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ORIGINAL ARTICLE

The Impact of a Multivisceral Resection and Adjuvant Therapy in Locally Advanced Colon Cancer

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Abstract

Background Multivisceral resection for locally advanced colon cancer is mandatory to achieve complete tumor resection. We aimed to determine if local multivisceral resections (LMR) for pT4 and pT3 tumors impact perioperative and long-term oncological outcomes.

Methods All stage II or III colon cancer patients who had surgery between 2004 and 2014 were identified. We analyzed patients with non-multivisceral resections (NMR) for pT4 tumors vs. pT4-LMR. In addition, outcomes were compared to both NMR and LMR pT3 patients.

Results LMR was performed in 55 (29.7%) of all patients with pT4 tumors and in 48 (8.9%) of all patients with pT3 tumors. The most commonly involved areas of extension were the abdominal wall and the small intestine. Transverse colon cancer was correlated with LMR. Morbidity rates were comparable between NMR and LMR, with the exception of higher rates of blood transfusion and postoperative ileus. Over one third of all pT4-NMR patients developed recurrent disease, which was higher compared to all other groups. Subsequently, overall and disease-specific survival, as well as disease-free survival (DFS), was worse for pT4-NMR, even after adjustment for pTN-staging, adjuvant therapy, and R0 resection. Furthermore, when analyzing only curative resections, radial margin < 1 cm along with nodal disease was independent predictor for worse DFS. Long-term outcomes were comparable between pT4-LMR and pT3 patients.

Conclusions Multivisceral resection for locally advanced colon cancer preserves long-term oncological outcomes without increased postoperative morbidity. Moreover, LMR in pT3 tumors does not contribute to postoperative morbidity. Our study underlines the feasibility and importance of performing LMR when locally advanced cancer is suspected.

Keywords Colon cancer · Surgery · Tumor invasion · Multivisceral resection · Morbidity · Survival

Introduction

Colon cancer is one of the most common cancers worldwide, with an estimate of almost 100,000 new patients every year in the USA.[1] Approximately 10% of all primary colon cancer patients have contiguous involvement of adjacent organs at initial presentation, which is classified as locally advanced disease or pathological T4 tumors (pT4).[2,3] An R0 resection in these tumors is mandatory to achieve the best long-term outcomes, and therefore, a local multivisceral resection (LMR) is recommended when tumors invade adjacent organs.[4–6] Depending upon the location of the tumor, surgical treatment ranges from en bloc resection of involved organs in the upper abdomen to a pelvic exenteration.

Despite increased survival rates after LMR, the vast majority of the patients with locally advanced colon cancer do not receive an extended resection. Previous literature demonstrated that only 26–39% of patients with locally advanced colorectal cancer underwent a multivisceral resection.[7] Surgeons may be reluctant to perform a LMR because of the associated morbidity. Complication rates around 22–36% have been

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described after LMR for colon cancer,[5,8,9] though there was substantial heterogeneity within studies. In addition, despite improvement in imaging techniques, it is not always clear preoperatively that LMR is required and therefore the decision to perform LMR often must be made intra-operatively. Furthermore, distinguishing oncological invasion from peritumorous inflammatory adhesions is often hard to discern and makes the intra-operative decision to perform an extended resection even more difficult.

In addition to complete surgical resection, adjuvant treatment plays an important role in locally advanced colon cancer. In node-positive disease, postoperative chemotherapy is clearly established and previous research has shown benefit in overall and disease-free survival.[10,11] Additional treatment is therefore recommended for all patients with stage III disease operated on with curative intent.[12] This recommendation is less clear in stage II disease. Despite multiple clinical trials and meta-analyses over the past decades, the beneficial role of adjuvant chemotherapy in node-negative disease remains controversial. Several high risk factors have been introduced into the current guidelines, including T4 tumors. According to the NCCN guidelines, adjuvant chemotherapy can be considered for patients with high-risk features.

To assess the impact of LMR and R0 resections in locally advanced colon cancer, we evaluated the short- and long-term outcomes in patients with pT4 colon tumors who either did or did not undergo a multivisceral resection and additionally compared them to less advanced disease (T3). In order to evaluate whether a LMR compromises morbidity rates, patients who were thought clinically to be invasive or adhesive though not confirmed on pathology (T3) were assessed as well as another comparison group.

Materials and Methods

Study Design and Population

We performed a retrospective analysis using a prospectively maintained database including all patients who had surgical treatment for primary colon cancer between January 2004 and December 2014 at Massachusetts General Hospital. This study was approved by the Institutional Review Board. A total of 773 patients underwent surgery for AJCC stage II or III, pT3–4 colon cancer during our study period. The majority had a pT3 tumor (562 patients had a pT3 tumor), 161 patients had a pT4a tumor, and 50 patients a pT4b tumor. A multivisceral resection was performed in 117 patients, mostly for pT4 tumors (56.4%). Patients who were deemed unresectable were excluded, including palliative cases ($n = 2$) and patients who presented with bowel perforation ($n = 22$). To compare oncologic outcomes in pT3–4 tumors, patients who received neoadjuvant treatment ($n = 10$) and patients who died within 30 days of surgery ($n = 14$) were additionally excluded, leaving a total of 725 patients for subsequent analyses (Fig. 1). We subdivided our cohort into four groups: patients with a pT3 tumor who either did (pT3-LMR) or did not (pT3-NMR) receive a multivisceral resection and patients with a pT4 tumor who did (pT4-LMR) or did not undergo (pT4-NMR) a multivisceral resection.

