

Material and Methods

Design and Setting

This single-centre observational cohort study focuses on patients treated at our institution from 2011 to 2019, who were diagnosed with colon cancer. We included all patients who were followed up at our hospital, regardless of whether they had their first surgery here or at another hospital.

Our study was designed in a retrospective manner thus randomisation was not possible, but also not required because we followed up the cohort as one without creating case-control groups.

Patient's consent was waived by our institutional ethics committee as the research did not pose any risk for the patients and all gathered data was anonymised.

Inclusion and Exclusion Criteria

The inclusion criteria were patients who underwent surgery with curative intent for colon cancer (stages I-III, UICC 8th edition), without preoperative chemotherapy and with pre- and postoperative good-quality contrast-enhanced computer tomography (CT). The exclusion criteria were stage IV colon cancer (UICC 8th edition), pT4b stage, palliative colectomies, synchronous rectal tumours, low-quality or unavailable CT examination, and inconclusive pathological results.

Data Extraction

Data were obtained from a prospectively maintained electronic database. Preoperative evaluation included demographic information (age, gender) and preoperative imaging staging (CT scans). Surgical data included operation date, type of colectomy (tumour location) and surgical procedures (CME or non-CME technique). The pathology report included pathological specimen parameters like pTNM staging, histological type of cancer, tumour differentiation, lymphovascular invasion, perineural invasion, number of harvested lymph nodes (LNs), number of positive lymph nodes detected, lymph node index (LNI) as the ratio between positive and total LNs and resection margins. The analysed postoperative data were extracted from eligible postoperative CT scans. Arterial stump angiometry parameters (ileocolic and inferior mesenteric arterial stump length) were used to add information about LRR type (15).

LRR was defined as tumoral growth at the perianastomotic site, mesocolic dissection margins, mesocolon or mesenteric fat, mesocolon or mesenteric LNs or central vascular LNs alongside the stump of the ileocolic artery (ICA), right colic artery, sigmoid trunk, left colic artery (LCA), inferior mesenteric artery (IMA) or up to the lateral wall of the aorta. The arterial stump length (ASL) was measured and analysed in compliance with CME and CVL technique: in right colectomies, the ASL was defined from the starting point of the ICA from

the superior mesenteric artery to the ligation point and in left-sided colectomies, the ligation point was analysed in relation to the IMA and LCA (high ligation of the IMA, at approximately 10 mm from the aorta and low ligation of IMA, just below the emergence of the left colic artery) (16-18).

Data Analysis

In order to assess the nodal status, descriptive statistics with accuracy, sensitivity and specificity, were used to compare CT with final histologic findings. Continuous variables were presented as mean ± standard deviation (SD), median and the values of quartiles Q25 and Q75. The reference threshold for the significance level p-value was considered to be 0.05. A p value lower than 0.05 indicated with 95% confidence that there was statistical significance.

Results

Patient Characteristics

A total of 434 patients were enrolled in the study after the exclusion criteria were applied (lack of pre- or postoperative CT images available in IRO electronic database, unavailable or incomplete pathological results, loss for the oncological follow-up, stage IV disease or pT4b on pathology, palliative colectomies) (*Fig. 1*).

Regarding the gender of the patients, 237 males (54.6%) and 197 females (45.4%) were included, with an average age at surgery of 63 years, 171 (39.4%) were diagnosed with right sided colon cancer and 263 (60.6%) with left sided colon cancer. Most patients had sigmoidectomies (43.3%; n=188) and right hemicolectomies (36.6%; n=159). The remaining patients underwent left hemicolectomies (10.3%; n=45), segmental resections for left colic flexure (6.3%; n=27), extended right hemicolectomies (2.8%; n=12), and extended left hemicolectomies (0.7%; n=3)

The preoperative imaging staging revealed that 73 patients were cT1-2 (16.8%) and 361 were cT3-4 (83.2%). Also, 54.6% had enlarged LN suggestive of MTS (n=237) and 45.4% (n=197) did not. The histopathological results showed that most patients had pT3 (65.9 %; n=286) and pT4a tumours (23.7%; n=103),

