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Are Metastatic Central Lymph Nodes (D3 volume) in right-sided Colon Cancer a Sign of Systemic Disease? A sub-group Analysis of an Ongoing Multicenter Trial

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Objective: Assess outcomes of patients with right-sided colon cancer with metastases in the D3 volume after personalized surgery.

Background: Patients with central lymph node metastasis (D3-PNG) are considered to have a systemic disease with a poor prognosis. A 3-dimensional definition of the dissection volume allows the removal of all central nodes.

Materials and Methods: D3-PNG includes consecutive patients from an ongoing clinical trial. Patients were stratified into residual disease negative (D3-RDN) and residual disease positive (D3-RDP) groups. D3-RDN was further stratified into 4 periods to identify a learning curve. A personalized D3 volume (defined through arterial origins and venous confluences) was removed "*en* bloc" through medial-to-lateral dissection, and the D3 volume of the specimen was analyzed separately.

Results: D3-PNG contained 42 (26 females, 63.1 SD 9.9 y) patients, D3-RDN:29 (17 females, 63.4 SD 10.1 y), and D3-RDP:13 (9 females, 62.2 SD 9.7 y). The mean overall survival (OS) days were D3-PNG:1230, D3-RDN:1610, and D3-RDP:460. The mean disease-free survival (DFS) was D3-PNG:1023, D3-RDN:1461, and D3-RDP:74 days. The probability of OS/DFS were D3-PNG:52.1%/50.2%, D3-RDN:72.9%/73.1%, D3-RDP: 7.7%/0%. There is a significant change in OS/DFS in the D3-RDN from 2011–2013 to 2020–2022 (both $P = 0.046$) and from 2014–2016 to 2020–2022 ($P = 0.028$ and $P = 0.005$, respectively).

Conclusion: Our results indicate that surgery can achieve survival in most patients with central lymph node metastases by removing a personalized and anatomically defined D3 volume. The extent of mesenterectomy and the quality of surgery are paramount since a learning curve has demonstrated significantly improved survival over time despite the low number of patients. These results imply a place for the centralization of this patient group where feasible.

Key words: lymph node metastases (D3 volume), D3 right colectomy, extended D3 mesenterectomy, oncologic outcomes, lymph node dissection

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The influence of central lymph node metastases (LNM) on the prognosis and recurrence of right-sided colon cancer remains controversial.[1,2] There is an ongoing debate about whether central LNM represents local or systemic disease.[1,2] Improving operative techniques (CME/D3)[3–5] for treating right-sided colon cancer has led to better oncological outcomes by setting the quality of surgery into the limelight. Despite these operative techniques, the 5-year overall survival (OS) is 35% to 48%[1,5–7] and 5-year disease-free survival (DFS) is 16.2%[1] in patients with central LNM. The few studies that compared conventional colectomy[8–10] to CME showed no difference in survival. It is important to stratify patients in groups with and without central LNM since these can follow the oncological or the linear spreading pathway claiming systemic disease or not.[11]

Currently, the only available definition of the "D3 volume" of the right colon, as a 3-dimensional structure, is described by Spasojevic et al in 2013.[12] It is based on the patient's individual anatomy, and in this way identifies the central lymph nodes to be harvested. It has also been shown that when this definition is used, the number of lymph nodes harvested is steady and reproducible.[13–15] When considering the alternatives to this definition, the remaining options are either to use only the tissue anterior to the superior mesenteric vein (SMV),[3] which is not entirely anatomically correct since lymph nodes and vessels have been shown to follow arteries and not veins.[14] The second option is to use the "apical lymph nodes," which are vaguely defined and may not always correlate with the anatomic boundaries required for complete resection—the "main nodes" in the JCCRC.[4] Both options do not provide confidence that the nodes are central and that all

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All authors contributed to the conception, design, and data collection. The authors have actively participated both in writing parts of the manuscript and in revising it, and in the end, have given final approval for the manuscript to be published.

Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography (MDCT) Angiography is ethically approved by Regional ethical committee, South-East Norway (REK Sor-Ost) no. 2010/3354

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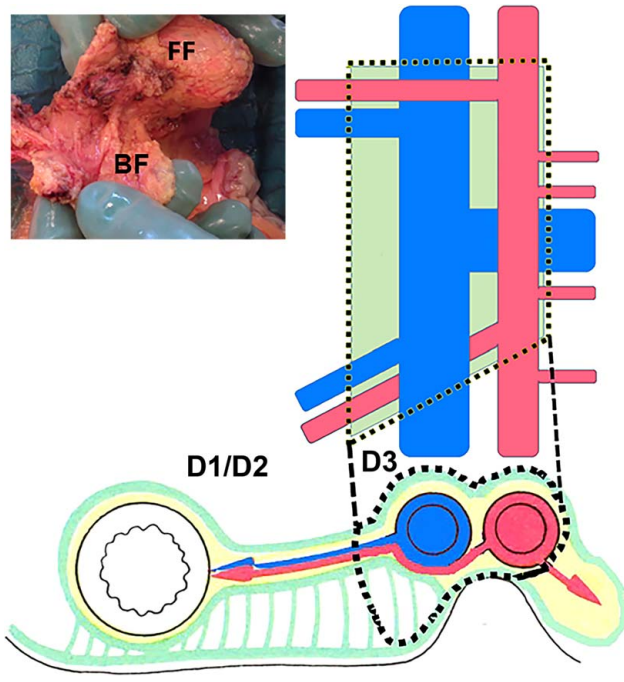

FIGURE 1. Showing composition of D3 volume after extended D3 mesenterectomy. FF: Front flap; BF: Back flap. D1/D2: D1/D2 volume; D3: D3 volume. The picture in the upper left corner shows the D3 volume after dissecting it from the main specimen. The main picture shows the operative area with separate marked D1/D2 volume and D3 volume in relation to the superior mesenteric artery and superior mesenteric vein. *From "Banipal et al.[11] Copyright 2022 by Springer Nature. Reprinted under Creative Commons attribution 4.0 international license.

relevant nodes have been harvested. The challenge in these techniques is the radicality required to remove central lymph nodes *en bloc* due to the complex anatomy of the mesenteric vessels, increasing the hazard for injury. Gundara et al postulated 2013[16] that redefining the central lymph nodes in right colectomy is necessary and should be based on fixed anatomic landmarks such as the ones we propose in this article.