The following data was prospectively obtained for each patient: patient demographics, comorbidities, pathological features, and both short- and long-term outcomes. Locoregional recurrence was defined as recurrent disease within the original tumor bed (perianastomotic, peritoneum, retroperitoneum, and pericolic mesenteric lymph nodes),[13,14] while distant recurrence included all recurrent disease at non-regional sites, such as the liver or lung. Data on long-term outcomes were updated periodically by reviewing patient's records and the Massachusetts General Hospital cancer registry. In case this information was not recently updated, the Social Security Death Index was used for survival data. According to the NCCN guidelines, routine pre-operative work-up was completed for all patients. This included physical examination, total colonoscopy (unless an obstruction was the case), abdominal computed tomography (CT), chest X-ray, complete blood count, and carcinoembryonic antigen (CEA). An anesthetic consultation was carried out to determine the American Society of Anesthesiologist score (ASA). In addition, adjuvant chemotherapy was recommended for all patients with lymph node-positive disease and considered for stage II patients with high-risk features (T4 tumors, poorly differentiated histology, vascular invasion, perineural invasion, < 12 lymph nodes examined, bowel obstruction, or positive or indeterminate margins). The decision whether or not to administrate additional treatment was made on an individual basis, regardless of the tumor stage.

Local multivisceral resection was defined as en bloc resection of the primary tumor with adjacent organs or tissues. There were no patients who had direct invasion into the liver. Laparoscopic surgery was introduced before 2004 and therefore used throughout our study period. Short-term morbidity was classified as all complications within 30 days of surgery.

Statistical Analyses

Differences in baseline characteristics and outcome variables between the groups were analyzed using a chi-square test (χ^2). Continuous data were compared using the Kruskal-Wallis test and presented as the mean with standard deviation or the median with an interquartile range according to the distribution (Kolmogorov-Smirnov and Shapiro-Wilk test). Post-hoc adjusted comparisons were performed with Bonferroni correction to decrease the chance of incorrect rejection of the null hypothesis due to multiplicity. A Dunn's test was used after a Kruskal-Wallis test was rejected. Survival analyses were

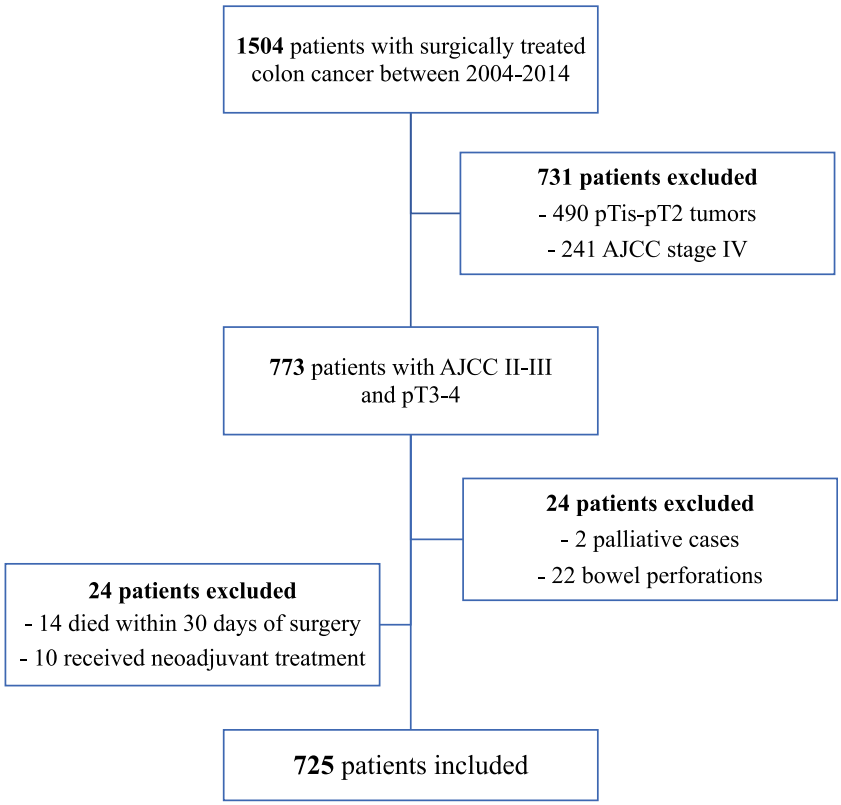

Fig. 1 Inclusion flowchart of the study

determined using the Kaplan-Meier method, and the differences between curves were assessed by the log-rank test. Cox proportional hazard models were used to determine the impact of multivisceral resection on oncologic outcomes, adjusted for potential confounders. A two-sided P value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.).