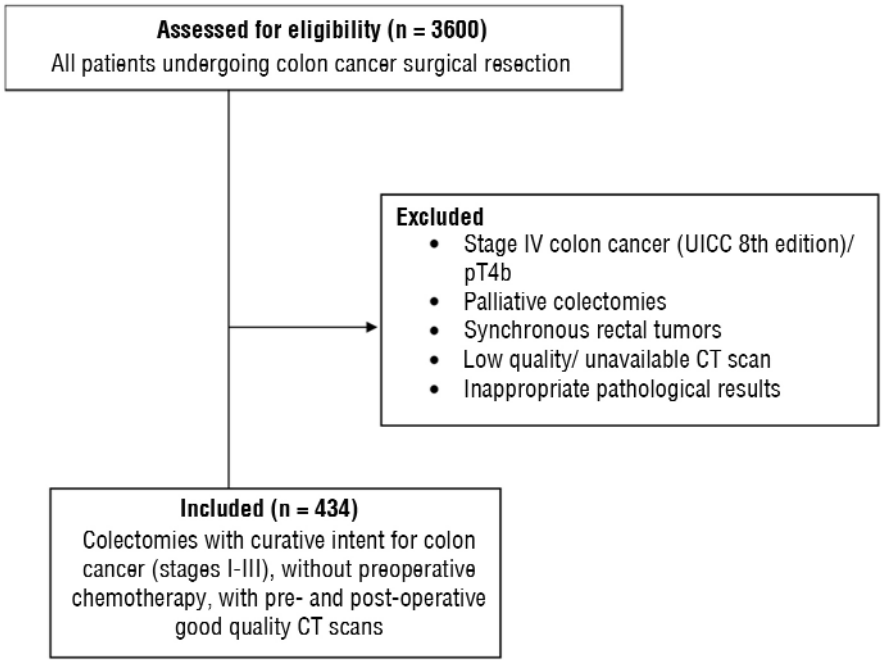

Figure 1. Flowchart of eligibility

with only 45 having pT1 (2.5 %; n=11) and pT2 (7.8%; n=34) tumours. In terms of nodal status, 200 of patients were pN0 (46.1%), 145 were pN1 (33.4%), and 89 were pN2 (20.5%). The number of patients with an LN count below 12, was 54 (12.3%). Demographic, clinical, and histologic results of the study population are described in *Table 1*.

Role of Preoperative CT in Establishing the Nodal Status Accuracy

The overall prediction accuracy of the N stage was 56.9%. The sensitivity and specificity were 60.6% and 52.5%, respectively (*Table 2*). Therefore, for 434 included patients, 237 patients cN+ (54.6%) and 197 cN- (45.4%), overstaging occurred in 95 patients (22%) and understaging in 92 patients (21%) (*Table 3*).

Mapping and Prediction of Loco-Regional Recurrences

Our study showed an overall LRR rate of 6.77%. At a median follow-up of 39 months (6, 82), 34 patients developed LRR, with a median LRR-free survival of 15 months. Among them, seven patients (20.6%) had local recurrences at the anastomosis site, 22 (64.7%) had nodal recurrences (16 mesenteric and six lomboaortic), and five patients (14.7%) had peritoneal or retroperitoneal recurrences with intestinal, psoas muscle, and prerenal fascia invasion. Regarding the patients with LRR, the mean ASL (± SD) value was 60 ± 9 mm and the mean LN harvest value was 24.85 ± 6.42. The values of patients without LRR were 47 ± 2.6 mm (mean ASL value) and 29 ± 6 (mean LN harvest) (*Table 4*) (p= 0.0001). Regarding nodal recurrences, these values were 65.7 ± 11.7 mm (mean ASL value) and 18.75 ± 12.573 (mean LN harvest).

In patients with nodal LRR, the preoperative CT scan underdiagnosed eight patients (36.3%) and overdiagnosed four patients (18.2%) (*Table 5*). Therefore, out of the 21% of total understaged patients, 8% had nodal recurrence.

CT scan predicted the pN2 status in all

Table 1. Demographics, clinical, and histological results of the study population

Variable	Data (n= 434)	
	N	%
Gender		
Male	237	54.6
Female	197	45.4
Median age at diagnosis (years)	63 (21- 92)	
Tumour location		
Right-sided (cecum, ascending colon, right flexure)	171	39.4
Left-sided (left flexure, descending colon, sigmoid co)	263	60.6
Surgical procedure		
Right hemicolectomy	159	36.6
Left hemicolectomy	45	10.3
Extended right hemicolectomies	12	2.8
Extended left hemicolectomies	3	0.7
Segmental resection (colic flexure)	27	6.3
Sigmoidectomies	188	43.3
Clinical stage		
cT1	6	1.4
cT2	67	15.4
cT3	266	61.3
cT4	95	21.9
cN-	197	45.4
cN+	237	54.6
Pathological T-stage		
pT1	11	2.5
pT2	34	7.9
pT3	286	65.9
pT4	103	23.7
Pathological N-stage		
pN0	200	46.1
pN1	145	33.4
pN2	89	20.5

Table 2. Diagnostic perfomance of CT nodal staging

	N Category	
	Value (%)	95% CI
Accuracy	56.9	52.1- 61.3
Sensitivity	60.6	54.3- 66.7
Specificity	52.5	45.6- 59.3
PPV	59.9	53.6- 65.9
NPV	53.3	46.3- 60.1

95% CI: 95% confidence interval; PPV: positive predictive value; NPV: negative predictive value

Table 3. CT scan preoperative N staging

CT N stage	Pathological N stage		
	N0	N1/N2	Total
cN0	105	92	197
cN1/N2	95	142	237
Total	200	234	434

Table 4. ASL for LRR vs. no LRR patients

	LRR Category			
	Value (n)	Value (%)	Mean ASL ±SD (mm)	p-Value
Nodal	22	64.7	65.7 ± 11.7	
Peritoneal	5	14.7	25.7 ± 5.2	
Anastomotic	7	20.6	56.8 ± 7.7	
Total LRR	34	100	60 ± 9	
No LRR Category				0.0001
Total No LRR	400	100	47 ± 2.6	

LRR: Locoregional recurrence; SD: Standard deviation; ASL: Arterial stump length; T-test was used to compare the mean ± SD ASL between patients with LRR and those without; a 95% CI was used and $p < 0.05$ was considered statistically significant.