This study aims to assess long-term outcomes in patients with right-sided colon cancer and LNM to the D3 volume following personalized D3 right colectomy with extended mesenterectomy anterior/posterior to the superior mesenteric vessels. The secondary aim is to assess a potential learning curve related to survival.

METHODS

Dataset

This study includes data from consecutive patients with positive nodes in the D3 volume [the D3 positive node group (D3-PNG)] in the ongoing clinical multicenter trial "Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography (MDCT) Angiography". The trial has been registered on ClinicalTrials.gov/ct2/show/NCT01 351714 and was ethically approved by the South-East Norway Regional Ethical Committee2010/3354. Hospitals including patients in the study were Akershus University Hospital (Ahus), Vestfold Hospital Trust (VHT), Viszeralchirurgie Klinikum Karlsruhe, Germany (KR), and Medical Park Usak Hospital, Turkey (MPT).

Inclusion criteria for the study are age under 75 years, medically cleared by an anesthesiologist for general anesthesia, histopathologically verified adenocarcinoma, and signed written consent before surgery. Exclusion criteria were recurrent cancer, distant metastasis from other malignancies, not being medically cleared by the anesthesiologist, and without written consent.

Surgical Procedure and the D3 Volume Specimen

Surgery was performed through all modes of surgical access with medial-to-lateral dissection (devascularization first). Reconstruction of vascular anatomy in 3D images using Osirix MD ver.13.01, 64-bit image processing application (Pixmeo, Bernex, Switzerland), Mimics Medical, ver. 24.0.0.427, and 3-matic medical software, ver.16.0.0.151, both Windows 10 Pro Editionx64 2021 (Materialise NV, Leuven, Belgium) was used for peroperative navigation and orientation.[12,17] The medial limit of the dissection was along the left border of the superior mesenteric artery (SMA). The ileocolic vessels were divided at the origin of the SMA/SMV. All mesenteric tissue, including lymph nodes and vessels, was removed ventrally and dorsally to the mesenteric vessels *en* bloc[14] (Figs. 1, 2). Further, the lymph nodes along the middle colic artery (MCA) trunk were completely dissected with ligation of the MCA right branch and/or main trunk itself, depending on the extent of right colectomy. Operative images after specimen removal were mandatory for quality control at open surgery, and videos were used for minimal surgical access. This operative technique has been previously described in detail.[14,15]

The specimen, after surgery, was divided into the respective D1/D2 and D3 volumes through a line 10 mm to the right of the superior mesenteric vein (SMV), 10 mm caudal to the ileocolic artery origin, and 5 mm cranial to the MCA origin (Fig. 1). Specimens D1/D2 and D3 were preserved separately in the glacial acetic acid.

Histopathology

Pathologists performed all histopathological examinations using the same methodology in their respective hospitals. Results were categorized according to AJCC classification (8th edition), while those where previous versions were used were reclassified. Evaluation of extramural vascular invasion (EMVI) was initially not done routinely in all patients and was therefore re-analyzed later. The specimens (D1/D2 and D3 volumes) were examined separately. All patients with metastatic nodes in the D3 volume, irrespective of lymph node status in the D1/D2 volume, were included in the study.

After the surgery and histopathological analysis, the D3-PNG patients were re-stratified into 2 groups:

1. The residual disease negative (D3-RDN): Patients received R0 resection (all gross disease removed with free margins).
2. The residual disease positive (D3-RDP): Patients with R1 (microscopic residual disease) and R2 (macroscopic residual disease) resection. Patients who were deemed resectable before surgery and had, at this time, liver and/or lung metastases, but for any reason, failed to receive further surgery were reclassified as D3-RDP. Patients were also reclassified to the D3-RDP group when recurrence occurred within 6 months after surgery (with chemotherapy) or within 3 months (without chemotherapy).

The site of the first recurrence was registered by follow-up imaging.

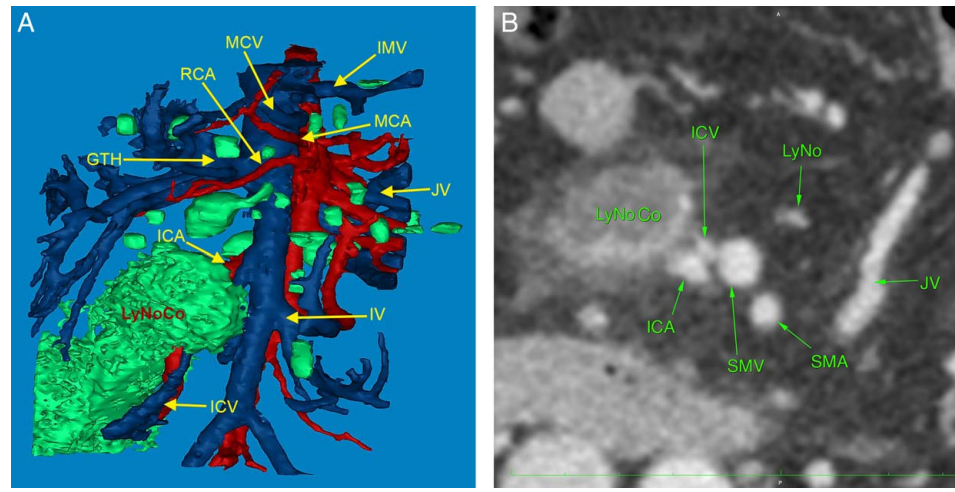

FIGURE 2. 3D segmentation of the D3 volume. A, Mimics 3D mask. B, An axial MIP of the same case. GTH indicates gastrocolic trunk of Henle; ICA, ileocolic artery; ICV, ileocolic vein; IMV, inferior mesenteric vein; IV, ileal vein; JV, jejunal vein; LyNoCo, lymph node conglomerate; LyNo, lymph node; MCA, middle colic artery; MCV, middle colic vein; MIP, maximal intensity projection; RCA, right colic artery.

