Abdominal lymph node recurrence from colorectal cancer: Resection should be considered as a curative treatment in patients with controlled disease

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Short title:

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ABSTRACT (word count=250)

Background: Lymph node recurrences (LNR) from colorectal cancer (CRC) still represent a therapeutic challenge, as standardized recommendations have yet to be established. The aim of this study was to analyze short- and long-term oncological outcomes following resection of LNR from CRC.

Methods: All patients with previously resected CRC who underwent histopathologically confirmed LNR resection in 3 tertiary referral centers between 2010 and 2017 were reviewed. Short- and long-term outcomes were analyzed, mainly recurrence-free and overall survival. Further recurrences following LNR resection were also analyzed.

Results: Overall, 18 patients were included. Primary CRC was left-sided in 16 (89%) patients, staged T3-4 in 15 (83%), N+ in 14 (78%) and presented with synchronous metastases in 8 (43%). Median time interval between primary CRC and LNR resections was 31 months. Performed lymphadenectomies were aortocaval (n=10), pelvic (n=7), in hepatic pedicle (n=3) and mesenteric (n=1). Four patients had associated liver metastases resection. Three (17%) presented with postoperative complications, of which one Clavien-Dindo 3. Fourteen (78%) patients presented with further recurrences after a mean delay of 9 months, with 36% of patients presenting with early (<6 months) recurrence. Five (36%) patients could undergo secondary recurrence resection and 3 (21%) patients radiotherapy. Median overall survival following LNR resection reached 44 months.

Conclusions: Current results suggest that LNR resection is feasible and associated with improved survival, in selected patients. Longer time interval

between primary CRC resection and LNR occurrence appeared to be a favorable prognostic factor whereas multisite recurrence appeared to be associated with impaired long-term survival.

INTRODUCTION

Despite a constant progress in therapeutics and screening resulting in improved survival (**1**), colorectal cancer (CRC) remains one of the most common cancers worldwide and a public health concern (**2**). Yet, among patients diagnosed with CRC, 50% to 60% develop metastases. These mostly affect the liver (**3**) and are synchronous (14-18%) (**4**) or metachronous sometimes in spite of adjuvant therapy for locally advanced disease (**5-8**). Among other metastatic sites, retroperitoneal lymph nodes represent the initial recurrence location in only 2% to 6% of patients (**7,9-11**), after an estimated time interval ranging between 23 and 28 months (**11,12**).

While the management of CRC liver and pulmonary metastases has become standardized (**13,14**), the treatment of lymph node recurrence (LNR) (isolated or associated with other lesions) remains unclear; Some authors have distinguished local from retroperitoneal LNR (**12,15**) and complex protocols have been proposed (**16**) although none is currently fully validated and adopted. An increasing trend toward surgery with curative intent has been observed in patients presenting with controlled retroperitoneal LNR (**11,17-19**), but with the absence of consensus, a clear indication regarding LNR resection has yet to be defined. The present series therefore aimed to retrospectively analyze patients who underwent surgical resection of LNR from CRC with curative intent, with emphasis on short- and long-term results of this therapeutic option.

PATIENTS AND METHODS

Patient's selection

Between January 2010 and December 2017, all consecutive patients who presented with intra-abdominal or retroperitoneal CRC LNR and underwent resection with curative intent, at three institutions (Avicenne Universitary Hospital, Assistance Publique – Hôpitaux de Paris, University Paris XIII, Bobigny, France; Tours university hospital, Tours, France; Institut Mutualiste Montsouris, Paris, France), were included for the purpose of this study. The decision for LNR resection was proposed by a multidisciplinary board that included surgeons, medical oncologists and radiologists, when the overall surgical strategy could complete tumor resection (LNR with or without associated distant intra-abdominal metastases that could be treated as well, through surgery or radiofrequency ablation) *and* the disease was controlled by chemotherapy. Patients who presented with preoperative evidence of vascular invasion (mainly vena cava and aorta) were excluded. Patients without evidence of CRC at final histopathological examination of the specimen or with extra-abdominal LNR were excluded. Informed consent was obtained from all individual participants included in the study. This study was approved by the local institutional review board.