Results

Baseline Characteristics

The study population consisted of 725 patients with a mean age of 69.4 years. A total of 540 patients (74.5%) had a pT3 tumor of whom 48 (8.9%) underwent a LMR. During the study period, 29.7% of patients with a pT4 tumor underwent a LMR. In patients with pathologically proven T4b disease, 66.0% underwent LMR, compared to 20.5% of all T4a tumors. Of the latter group, all the patients who had clinical T4b tumors (5.5%) underwent LMR. We also noted a slight increase in the number of LMR performed over the time of our study period. In particular, 38.8% of all LMR resections and 40.0% of LMR in pT4 tumors were performed in the latter third. The main reason a multivisceral resection was not performed in cases where the tumor was found to invade adjacent organs (pT4b) was when surgeons encountered adhesions which were thought to be inflammatory (58.3%) and actually were microscopically invasive on pathology (33.3%). None of the pT4b-NMR procedures were emergent cases, and palliative cases were excluded beforehand.

R0 resection was achieved in almost all T3 tumors (NMR 99.4%, LMR 95.8%), whereas rates of tumor free margins were significantly lower in T4 tumors (NMR 70.8%, LMR 89.1%) ($P < 0.001$). All incomplete resections, regardless of pT-stage, had positive radial margins. Transverse colon tumors were proportionally the most frequent in the LMR group (17.5%) (Fig. 2). The most involved organs were the abdominal wall (41.7%), small intestine (31.1%), reproductive organs (8.7%), and the bladder (6.8%). When analyzing the site of LMR by pT-stage, we found a higher frequency of small bowel resection in pT4b tumors (48.1%) compared to both pT4a (25.0%) and pT3 (25.0%) tumors. The latter two had more en bloc resections of the abdominal wall (46.4% and 52.1%, respectively, vs 37.0% in pT4b). Baseline characteristics demonstrated significant difference in BMI, pre-operative CEA, and clinical presentation between the groups (Table 1). Post-hoc adjusted analysis with Bonferroni correction revealed that pT3-NMR patients had a significant higher BMI compared to pT3-LMR patients (mean 27.3 vs 24.8 kg/m^2, $P = 0.003$). Patients who underwent LMR presented more often with abdominal pain ($P < 0.001$), without any

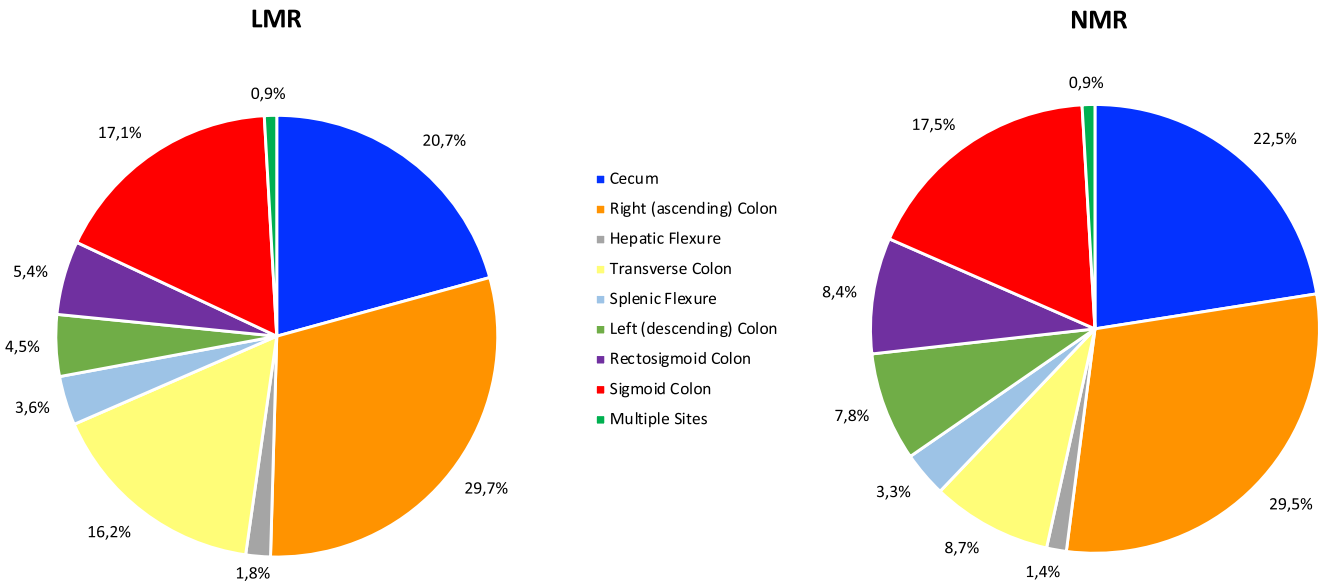

Fig. 2 Primary tumor location in LMR and NMR patients

differences neither in urgent admissions nor in related symptoms, including changes in stool habit, constipation, or bowel obstruction. Differences in pre-operative CEA within the groups were not significant after Bonferroni correction.