Complications

Thirty-day and 90-day mortality rates were calculated. Vascular injuries were reported when a vascular surgeon was summoned. The Clavien-Dindo classification was used to register postoperative complications.[18]

Follow-up

Follow-up examinations consisted of physical examination, blood tests (Hb, liver tests, Glomerular filtration rate, and Carcinoembryonic antigen), computer tomography of the chest, abdomen, and pelvis at 1, 6, 12, 24, 36, 48, and 60 months, and colonoscopy at 60 months after surgery until December 2019[19] in Norway and up to date in Germany.[20] In Norway,[19] new follow-up guidelines were introduced in January 2020 with clinical assessment at 1, 6, 12, and 36 months, computer tomography of the chest, abdomen, and pelvis at 12, 24, and 36 months after surgery, and colonoscopy at 60 months.

Adjuvant Chemotherapy

Adjuvant chemotherapy was offered to patients under the age of 75 after curative resection (R0). Patients between 70 and 75 years old received either 5-fluorouracil or capecitabine (Xeloda). The treatment of patients under 70 was routinely XELOX (6 cycles of capecitabine plus oxaliplatin) or XELOX/FOLFOX/FLOX (12 cycles of capecitabine or 5-fluorouracil and oxaliplatin). Palliative treatment (FLOX/FLIRI or 5-fluorouracil/Capecitabine as a monotherapy in elderly patients)[19] was considered for patients with R1/R2 resections. After 2019, immune therapy (pembrolizumab) was routinely considered for patients with microsatellite instability-high tumors (MSI-H).

Patients receiving half the number or more chemotherapy cycles were considered as having received a sufficient dose.

Multi-disciplinary Team (MDT) Meeting

All patients were discussed in the MDT meetings, where a team of specialists was present, including oncologists, radiologists, pathologists, gastrointestinal surgeons, and cancer specialist nurses. These meetings were used in deciding staging and further treatment regarding neoadjuvant and/or adjuvant chemotherapy and surgery.

Assessing the Learning Curves

The study period was divided into four 3-year periods: 2011 to 2013, 2014 to 2016, 2017 to 2019, and 2020 to 2022. OS and DFS were compared in different time periods to demonstrate the effect of surgical volume on OS and DFS.

Statistical Analysis

Patient demographic and clinical characteristics were presented as mean and SDs or frequencies and percentages, as appropriate. Groups were compared by χ^2-test or independent samples *t*-test when possible, given the sample size. Survival outcomes were presented as the number of deceased, censored, and survived together with the probability of survival at 1, 2, 3, 4, and 5 years after diagnosis. Kaplan-Meier curves were presented to compare OS and DFS in days between the 2 groups of patients (D3-RDN and D3-RDP). Mean survival time with 95% confidence interval (CI) was presented. Learning curves were illustrated graphically. A z-test for proportions was used to compare the survivors at different time points. The tests were 2-sided, and results with *P* values below 0.05 were considered statistically significant. The statistical analyses were performed in SPSS v27 and STATA v17.

RESULTS

Patient Characteristics

A total of 623 patients were included in the multicenter clinical trial. Of these, 42 (6.7%, 26 females, age 63.1 SD 9.9) were diagnosed with positive lymph node metastases in the D3 volume at histopathology. Preoperative radiology (MDCT) showed suspicion of central lymph node metastases in 21/42 (50%) patients. The 42 patients with LNM were then divided into D3-RDN: 29/42 (17 female, age 63.4 SD 10.1) and D3-RDP: 13/42 (9 female, age 62.2 SD 9.7). The demographic and clinical data for the entire D3-PNG and subgroups are presented in Table 1.

1. D3-RDN: There were 21/29 (72.4%) patients without recurrence. Recurrence occurred in the liver in 2 (6.9%), retroperitoneal lymph nodes in 3 (10.3%), and peritoneal carcinomatosis in 3 (10.3%) patients. One patient received synchronous surgery for liver metastasis (bisegmentectomy for 2 metastases) without developing recurrence. Death due to recurrence occurred in 6/29 (20.7%). Of these, 3 (10.3%) died due to peritoneal carcinomatoses, 2 (6.7%) due to retroperitoneal lymph node metastases, and 1 (3.4%) due to

TABLE 1. Table Showing Patient Demographics and Characteristics

Characteristic	D3-PNG N = 42	D3-RDN N = 29	D3-RDP N = 13	*P*
Female, n (%)	26 (61.9)	17 (58.6)	9 (69.2)	0.513*
Age, mean (SD)	63.1 (9.9)	63.4 (10.1)	62.2 (9.7)	0.724†
ASA, n (%)				
1	9 (21.4)	4 (13.8)	5 (38.5)	—
2	27 (64.3)	20 (69.0)	7 (53.8)	—
3	5 (11.9)	4 (13.8)	1 (7.7)	—
4	1 (2.4)	1 (3.4)	0	—
Metastases, n (%)	—	—	—	—
No metastases	21 (50.0)	21 (72.4)	0	—
Liver	2 (4.8)	2 (6.9)	0	—
Lung	0	0	0	—
Retroperitoneal lymph nodes	3 (7.1)	3 (10.3)	0	—
Peritoneal carcinomatosis	3 (7.1)	3 (10.3)	0	—
D3-RDP	13 (31.0)	0	13 (100)	—
Surgical resection, n (%)	—	—	—	0.027*
Right colectomy	26 (61.9)	14 (48.3)	11 (84.6)	—
Extended right colectomy	16 (38.1)	15 (51.7)	2 (15.4)	—
Surgical access, n (%)	—	—	—	—
Open	31 (73.8)	18 (62.1)	13 (100)	—
Minimal invasive, n (%)	10 (23.8)	10 (34.4)	0	—
Converted from laporoscopy	1 (2.4)	1 (3.4)	0	—
Additional procedures, n (%)	—	—	—	—
None	38 (90.5)	25 (86.2)	13 (100)	—
Liver surgery	3 (7.1)	3 (10.3)	0	—
Local recurrence surgery	1 (2.4)	1 (3.4)	0	—
Preoperative MDCT, n (%)	—	—	—	0.189*
None	9 (21.4)	9 (31)	0	—
D1/D2 volume	12 (28.6)	8 (27.6)	4 (31.0)	—
D3 volume	21 (50.0)	12 (41.4)	9 (69.0)	—
Adjuvant treatment (Curative), n, (%)	—	—	—	—
Completed	20 (47.6)	20 (69.0)	8	—
Not completed	9 (21.4)	9 (31.0)	5	—
Toxicity, (%)	6/9 (66.7)	6/9 (66.7)	3	—
Comorbidity, (%)	3/9 (33.3)	3/9 (33.3)	2	—
Palliative	13 (100)	—	13 (100)	—