Perioperative protocol

Patients with suspicion of intra-abdominal LNR underwent preoperative abdominal, pelvic and thoracic computed tomography (CT scan), liver

magnetic resonance imaging (MRI) as well as positron emission tomography (PET) CT. Neoadjuvant treatment was proposed prior to LNR resection (mostly LV5FU2, FOLFOX or FOLFIRI regimens) and patients with objective response to chemotherapy (controlled disease) were assessed for surgical resection. Surgical procedure consisted of intra-abdominal LNR resection. The extent of lymphadenectomy was not standardized. Metallic clips were used as a sealing device, but also in order to ensure LNR resection site follow-up. Upon abdominal exploration, unexpected vascular or ureteral invasion led to corresponding resection and reconstruction. Combined procedures (such as colectomy or hepatectomy) were recorded. Closed-suction abdominal drainage was routinely placed.

During postoperative course, management was standardized in all centers: patients had physical examination on a daily basis, and blood tests at postoperative day (POD) 3, 5, 7. Patient resumed normal diet at POD 2 with intravenous catheter removal. Drain was removed between POD 5 and 7 if output < 50cc/day; otherwise, it was left in place until the output decreased. In case of septic signs or inflammatory syndrome (elevated C-reactive protein), abdominal CT-scan was requested, especially when LNR resection was associated with colectomy or hepatectomy.

Follow-up

Adjuvant chemotherapy was proposed following LNR resection and consisted of 4 to 12 cycles; chosen regimen was based on preoperative objective pathological response. In accordance with French Guidelines, follow-up evaluation was performed every three months during the first 2 years and every six months thereafter. Physical examination, CEA level determination and abdominal, pelvic and thoracic CT scan were performed at each patient visit.

Statistical analysis

Baseline characteristics of the studied population, intraoperative and pathological characteristics, as well as postoperative outcome were retrospectively retrieved from medical charts and analyzed. Categorical variables were compared using the χ^2 test or Fischer's exact test when appropriate. The Kaplan–Meier method was used to estimate recurrence-free survivals (RFSs) and overall survival (OS), which were compared using the Log-rank test. Patterns of recurrence and OS according to recurrence status were analyzed. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL) and statistical significance was accepted at the 0.05 level.

RESULTS

Studied population and primary lesion

Patients' characteristics are described in table 1. During the study period, 18 patients underwent intra-abdominal CRC LNR resection including 10 (56%) men and 8 (44%) women, with a median age of 60.1 years (range: 30.7-73.4). Primary lesion was located in the left colon or rectum in 16 (89%) patients and in the right colon in 2 (11%) patients. Among patients presenting with left-sided colorectal cancer, colic and rectal cancer were found in 10 and 6 patients, respectively. In the 6 patients presenting with rectal cancer, 3 had low rectal cancer; including 2 who received neoadjuvant chemoradiotherapy. Primary CRC resection was performed laparoscopically in 5 (28%) patients. Histopathological examination of the primary lesion revealed T3/T4 status in 15 (83%) patients. Fourteen (78%) patients presented with N+ status, including 79% N2 status. Synchronous metastases were detected in 8 (43%) patients, in liver (n=5), peritoneum (n=1), lungs (n=1) and ovary (n=1). Following primary CRC resection, 16 (89%) patients underwent adjuvant chemotherapy consisting of a minimum of 6 cycles.

LNR resection

Following neoadjuvant chemotherapy, median time between primary lesion resection and LNR resection reached 30.8 months (range: 4.1-73 months); lymphadenectomy sites were aortocaval, pelvic, hepatic pedicle and mesenteric in 10 (56%), 7 (39%), 3 (17%) and 1 (6%) patients, respectively. Aortocaval lymphadenectomy was performed because of infrarenal

localization and multiple LNR in 9 and 5 patients, respectively. Concomitant liver resection for colorectal liver metastases was performed in 4 (22%) patients. Concomitant colorectal resection was performed in 2 (11%) patients, as recurrence was peri-anastomotic; with stoma placement in one patient and colorectal anastomosis redo surgery in the other.

Histopathological examination showed LNR from CRC in all patients. Mean number of harvested lymph nodes and mean number of LNR were 9.2 and 4.4, respectively. Five (28%) patients had lesion described as "tumoral mass". In 2 (11%) patients, lymph node capsular rupture was found. One (5%) patient presented with R2 resection. Finally, all specimens of concomitant hepatectomy showed colorectal metastasis.

Postoperative course was uneventful except for 3 (17%) patients: one patient developed a colo-vesical fistula (Clavien-Dindo≥3) after extensive pelvic dissection for LNR developing after iterative proctectomy; conservative treatment was decided in this patient with diverting stoma placement. No symptomatic lymphatic fluid collection or leak was diagnosed. Median length of hospital stay reached 8 (range: 5-21) days.