With regard to pathologic outcomes, the incidence of lymph node-positive disease was different between the groups with significantly more stage III patients in the pT4-NMR cohort compared to pT3-NMR ($P < 0.001$). Patients who underwent a LMR had larger tumors than NMR patients, regardless of the T-stage (pT3 $P = 0.005$; pT4 $P < 0.001$). The surgical specimen was, as would be expected, larger, though colonic specimen length was comparable between the groups ($P = 0.541$). Although lymph node yield was higher after pT4-LMR, the difference compared to pT4-NMR was not significant after correction ($P = 0.257$). Moreover, the vast majority in all groups had more than 12 lymph nodes retrieved. Concerning histopathological risk factors, both extramural vascular and lymphovascular invasion as well as perineural invasion were more often identified in pT4 tumors ($P < 0.001$, $P = 0.034$, $P < 0.001$, respectively).

Perioperative and Short-Term Outcomes

Table 2 demonstrates differences in perioperative outcomes and morbidity rates. Surgical approach was significantly different between the groups ($P = 0.024$), with more laparoscopic surgery in the pT3-NMR group (34.1%). Duration of surgery was longer when a multivisceral resection was performed ($P < 0.001$) and also significantly longer in pT4-LMR cases compared to pT3-LMR ($P < 0.001$). Short-term outcomes were worse for patients who underwent a LMR, with significantly longer length of stay ($P < 0.001$) and a higher requirement for blood transfusion ($P < 0.001$). In addition, the overall morbidity rate (excluding the need for blood transfusion) was higher in pT4-LMR patients compared to pT4-NMR patients, which was mainly explained by more postoperative ileus (20.0% vs 7.7%, $P = 0.064$). Rates of readmission and reoperation were not different.

Long-Term Oncological Outcomes

Mean follow-up duration in the study was 48.5 months and significantly shorter in the pT4-NMR group compared to pT3-NMR (35.8 vs 51.6 months, $P = 0.001$) (Table 3). In line with the current guidelines, we found higher rates of adjuvant chemotherapy in pT4 tumors ($P < 0.001$) with a significant difference in node-negative disease ($P < 0.001$) but not in stage III ($P = 0.065$). No differences within the pT4 cohort or in the pT3 cohort were found regarding postoperative treatment. As demonstrated in our results, not all patients with node-positive disease or T4 tumors received additional treatment. In stage II, the main reason to forgo further treatment was age. The median age of patients with stage II disease and T4 tumors who did not receive adjuvant treatment was 78.2 years compared to 63.2 years in the adjuvant T4 group ($P < 0.001$). Furthermore, 17.7% of all eligible T4 stage II patients declined further treatment. With regard to stage III disease, 25.2% of all patients who did not receive adjuvant chemotherapy declined treatment (T3 20.6%, T4 34.4%). Similar to the node-negative cohort, median age was significantly higher in the non-adjuvant group (81.3 years vs. 62.2 years, $P < 0.001$).

While disease recurrence occurred as often in patients with pT4-LMR compared to pT3 tumors, we found a significantly higher rate in pT4-NMR patients compared to less advanced disease ($P < 0.001$). This was especially true when analyzing locoregional recurrence only ($P < 0.001$). In the majority of

Table 1 Baseline characteristics

	NMR pT3 492 (67.9%)	LMR pT3 48 (6.6%)	NMR pT4 130 (17.9%)	LMR pT4 55 (7.6%)	*P* value
Age	70.0 (57.7–79.8)	69.5 (62.6–81.2)	67.0 (59.9–80.2)	68.1 (58.9–83.2)	0.717
Gender, male	48.6	47.9	43.1	36.4	0.287
ASA	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.448
BMI	27.3 (23.6–30.8)	24.8 (21.9–27.4)	25.2 (22.7–30.6)	25.7 (21.4–29.5)	0.001^{β}
Prior abdominal surgery	45.3	47.9	40.8	43.6	0.774
Pre-operative CEA*	2.9 (1.6–5.9)	3.6 (2.0–13.6)	4.0 (2.3–6.5)	4.3 (2.0–16.7)	0.032
Symptoms					
Anemia	29.3	33.3	33.1	32.7	0.784
Abdominal pain	25.0	45.8	30.0	54.5	$< 0.001^{\alpha\beta\gamma}$
Pathology					
Nodal disease	39.6	41.7	56.9	50.9	0.003^{δ}
Tumor size (cm)	4.5 (3.5–6.0)	5.9 (4.1–7.4)	4.5 (3.7–6.0)	7.0 (4.5–9.5)	$< 0.001^{\alpha\beta\gamma}$
Colonic resection length (cm)*	21.5 (16.5–27.0)	22.0 (16.7–32.8)	21.0 (15.3–29.1)	21.0 (17.0–30.5)	0.541
Lymph-node harvested	21 (16–29)	23 (16–31)	21 (17–28)	25 (18–33)	0.042^{γ}
LN > 12	91.5	91.7	93.8	98.2	0.300
Poor differentiation	18.9	27.7	25.8	25.9	0.443
EMVI	18.3	20.8	37.7	41.8	$< 0.001^{\gamma\delta}$
LVI	46.7	39.6	68.5	61.8	0.001^{δ}
Perineural invasion	18.0	12.5	41.5	38.2	$< 0.001^{\gamma\delta}$
R0 resection	99.4	95.8	70.8	89.1	$< 0.001^{\alpha\gamma\delta}$
Site of tumor					0.074
Right-sided	55.7	54.2	51.5	54.5	
Transverse	7.7	14.6	12.3	20.0^{γ}	
Left-sided	10.6	8.3	15.4	9.1	
Sigmoid	26.0	22.9	20.8	16.4	