*χ^2-test.
†*T*-test.
D3-PNG indicates positive nodes in the D3 volume; D3-RDN, residual disease negative; D3-MDCT, multi-detector computed tomography; RDP, residual disease positive.

liver metastases. In short, one with resected liver metastases and another with retroperitoneal lymph node metastases survived.

2. D3-RDP: Death due to recurrence occurred in 12/13 (92.3%), while 1 patient (7.7%) received immunotherapy due to MSI-H positive tumor and survived 5 years despite developing peritoneal carcinomatosis 15 months after surgery. Among the remaining 12 patients, carcinomatosis was found in 4 patients at surgery, not previously diagnosed by MDCT. Another 4 patients had nonresectable paraaortic lymph node metastases.
3. The patients re-allocated to the D3-RDP from the D3-RDN group were 2 patients that developed paraaortic lymph node metastases shortly after surgery and 2 patients diagnosed with resectable liver metastases that were planned for liver surgery after neoadjuvant therapy but developed multiple nonresectable metastases.

Surgical Procedures

The surgical procedure with access mode is shown in Table 1. A total of 5 patients received multi-visceral resection, 3 in the D3-RDN group (wedge resection of the stomach and extirpation of the ovaries), and 2 in the D3-RDP group (wedge resection of the stomach and small intestine). The operating surgeons were not made aware of these at the MDT meetings. Further, one conversion from laparoscopy to open procedure was due to bleeding from the ileocolic vein (ICV) in D3-RDN. All D3-RDP patients were operated through open access.

In the D3-RDN group, 3 patients (10.3%) had liver resection and 1 (3.4%) had local recurrence surgery after primary surgery.

Histopathology

The histopathological results, tumor location, tumor depth (T stage), N stage, EMVI, tumor differentiation, distal and proximal resection margin, the total number of lymph nodes on D1/D2 and D3 volume, the total number of metastatic lymph nodes in D1/D2 and D3 volume, and lymph node ratio (LNR) are shown in Table 2.

D3-PNG: There were 41/42 (97.6%) with adenocarcinoma and 1/42 (2.4%) with undifferentiated carcinoma; 21/42 (50%) had T3 and 20/42 (47.6%) had T4. N2 stage was found in 31/42 (73.8%) patients. Transverse colon and coecum were the most common tumor sites: 14/42 (33.3%) and 13/42 (31.0%), respectively; EMVI was positive in 6/42(14.3%) patients, and 21/42(50%) patients had low tumor differentiation. The only undifferentiated carcinoma belonged to the D3-RDP group. At the same time, D3-RDP had more T4 stage (84% vs. 31%), 100% N2 stage, and EMVI (15.4% vs. 13.8%) compared with D3-RDN.

Short-term Outcomes

Operating time, blood loss, and length of hospital stay in the D3-PNG and subgroups are shown in Table 3.

1. D3-PNG: There was no 30-day mortality registered and 90-day mortality was 2/42 (4.8%). There were 4/42 (9.5%) vascular injuries; otherwise, no other intraoperative complications. The Clavien-Dindo I, II, and III were 7/42 (16.7%), 2/42 (4.8%), and 7/42 (16.7%), respectively. There were 5/42 (11.9%) patients with anastomotic leakage and 2/42 (4.8%) reoperated for chylous ascites in the early stage of this study.
2. D3-RDN: There was no 30-day and 90-day mortality registered. There were 4/29 (13.8%) vascular injuries, else no other intraoperative complications. The Clavien-Dindo I, II, and III were 2/29 (6.9%), 2/29 (6.9%), and 5/29 (17.2%), respectively. There was 3/29 (10.3%) anastomotic leakage; in one of these patients, the surgeon was in doubt about finding leakage but likewise decided to perform an ileostomy. There was 2/29 (6.9%) reoperated for chylous ascites in the early stage of this study.
3. D3-RDP: There was no 30-day mortality registered, and the 90-day mortality was 2/13 (15.4%). There were no intraoperative complications. The Clavien-Dindo I, II, and III were 5/13 (38.5%), 0, and 2/13 (15.4%), respectively. There were 2/13 (15.4%) anastomotic leakages (Table 3).