Table 5. TCT scan preoperative N staging- nodal LRR

CT N stage	Pathological N stage		
	N0	N1/N2	Total
cN0	2	8	10
cN1/N2	4	8	12
Total	6	16	22

patients with nodal LRR effectively, but regarding pN1 patients, only two were correctly estimated, the rest of them being understaged. Most of the understaged patients developed mesenteric and para-aortic recurrences.

Discussion

To our knowledge, this is the first observational study to correlate the sensitivity and specificity of preoperative CT to local nodal recurrences in colon cancer patients. Even if achieving the best diagnostic accuracy is a fundamental objective in terms of treatment strategy, conventional CT imaging has shown limited accuracy in determining positive nodes, both in literature studies and in our analysis. Our study, based on the above results, showed that in almost half of patients, imaging nodal status on CT did not correspond to the histopathological one. The accuracy of preoperative imaging to predict nodal status was 56.9% and the sensitivity and specificity 60.6 % and 52.5 %.

The findings obtained in our analysis are similar to those previously reported by other studies that have focused on this topic. A meta-analysis that included 16 articles, published in 2016 by Nerad et al. (19), obtained a CT sensitivity and specificity for colon cancer N staging of 71% and 67%. A 2019 retrospective study by Fernandez et al. showed values of 47% and 71%, with a rate of understaged patients of 50% (20). Furthermore, Olsen et al. performed a retrospective evaluation of CT, involving 4832 patients with colon cancer from a Danish national health database and obtained rates of 57% and 66% in terms of sensitivity and specificity of nodal staging on CT scan (21).

Based on these results and considering that 21% of our patients were understaged in terms of nodal status and almost one in three had a nodal recurrence, choosing surgical approach should not be guided by the preoperative CT scan. Starting from this and since our study demonstrated that the difference is due to the surgical approach (CME vs non-CME colectomies), we conclude that CME with central vascular ligation should be applied to all patients as a standardised surgical technique. Bertelsen and West provide evidence to support these conclusions when their data indicate that CME surgery with extrafascial plane dissection and CVL is associated with better RFS than conventional colon cancer resection for patients with stage I-III colon cancer (22-24).

Detection of nodal involvement resulted in worse outcomes. Therefore, for 434 included patients, overstaging occurred in 95 patients (22%) and understaging in 92 patients (21%). In patients with nodal LRR (22 patients), the preoperative CT scan underdiagnosed eight patients (36.3%). It indicates that if the surgeon had relied on the preoperative imaging and had conducted a restricted resection without following a standardised surgical method, the patients would have been at risk of developing local nodal recurrences.

Most of the underdiagnosed patients with nodal LRR, developed mesenteric and para-aortic recurrences, and their histopathological and imaging features confirmed that the surgical principles in accordance with CME and CVL were not respected. Therefore, the

mean ASL value was 65.7 ± 11.7 mm. This value is significantly higher than that of patients without LRR, suggesting that surgical technique is particularly important in increasing the risk of LRR, and by CT- understaging, there is a greater risk of performing a suboptimal surgery technique that will translate into poorer long-term results. Moreover, regarding the LN harvest, four cases had less than 12 LN in the histopathological report.

Also, five (25%) of these patients developed nodal LRR even if they were cN0-pN0, the association with the characteristics listed above, suggesting that the patient's prognosis in terms of nodal LRR was directly influenced by non-compliance with CME and CVL. Moreover, even in patients with enlarged LN on preoperative CT scan (9 patients) who developed nodal LRR, non-CME colectomies were performed.

Therefore, it can be concluded that the patient's prognosis in terms of nodal LRR was directly influenced by non-compliance with CME and CVL, suggesting that a proper surgical act would have reduced the LRR rate.

Finally, the high percentage of patients underdiagnosed by CT evaluation (21%) demonstrated a limited accuracy of CT in detecting colon cancer patients at high risk of developing nodal LRR. Distinguishing lymph node metastasis with CT scan remains questionable.

There are limitations to our study. The retrospective design, small sample size, and heterogeneity of CT images performed in different institutions with different equipment and technical details limited the strength of the study. Details of the specific imaging tools used for preoperative staging, including technical parameters such as the use of intravenous and, or oral contrast, section thickness, and the availability of multiplanar reconstructions were not known. This lack of information did not allow us to objectively assess how better technological tools might have influenced the accuracy of CT evaluation.

Conclusion

Conventional CT, as a preoperative evaluation tool for surgical planning, still has limited diagnostic accuracy in terms of lymph node status. With a CT assessment accuracy of approximately 57%, performing extended nodal dissection with central venous ligation only to radiologic cN+ would have failed to provide adequate treatment to a signifcant proportion of patients. Therefore, preoperative staging protocols still need improvement and standardisation to offer more individualised treatment and minimise the risk of unnecessary morbidity.

Conflicts of Interests

No funding or financial assistance was received by the authors. The authors have no conflicts of interest to disclose.

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