Proportions are presented for categorical data, median with IQR for continuous data

ASA American Society of Anesthesiologists, *BMI* body mass index (kg/m^2), *AJCC* American Joint Committee on Cancer, *EMVI* extramural vascular invasion, *LVI* lymphovascular invasion

*Missing data: CEA, $n = 415$; resection length, $n = 717$

$^{\alpha}$ pT4 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\beta}$ pT3 NMR vs pT3 LMR: $P < 0.05$ after Bonferroni correction

$^{\gamma}$ pT3 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\delta}$ pT3 NMR vs pT4 NMR: $P < 0.05$ after Bonferroni correction

these cases, the location of recurrence was the peritoneum (53.3%) followed by the retroperitoneum (30.0%) and mesenteric lymph nodes (16.7%). When analyzing only patients who underwent an R0 resection, risk ratios of disease recurrence, both locoregional and distant, remained higher in the pT4-NMR group compared to pT4-LMR (local RR 1.47 (0.7–3.06), distant RR 1.81 (0.89–4.07)). A difference in median circumferential (radial) margin in patients who developed local recurrence was found between the pT4 groups (pT4-NMR median 0.6 cm (0.2–4.3) vs. pT4-LMR median 4.8 cm (0.6–5.9), $P = 0.061$). Furthermore, rates of overall and colon cancer mortality were higher in the pT4-NMR group compared to pT4-LMR (overall mortality 48.5% vs. 34.5%, $P = 0.328$, colon cancer mortality 26.9% vs. 10.9%, $P = 0.068$). Survival outcomes were significantly worse after pT4-NMR compared to less advanced disease, whereas rates were comparable between pT4-LMR and T3 disease.

The poor prognostic outcomes were underlined by log-rank testing. Kaplan-Meier survival curves demonstrated significant differences in overall (OS), disease-specific (DSS), and in disease-free survival (DFS), regardless of accomplishment of clear tumor margins (all $P < 0.001$) (Fig. 3). When comparing differences between the groups, we found significantly poorer outcomes after pT4-NMR compared to all other groups in both overall (vs pT4-LMR $P = 0.020$, vs pT3-NMR $P < 0.001$, vs pT3-LMR $P = 0.036$) and colon

Table 2 Perioperative and short-term outcomes

	NMR pT3	LMR pT3	NMR pT4	LMR pT4	*P* value
Intraoperative					
Operation after July 2009	49.8	58.3	51.5	50.9	0.725
Surgery duration (min)	120 (73–171)	164 (122–236)	109 (67–174)	170 (105–255)	$< 0.001^{\alpha\beta\gamma}$
Laparoscopic approach	34.1	22.9	26.2	18.2	0.024
Conversion to open surgery	4.9	10.4	1.5	7.3	0.071
Admission					
Admission duration	4 (3–7)	7 (4–11)	4 (3–6)	7 (5–10)	$< 0.001^{\alpha\beta\gamma}$
In-hospital morbidity	25.6	27.1	20.8	41.8	0.029^{α}
Morbidity rate plus transfusion	39.4	62.5	33.8	69.1	$< 0.001^{\alpha\beta\gamma}$
Ileus	10.2	16.7	7.7	20.0	0.046
Wound infection	6.1	2.1	3.1	3.6	0.354
Anastomotic leakage	1.6	4.2	3.1	1.8	0.534
Blood transfusion	19.1	43.8	17.7	41.8	$< 0.001^{\alpha\beta\gamma}$
Cardiac	7.7	6.3	3.8	14.5	0.085
Respiratory	3.9	4.2	2.3	3.6	0.857
Renal failure	2.2	4.2	1.5	0.0	0.484
ICU transfer	2.0	4.2	2.3	5.5	0.392
Readmission	7.1	6.3	5.4	5.5	0.886
Reoperation	1.8	4.2	1.5	1.8	0.705

Proportions are presented for categorical data, median with IQR for continuous data

$^{\alpha}$ pT4 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\beta}$ pT3 NMR vs pT3 LMR: $P < 0.05$ after Bonferroni correction

$^{\gamma}$ pT3 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\delta}$ pT3 NMR vs pT4 NMR: $P < 0.05$ after Bonferroni correction