TABLE 2. Table Showing Histopathology Results of the Patients and Lymph Node Ratio (LNR) in D1/D2 and D3 Volume Results

Parameter	D3-PNG N = 42	D3-RDN N = 29	D3-RDP N = 13	*P*
Histopathology, n (%)				
Adenocarcinoma	41 (97.6)	29 (100)	12 (92.3)	—
Undifferentiated carcinoma	1 (2.4)	0	1 (7.7)	—
Tumor localization, n (%)				
Coecum	13 (31.0)	7 (24.1)	6 (46.1)	0.291*
Ascending colon	8 (19.0)	7 (24.1)	1 (7.7)	—
Hepatic flexure	7 (16.7)	6 (20.7)	1 (7.7)	—
Transversum	14 (33.3)	9 (31.0)	5 (38.5)	—
T stage (TNM), n (%)	—	—	—	—
T1-T2	1 (2.4)	1 (3.4)	0	—
T3	21 (50.0)	19 (65.5)	2 (15.4)	—
T4	20 (47.6)	9 (31.0)	11 (84.6)	—
N stage (TNM), n (%)	—	—	—	—
N1	11 (26.2)	11 (37.9)	0	—
N2	31 (73.8)	18 (62.1)	13 (100)	0.892*
EMVI, n (%)				
Yes	6 (14.3)	4 (13.8)	2 (15.4)	—
No	36 (85.7)	25 (86.2)	11 (84.6)	—
Tumor differentiation, n (%)	—	—	—	—
High	1 (2.4)	1 (3.4)	0	—
Middle	17 (40.5)	13 (44.9)	4 (30.8)	—
Low	21 (50.0)	13 (44.8)	8 (61.5)	—
Undifferentiated	3 (7.1)	2 (6.9)	1 (7.7)	—
Total lymph nodes, mean (SD)	41.4 (15.4)	40.1 (14.1)	44.2 (18.3)	0.429†
Total lymph nodes in D1/D2 vol, mean (SD)	26.9 (11.5)	26.6 (11.5)	27.6 (12.1)	0.800†
Total lymph nodes in d3 volume, mean (SD)	14.4 (7.6)	13.1 (6.4)	17.1 (9.4)	0.121†
Total lymph nodes (metastasis), mean (SD)	12.9 (10.2)	8.8 (8.2)	22.2 (7.9)	< 0.001†
Total lymph nodes (metastasis) D1/D2 vol, mean (SD)	7.7 (7.1)	5.5 (6.2)	12.6 (6.7)	0.002†
Total lymph nodes (metastasis) D3 vol, mean (SD)	5.2 (5.7)	3.2 (3.9)	9.6 (6.6)	< 0.001†
Distal resection margin, mean (SD)	137.7 (86.6)	135.9 (90.6)	141.9 (80.4)	0.837†
Proximal resection margin, mean (SD)	208.3 (105.4)	209.9 (112.0)	204.8 (93.2)	0.886†
LNR (D2 vol), mean (SD)	0.32 (0.30)	0.25 (0.27)	0.49 (0.30)	0.012†
LNR (D3 vol), mean (SD)	0.40 (0.36)	0.29 (0.30)	0.64 (0.36)	0.003†
LNR (Total vol), mean (SD)	0.35 (0.28)	0.24 (0.22)	0.58 (0.27)	< 0.001†

*χ^2-test.
†*T*-test.
D3-PNG indicates positive nodes in the D3 volume; D3-RDN, residual disease negative; D3-RDP, residual disease positive; EMVI, extramural vascular invasion; LNR, Lymph node ratio.

Adjuvant Treatment

1. D3-PNG: A total of 29/42 (69.0%) received adjuvant chemotherapy; of these, 20/42 (47.6%) received sufficient adjuvant chemotherapy, and 9/42 (21.4%) were not able to complete the treatment due to the side effects, or not started due to comorbidity. There were 13/42 (31.0%) that received palliative treatment at the decision of the oncologist.
2. D3-RDN: A total of 20/29 (69.0%) received sufficient treatment. Of these, 14/20 (70.0%) did not develop recurrence, while 9/29 (31%) did not receive sufficient treatment due to the side effects of chemotherapy (6/9, 66.7%) and not started due to comorbidity (3/9, 33.3%). Of these, 7/9 (77.7%) did not develop recurrence.
3. D3-RDP group: A total of 8/13(61.5%) received sufficient treatment; only 1 patient received immunotherapy due to MSI-H being positive. In comparison,5/13 (38.5%) did not receive sufficient treatment due to side effects of chemotherapy (3/5, 60%) and not started due to comorbidity (2/5, 40%) (Table 1).

Long-term Outcomes

1. D3-PNG: The mean OS and DFS (95% CI) were 1230 (1018; 1442) and 1023 (766; 1279) days. The OS at 1, 3, and 5 years was 81.0%, 61.9%, and 52.1%, respectively. The DFS at 1, 3, and 5 years was 61.9%, 53.8%, and 50.2%, respectively.
2. D3-RDN: The mean OS and DFS (95% CI) were 1610 (1461;1761) and 1461 (1224; 1699) days, respectively. The OS at 1, 3, and 5 years was 100%, 87.5%, and 72.9%, respectively. The DFS at 1, 3, and 5 years was 86.5%, 78.4%, and 73.1%, respectively.
3. D3-RDP: The mean OS and DFS (95% CI) were 460 (219; 701) and 74 (0;153) days, respectively. The OS at 1, 3, and 5 years was 38.5%, 7.7%, and 7.7%, respectively. The DFS at 1, 3, and 5 years was 7.7%, 0, and 0, respectively (Table 3 and Fig. 3).

Learning Curves

Significant differences in OS and DFS were found within the D3-RDN group between the periods of 2011 to 2013 and 2020 to 2022 (both $P = 0.046$) and between 2014 and 2016 and 2020 and 2022 ($P = 0.034$ and $P = 0.007$, respectively). The D3-RDP group was too small for this type of analysis (Fig. 4).

DISCUSSION

The most important finding in this article is that survival is achievable in most patients with lymph node metastasis to

TABLE 3. Table Showing Short- and Long-term Outcomes of the Patients

Parameter	D3-PNG N = 42	D3-RDN N = 29	D3-RDP N = 13	*P*
Intraoperative surgical complications, n (%)	—	—	—	—
No	38 (90.5)	25 (86.2)	13 (92.3)	—
Vascular lesion	4 (9.5)	4 (13.8)	0	—
Clavien-Dindo, n (%)	—	—	—	—
None	26 (61.9)	20 (69.0)	6 (46.2)	—
Clavien- Dindo I	7 (16.7)	2 (6.9)	5 (38.5)	—
Clavien- Dindo II	2 (4.8)	2 (6.9)	0	—
Clavien- Dindo III	7 (16.7)	5 (17.2)	2 (15.4)	—
Reoperations, n (%)	—	—	—	—
Anastomosis leakage	5 (11.9)	3 (10.3)	2 (15.4)	—
Other	2 (4.8)	2 (6.9)	0	—
None	35 (83.3)	24 (82.8)	11 (84.6)	—
Mortality	—	—	—	—
30-days, n (%)	—	—	—	—
None	42 (100)	29 (100)	13 (100)	—
90-days, n (%)	2 (4.8)	—	2 (15.4)	—
None	40 (95.2)	29 (100)	11 (84.6)	—
Blood loss, mean (SD)	334.2 (701.9)	360.9 (834.7)	274.6 (228.3)	0.718*
Operating time, mean (SD)	245.5 (93.8)	249.0 (85.5)	237.7 (113.5)	0.724*
Hospitalization days, mean (SD)	10.7 (7.6)	9.7 (7.6)	12.9 (7.5)	0.208*
Overall survival (d)	—	—	—	—
Mean (95% CI)	1230 (1018; 1442)	1610 (1461; 1761)	460 (219; 701)	—
Median (95% CI)	†	†	330 (264; 396)	—
Disease-free survival (d)	—	—	—	—
Mean (95% CI)	1023 (766; 1279)	1461 (1224; 1699)	74 (0; 153)	—
Median (95% CI)	1328‡	†	0	—
Total survival, y, $n_d/n_c/N$§ (n (%))	—	—	—	—
≤ 1 y or (0; 365) d	8/3/42 [31 (81.0)]	0/3/29 [26 (100.0)]	8/0/13 [5 (38.5)]	—
≤ 2 y or (0; 730) d	3/2/31 [26 (73.1)]	0/2//26 [24 (100.0)]	3/0/5 [2 (15.4)]	—
≤ 3 y or (0; 1095) d	4/3/26 [19 (61.9)]	3/3/24 [18 (87.5)]	1/0/2 [1 (7.7)]	—
≤ 4 y or (0; 1461) d	3/2//19 [14 (52.1)]	3/2/18 [13 (72.9)]	0/0/1 [1 (7.7)]	—
≤ 5 y or (0; 1826) d	0/4/14 [10 (52.1)]	0/4/13 [9 (72.9)]	0/0/1 [1 (7.7)]	—
Disease-free survival, y, $n_d/n_c/N$§(n (%))	—	—	—	—
≤ 1 y or (0; 365) d	16/3/42 [23 (61.9)]	4/3/29 [22 (86.5)]	12/0/13 [1 (7.7)]	—
≤ 2 y or (0; 730) d	3/2/23 [18 (53.8)]	2/2//22 [18 (78.4)]	1/0/1	—
≤ 3 y or (0; 1095) d	0/3/18 [15 (53.8)]	0/3/18 [15 (78.4)]	—	—
≤ 4 y or (0; 1461) d	1/2/15 [12 (50.2)]	1/2/15 [12 (73.1)]	—	—
≤ 5 y or (0; 1826) d	0/4/12 [8 (50.2)]	0/4/12 [8 (73.1)]	—	—

*T-test.
†Median could not be calculated.
‡95% CI for median could not be calculated.
§nd/nc/N is number of dying/censored/total; n (%) is number of those surviving (probability of survival).
D3-PNG indicates positive nodes in the D3 volume; D3-RDN, residual disease negative; D3-RDP, residual disease positive.

the D3 volume of the right colon after radical surgery. Our results imply that the definition of "systemic disease" when these lymph nodes are affected should be reconsidered. At the same time, the introduction of CME[3] and Japanese D3[4] have standardized the operative technique and improved OS/DFS. Our results imply that there seems to be a place for further improvement through the customization of surgery to the personalized anatomy of the patient. This study relates to a defined personalized 3-dimensional D3 volume with clear borders, described by Spasojevic[12] and Nesgaard.[21] While Spasojevic defines the 3D structure of the D3 volume, Nesgaard reports on the clearances of the right colonic lymphovascular bundles, in this way defining the borders with a clearance of up to 1 cm proximal/distal to vessel origins. The finding of a 20% decrease in DFS when the ileocolic artery crosses posteriorly to the SMV[22] seems to confirm the value of removal of the tissue posterior to the superior mesenteric vessels since the removal of this tissue is not included in the Japanese or the European surgical techniques. It is also worth mentioning that both Spasojevic et al[23] and Munkedal et al[24] found significantly longer arterial stumps on the postoperative CT scans despite CME, implying a potential to improve through awareness of the patient's anatomy.[25] A further aspect is a surgical approach to vessels requiring ligation. If injury to the lymph vessels in the lymphovascular bundle occurs, the consequent lymphatic spillage could spread cancer cells. On the other hand, dissecting free the mesenteric tissue within the arterial/venous sheaths of the SMA/SMV through "lifting the carpet",[14] as in D3 right-sided colectomy with extended mesenterectomy, leads to not only removing the anterior and posterior flaps (anterior/posterior to the SMA/SMV) *en* bloc with the specimen but also preventing lymphatic spillage of cancer cells.[26] Our results demonstrate that extended D3 volume dissection can provide a better chance for R0 resection in stage III colon cancer (29 patients with D3-RDN vs. 13 with D3-RDP).