cancer-specific survival ($P = 0.007$, $P < 0.001$, $P = 0.018$, respectively) as well as significantly worse DFS ($P = 0.034$, $P < 0.001$, $P = 0.010$, respectively). Nevertheless, patients with pT4 tumors who underwent LMR had comparable outcomes to patients with less advanced disease. The significantly poorer outcomes in patients with locally advanced cancer who did not undergo a multivisceral resection also withstood multivariate analysis, as shown in the Cox proportional hazard models adjusted for pT-stage (subdivided into pT3, pT4a, and pT4b), pN-stage, adjuvant chemotherapy, and R0 resection (Fig. 4). Compared to patients with a pT4 tumor who did undergo a multivisceral resection, pT4-NMR patients had a 72% increase in the relative hazard of overall survival (HR 1.72, 95% CI 1.02–2.90, $P = 0.041$) and almost threefold higher hazard ratios in the disease-specific survival model (HR 3.36, 95% CI 1.40–8.09, $P = 0.007$). Moreover, DFS remained significantly worse after adjustment (HR 2.47, 95% CI 1.21–5.03, $P = 0.013$). In addition to surgical approach, node-positive disease and clear tumor margins were independent predictors in all three models. Adjuvant chemotherapy was only predictive in overall survival. When adjusting for radial margin instead of radical resection, pT4-NMR was no longer a poor predictor for DFS. Radial margin < 1 cm (HR 2.03, 95% CI 1.16–3.53), $P = 0.013$) was along with node-positive disease (HR 2.64, 95% CI 1.86–3.74, $P < 0.001$) independently predictive for poor DFS.

Discussion

There is clear evidence that an R0 resection is a strong predictor for both overall and disease-free survival in colon cancer.[5,15] A recent single-center study compared R0 with R1 resection in colon cancer and found a recurrence rate of 18.9% and 55.5%, respectively, with a corresponding 5-year survival of 60% and 25%.[16] However, R0 resection is more challenging to achieve if the tumor invades adjacent organs, which is the case in approximately 10% of all primary colon cancers. Multivisceral resection is then necessary to achieve complete tumor resection with negative margins. Although there is widespread knowledge of the importance of R0 resection, a recent population analysis demonstrated that the vast majority of the patients with locally advanced colon cancer did not receive LMR.[7] Our study underscored the problem of infrequently performed LMR for locally advanced colon cancer with a performance rate of 29.7%. In our cohort, the main

Table 3 Long-term oncological outcomes

	NMR pT3	LMR pT3	NMR pT4	LMR pT4	*P* value
Follow-up duration (months)	51.6 (25.1–81.9)	47.9 (22.7–70.2)	35.8 (16.3–59.4)	49.2 (22.5–82.8)	0.001^{δ}
Recurrent disease	16.2	16.7	36.2	18.9	$<0.001^{\delta}$
Locoregional	5.1	8.3	21.5	14.5	$<0.001^{\delta}$
Distant	13.0	12.5	22.3	10.9	0.046^{δ}
Adjuvant therapy	35.0	27.1	56.2	60.0	$<0.001^{\delta}$
Stage II	10.4	14.3	44.6	48.1	$<0.001^{\gamma\delta}$
Stage III	73.3	45.0	67.6	71.4	0.065
Deceased	25.2	31.3	48.5	34.5	$<0.001^{\delta}$
Deceased after R0	24.9	28.3	45.7	28.6	0.001^{δ}
Colon cancer mortality	7.1	10.4	26.9	10.9	$<0.001^{\delta}$
Colon cancer mortality after R0	6.7	8.7	23.9	6.1	$<0.001^{\alpha\delta}$
5-year overall survival	78.6	63.3	46.3	70.0	<0.001*
5-year OS after R0	78.9	66.2	46.2	75.0	<0.001*
5-year disease-specific survival	92.8	85.3	67.2	89.6	<0.001*
5-year DSS after R0	93.4	87.2	67.7	92.7	<0.001*
5-year disease-free survival	82.8	81.9	52.7	74.1	<0.001*
5-year DFS after R0	83.2	81.9	53.2	78.1	<0.001*

Proportions are presented for categorical data, median with IQR for continuous data

*Log-rank test

$^{\alpha}$ pT4 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\beta}$ pT3 NMR vs pT3 LMR: $P < 0.05$ after Bonferroni correction

$^{\gamma}$ pT3 NMR vs pT4 LMR: $P < 0.05$ after Bonferroni correction

$^{\delta}$ pT3 NMR vs pT4 NMR: $P < 0.05$ after Bonferroni correction

reason to not perform a multivisceral resection was not reluctance of the surgeon, but a false discernment of oncological invasion as periinflammatory adhesions. An increase in LMR was seen over the study period, in particular in the latter third, which accounted for 40% of all multivisceral resections in locally advanced cancer. Perhaps more importantly, the majority of patients with pT4b tumors received LMR (66.0%) while the incidence of en bloc resections in tumors that did not invade the serosal surface on pathology was much lower (pT4a 20.5%; pT3 8.9%).

The benefit of LMR in locally advanced colon cancer was emphasized by our study with significantly better long-term outcomes in pT4-LMR patients compared to pT4-NMR patients and comparable oncologic outcomes to patients with less advanced disease. Overall survival, colon cancer mortality, and disease-free survival were all worse in pT4-NMR patients compared to pT4-LMR, even after adjustment for potential confounders including pTN-stage, adjuvant therapy, and the achievement of R0 resection. The estimated 5-year OS and DSS in our study was 70.0% and 89.6% when a