Our results demonstrate a projected OS/DFS of 72.9/73.1% for D3-RDN patients and a steady 6.7%[11] flow of

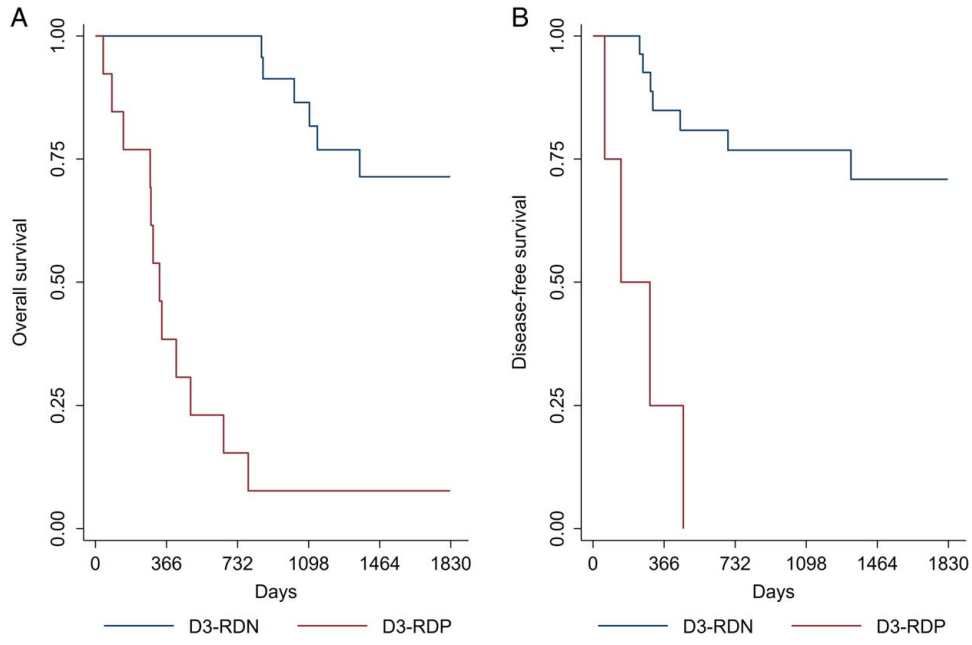

FIGURE 3. Kaplan Meier curves showing the 5-year overall survival and 5-year disease-free survival. A, Represents the overall survival. B, represents the disease-free survival. D3-RDP indicates residual disease positive; D3-RDN, residual disease negative.

D3-PNG patients through the years. The OS and DFS in our patient group differ substantially from what is found in the literature. The most recent publication states data on 16 patients (8.6% of 185 patients, LNR:0.3) with positive apical nodes and reports an OS of 35.0%[1] and DFS of 16.2%.[1] Liang et al reported DFS in 48 patients (19.6% of 244 patients) with positive apical nodes at 48% at 5 years.[5] Wang et al report on 28 patients (11% of 254 patients, LNR:0.21) with positive apical nodes reporting OS 64% and DFS 55%.[27] Banipal et al report 6 patients (6.9% of 87 patients, LNR:0.43) with OS and DFS at 50%, results from our ongoing trial from the initial period 2011 to 14 presented in Fig. 4.[11] Toyota reports OS among 8 patients (4% of 197) with positive apical nodes to be 32% in 1995.[6] What can be seen from this short literature overview is a large gap between the positive central node incidence rates when the apical node is used as a definition (4–19.6%), confirming our statement on the need to define the D3 volume, stated in the introduction. In this literature review, the LNR's and node numbers of the D3 volume are missing for comparison to our presented results (LNR was 0.4 while RDN had LNR: 0.29 and the RDP was 0.64). A comparison of these would enable a judgment of the completeness of the lymphadenectomy.

Patients undergoing surgery for cure (D3-RDN) had no 30 to 90-day mortality, while Clavien-Dindo III events occurred in 5/29 (3 anastomotic leaks 10.3%, 2 chylous ascites 6.9%), Chylous ascites occurred in the early phase of the study (2011–14) and became obscure after the implementation of a routine fat-free 3-day diet after surgery.[28] Intraoperative bleeding occurred in 4 (13.8%) patients (1 ICV, 2 SMV, 1 GTH). We have previously published relatively higher blood loss and operative time for open surgical access due to the complexity of the surgery.[13] The literature states that Clavien-Dindo III events occur up to 24.3%,[1,29] and 30 and 90-day mortalities are reported to be 5%[29] and 7%,[29] respectively. In comparison, in our study, D3-RDN had no 30 and 90-day mortalities. The literature shows anastomotic leak rates between 2.6% and 12,07% in right hemicolectomy.[3,30] In our series, 2 of the 3 leaks in the D3-RDN group occurred in the early phase of the study, while the third leak occurred in the third time period (2017–2019) of patient inclusion. The advanced stage of the disease and the condition of the patients in the D3-RDN group may contribute to the development of surgical complications.[13]

When high-quality and complex surgical procedures are a concern, there is a consensus that increasing surgical volume leads to improved results.[31] Our results show significant improvement in survival through the different time periods. Considering the steady flow of 6.7%[11] patients with D3 LNM and the complexity of the surgery, it seems beneficial to centralize treatment in fewer hands, where feasible. Recent publications[32,33] (at the level of hospital, patient, insurance company, and political level) show improvement in long-term oncological outcomes through centralization, even though the economic benefits are unclear.[32] Moreover, the increased number of patients gained through centralization would shorten the long learning curves presented in our article. We can add radiology as a priority among the long list of prerequisites in the literature on centralization. The radiologist can, through the improvement of the preoperative CT scan evaluation, effectively enable this task. Recent radiologic studies have shown a diagnostic accuracy of potential lymph node metastases of approximately 72%[34,35] of patients, while no data is found for the D3 volume. Persuading radiologists about the importance of the D3 volume would significantly help the diagnosis and, thus, the centralization, resulting in shorter learning curves and improved survival.