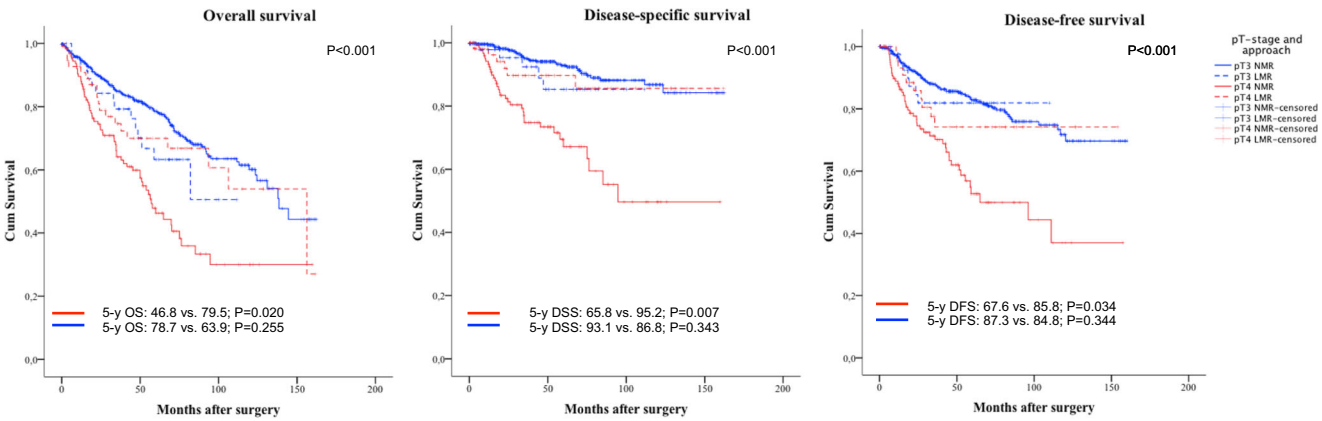

Fig. 3 Kaplan-Meier survival curves

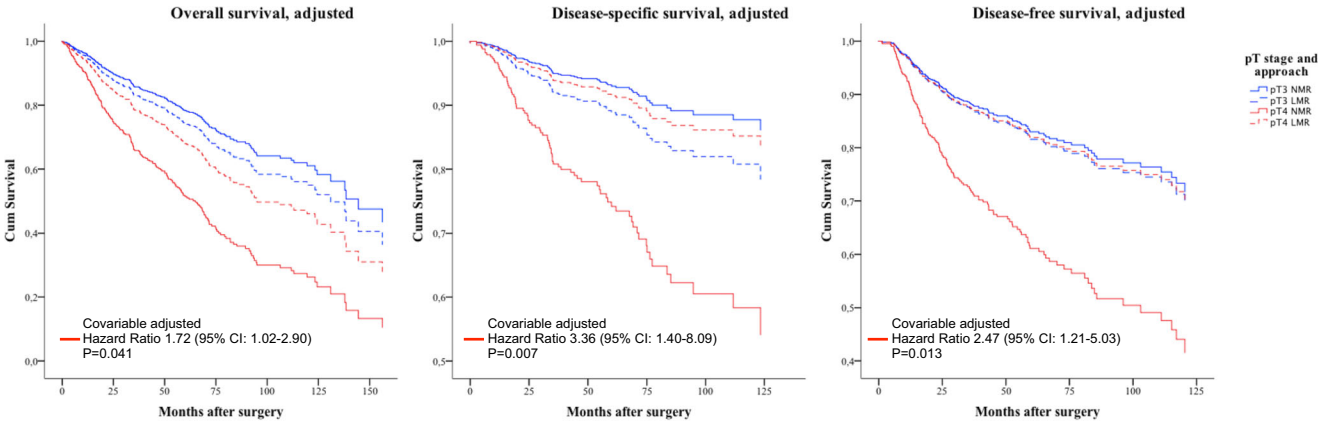

Fig. 4 Multivariate Cox proportional hazards survival estimates. Covariables included baseline pT-stage (subdivided into pT3, pT4a, pT4b) pN-stage, adjuvant chemotherapy, and R0 resection

multivisceral resection was performed in pT4 disease. These outcomes were comparable to previous reported outcomes[9,17] and even more notably, comparable to patients with less advanced disease and no tumor invasion (78.6%, 92.8%, respectively). On the contrary, when a patient with true tumor invasion did not receive LMR, both OS and DSS were significantly worse (46.3%, 67.2%). This poor prognosis remained true in the Cox proportional hazard models, including almost threefold higher ratios of colon cancer mortality compared to pT4-LMR (HR 3.36, $P = 0.007$).

In terms of disease-free survival, poorer outcomes were mainly explained by a higher rate of locoregional recurrence particularly the peritoneum, where the majority of recurrent disease was located. Despite free tumor margins, locoregional recurrence remained higher in patients with pT4 tumors who did not undergo a LMR. A possible explanation could be the limited circumferential clearance, which was less than 1 cm in pT4-NMR patients who developed locoregional recurrence. Although the impact of radial margin clearance is extensively investigated for rectal cancer and has been demonstrated to be a poor prognostic factor, the outcomes in colon cancer are less well detailed. The extent of a curative resection for colon cancer generally includes a proximal and distal margin of ≥ 5 cm.[18,19] However, knowledge about accurate circumferential margins in colon rectal cancer is lacking, other than recommendations to assess the radial margin in the current guidelines[12] and reported poor prognostic outcomes in patients with colon cancer and positive radial margins.[20] Our study demonstrated that a radial margin of less than 1 cm was independently predictive for disease recurrence, in particular locoregional recurrence. Additionally, lymph node-positive disease remained associated with worse outcomes after adjustment, which is in line with previous studies.[21] Because of the established risk factor of lymph node status in colon cancer, adjuvant therapy is highly recommended.[12] However, adjuvant therapy was only predictive for overall survival in the Cox proportional hazard model, which suggests that achieving accurate clearance of all tumor margins by LMR has a greater impact on disease-specific survival and recurrence than could be realized by postoperative therapy. Nonetheless, the number of patients that received additional treatment should be taken into account. In accordance with current guidelines, the administration of adjuvant therapy was higher in node-negative disease. However, about one third of all stage III patients did not receive additional treatment mainly because of older age.

Despite our promising results, 34% of the patients with true tumor invasion on pathology did not receive a LMR. In the majority of those cases, invasion was misinterpreted as inflammatory adhesions. The problem remains that it is difficult to discern between true invasion and inflammatory adhesions. In our study, only 49.1% of all T4-LMR tumors had pathologic confirmed invasion. A multivisceral resection might not have been necessary in the remaining 50.9% of T4 tumors to achieve a complete resection. Since it is not possible to make this distinction through imaging, as of yet, the decision is based on a surgeon's perspective only.

Several factors may play an important role in the decision whether or not to perform an extended resection. First is the associated morbidity after a multivisceral resection. A recent systematic review reported a mean complication rate of 41.5% after multivisceral resections, which was significantly higher than the previously described morbidity rate of 20–30% after surgery for colon cancer in general.[22] Morbidity rates in our study were in line with the systematic review by Longo et al., with higher complication rates compared to standard procedures. Nonetheless, this significant difference was mainly explained by a higher requirement of blood transfusion and more postoperative ileus. Differences in surgical approach and a longer operation duration in LMR cases might have led to these outcomes since open surgery is correlated with the need for blood transfusion and postoperative ileus. Additionally, a prolonged operative time is known to be a risk factor for ileus.[23–25] Other than these two factors, postoperative

complications were comparable as were readmission and re-operation rates when comparing LMR to NMR. This underscores the safety of a multivisceral resection.

Previous studies found several baseline factors between patients who did and did not receive LMR, though disparities in our study were practically non-existent. One might assume that surgeons are reluctant to perform LMR in older patients with more comorbidities. Even though age per se is not a contraindication for more extensive surgical procedures, elderly patients are often deprived of aggressive surgical treatment.[7,26] Our study did not support this theory with a similar distribution of both age and ASA score over all four groups. Nevertheless, patient's age was one of the reasons to forgo adjuvant therapy which might be considered as an incomplete treatment, in particular when an R0 resection is not achieved.

The inability to distinguish oncologic invasion from inflammatory adhesions is a well-known problem. These adhesions are often hard to discern from true tumor invasion,[17,27] subsequently leading to compromised oncological outcomes when oncological invasion is misinterpreted as inflammatory adhesions. Nonetheless, achieving R0 resection with accurate tumor clearance remains most important. This is underlined by our study, demonstrating significantly poorer outcomes in terms of both disease recurrence and survival in patients with pT4 tumors who did not receive a multivisceral resection. On the other hand, when LMR was performed in T4 patients, oncologic outcomes were practically similar to those patients with less advanced disease. Furthermore, in patients with clinical tumor invasion but T3 disease on pathology, LMR does not compromise short-term outcomes as morbidity rates are comparable with NMR patients. Therefore, a resection with wide margins is recommended and should be the standard of care when tumor invasion is expected.

The limitations of this study are inherent to the retrospective design and the tertiary setting of our institute. The latter affects the generalizability of our results as patient and disease characteristics may differ from patients in non-referral centers. Furthermore, it is difficult to determine resectability in hindsight, since this may differ between surgeons and may change over time. Nevertheless, this study presents one of the few analyses of both short- and long-term outcomes in patients who did or did not receive LMR for true tumor invasion in colon cancer and in addition evaluates the potential harm of a LMR in patients who did not warrant it.

Conclusion

Our study confirms the importance of LMR in patients with extracolonic extension. Patients with pT4 colon cancer who did not receive LMR had significantly worse prognosis in terms of disease recurrence and survival, even after adjustment for staging, adjuvant therapy, and R0 resection. The additional impact of adjuvant chemotherapy on oncologic outcomes was only confirmed on overall survival, which underlines the importance of clear tumor margins by LMR on disease-specific survival and recurrence. Furthermore, when LMR was performed in pT4 colon cancer, long-term outcomes were practically similar to patients with less advanced disease. Postoperative morbidity was comparable between both LMR and NMR groups, with the exception of a higher requirement of blood transfusion and more frequent postoperative ileus. This emphasizes the safety and feasibility of a multivisceral resection and supports the decision to perform LMR in all cases when locally advanced cancer is suspected.

Authors' Contribution All authors have contributed to this manuscript in the following way: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data. Furthermore, all authors drafted or revised the manuscript critically for important intellectual content. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with Ethical Standards

This study was approved by the Institutional Review Board.

Conflict of Interest The authors declare that they have no conflict of interest.

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