When closely analyzed, the D3-RDN group has only 1 patient with T1/T2 tumor that presented with a skip metastasis to the D3 volume. Most patients (18/29) were T3/T4 with N2 lymph node status; 3 received multi-organ resections (10.3%), while 3 had additional liver surgery (10.3%), and 1 was operated on for local lymph node recurrence (3.4%). All were referred to adjuvant chemotherapy, and 20/29 (69.0%) patients received sufficient adjuvant treatment. While the number of patients is small, it must be mentioned that of none of the 6 patients that developed recurrence survived, despite receiving sufficient chemotherapy. In contrast, of the nine patients that did not receive sufficient chemotherapy, 1 patient developed a solitary liver metastasis, which

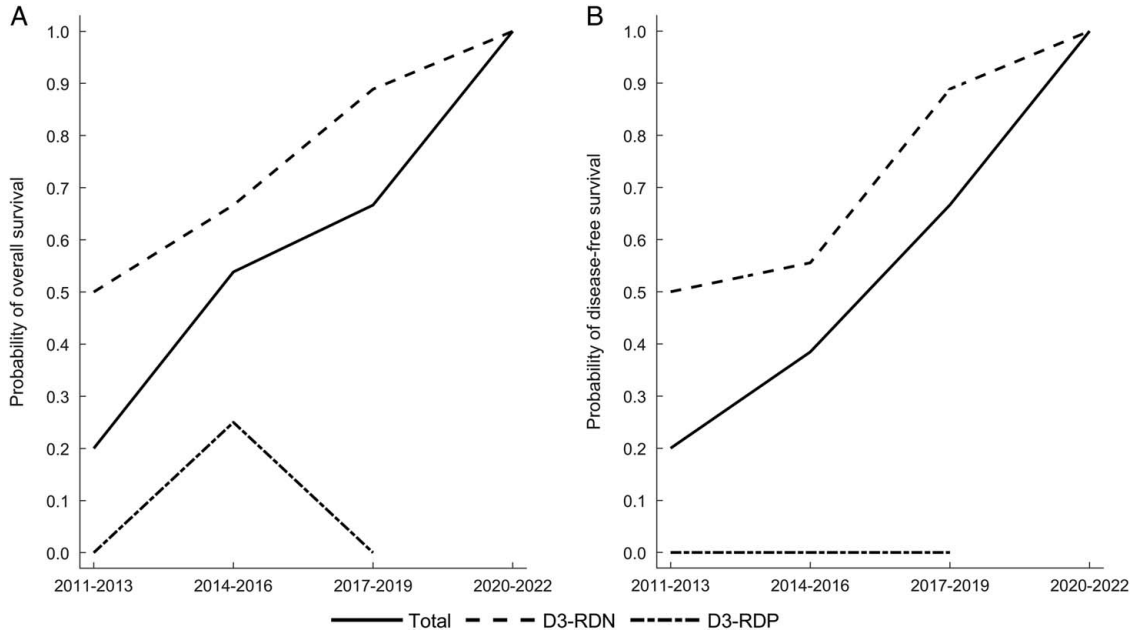

FIGURE 4. Graphical illustration of learning curves in different time periods in relation to 5-year overall survival and 5-year disease-free survival. A, Represents the probability of 5-year overall survival in different time periods. B, Represents the probability of 5-year disease-free survival in different time periods. D3-PNG indicates positive nodes in the D3 volume (Continued line); D3-RDN, residual disease negative (Long dotted line). D3-RDP, residual disease positive (Short dotted line).

was removed surgically, remaining recurrence-free, and alive at 5 years. Another patient developed recurrence in retroperitoneal lymph nodes and is alive at 5 years with the disease. Based on the findings of this study, it appears that improved surgery has led to a decrease in the number of widespread recurrences compared with earlier results. This could be because a clear definition of the central lymph nodes (D3 volume) allows for their complete removal in most patients, which decreases the likelihood of recurrence. When examining both the parallel progression theory[36,37] and the linear progression theory,[38,39] radical resection may have a therapeutic effect by removing occult metastatic lymph nodes, indicating that tumor biology plays a crucial role in the evolution of the disease.[40,41] Recent research has shown a relationship between the primary tumor immune response and lymph node yield, leading to better survival rates.[42]

When treating metastatic colon cancer patients with chemotherapy alone, recent publications present that a cure without salvage surgery might be possible for a small but important number of patients. The results show 1.1% to 10.8% long-term survivors and 0.4% to 2.2% of patients without evidence of disease or disease progression.[43,44] In contrast, stage III colon cancer patients routinely receive adjuvant chemotherapy after surgery. Murray et al[45] point out that patients without minimal residual disease have an excellent prognosis (87% DFS), comparable to our D3-RDN group of patients. Another view on the effect of chemotherapy highlights only a delay of recurrence in patients who have received adjuvant chemotherapy,[11,45,46] implying a more important role for D3 extended mesenterectomy. Our results (9 D3-RDN patients (31%) did not receive adjuvant chemotherapy because of comorbidity and/or toxicity, and 7 did not develop recurrence) also show that patients with positive nodes in D3 volumes can survive without adjuvant chemotherapy, indicating that they did not suffer from systemic disease, further supporting the significant role of tumor biology and the linear progression theory.

These results seem to enhance the value of extended mesenterectomy, demonstrating that the influence of personalized surgery on long-term survival should not be overlooked.

The strength of this work is the inclusion of consecutive patients in a prospective trial with long-term follow-up. Another strength is personalized surgery to the patient's individualized anatomy through 3D vascular reconstruction derived from the preoperative staging CT, in this manner allowing for the removal of all significant nodes (D3 volume defined to the patient´s anatomy). A clear 3D definition of the D3 volume was consistently used, and the D3 volume was removed from the specimen after surgery and analyzed separately. A limited number of surgeons following a strict surgical protocol performed the procedures. The most significant limitation and possible source of bias is the low number of patients (42) through the 12-year inclusion period due to a 6.7% incidence. Centralizing these patients would potentially lead to higher numbers and more valuable data.

CONCLUSION

The presence of LNM in the D3 volume of the right colon has been looked upon as a poor prognostic factor. Our results indicate that surgery can achieve survival in most patients through the removal of a personalized and anatomically defined D3 volume. The extent of mesenterectomy and the quality of surgery are paramount since a learning curve has demonstrated significant improvement in survival over time, despite the low number of patients in this study. These results also imply room for eventual centralization of this patient group where feasible.

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