Adjuvant treatment and long-term outcomes

After LNR resection, 11 (61%) patients received adjuvant chemotherapy. Additionally, 3 (17%) patients were treated with adjuvant radiotherapy. Patients' characteristics based on further recurrence are summarized in **Table 1**.

Four (22%) patients presented with no recurrence after a mean follow-up of 49.8 (36.9-80) months. These patients were all women with a mean age of 51.6 (38.1-69.5) years at the time of LNR resection. Primary lesion was a left-sided colorectal cancer, with T3-4, N+ status and synchronous metastases (liver n=3, 1, ovary n=1). All of them underwent adjuvant chemotherapy. Mean delay between colectomy and LNR resection was 48.8 (29-73) months. Lymph node recurrence site was retroperitoneal and in the hepatic pedicle in 3 and 1 patients, respectively. Regarding surgical procedure, one patient underwent hepatic resection concomitant to LNR resection; outcomes were unremarkable. All these patients who did not present with recurrence are currently alive.

Fourteen patients (78%) presented with further recurrences. These patients were mainly men (71%) with a mean age of 59.7 (30.6-73.4) years. Primary CRC was left-sided in 12 (86%) patients and right-sided in 2 (14%). Primary lesion was classified as T3-T4 in 12 (86%) patients, N+ in 11 (79%) and with synchronous metastasis in 4 (29%). Twelve (86%) patients received adjuvant chemotherapy following primary CRC resection (one patient had no indication and the other could not because of severe postoperative complication). Also, the statistical analysis did not demonstrate the influence of LNR number on recurrence. Further recurrence was diagnosed after a mean delay of 9.1 (2.1-27.9) months following LNR resection. Further

recurrence occurred within 6 postoperative months in 5 (36%) patients and within 12 postoperative months in 12 (86%) patients.

In terms of further recurrences, there were 2 patients with isolated LNR, 8 patients with pulmonary metastases, 4 patients with liver metastases and 4 patients with localized carcinomatosis (4 patients). Patients with further recurrences were treated, mainly with chemotherapy (14/14), further surgery (5/14) and radiotherapy (3/14). Patients who underwent surgery for further recurrences, had hepatectomy (n=2), secondary LNR resection (n=2) or local carcinomatosis resection (n=1). Overall mortality rate reached 25% and median survival after LNR resection was 44 months (range: 10.4-95.2, Figure 1).

DISCUSSION

Herein are presented long-term results of surgical resection with curative intent in 18 patients who presented with LNR from CRC with objective response to neoadjuvant treatment. After LNR surgical resection, 5-year overall survival and recurrence rates reached 75% and 78%, respectively. Median disease-free and overall survivals were 6.6 months and 44 months, respectively. Among the 14 patients who developed recurrence after LNR resection, 4 patients died after a median follow-up of 49.3 months. In patients presenting with metastatic disease without curative alternative, these results are in accordance with encouraging previously published reports (**11,15-20**). Indeed, LNR from CRC has traditionally been associated with poor prognosis with reported 1-, 2-, and 4-year overall survivals reaching 31%, 7.9% and 0.9% (**21,22**), respectively, in patients who could not undergo surgical treatment.

Recently, several authors have advocated for complete surgical resection whenever possible as it was the only potentially curative treatment. Reported 5-year survival rates of patients who underwent curative resection of extra-regional lymph node metastases from CRC was significantly improved compared with patients who received palliative treatment (**17,23**), ranging from 15 to 29% (**11,17-19**). The absence of any residual tumor following LNR resection (with negative microscopic margins) has been reported as a major prognostic factor contributing in improved long-term survival (**16-18**), with median survival up to 40 months (**11**) and 5-year survival rate of 15% after repeat resection (**19**). Other long-term prognostic factors in patients

undergoing LNR resection have also been identified: single recurrence site, disease limited to the perianastomotic region, normal CEA, absence of distant disease (**20**), disease-free survival > 24 months and tumor size (**11**) have been associated with the ability to achieve complete resection and improved survival (**11**). Factors such as peritoneal disease, nodal/mesenteric recurrence, multiple recurrence sites, elevated CEA, and synchronous distant disease were associated with incomplete resection and significantly poorer survival, resulting in patients benefiting from alternative treatment strategies in addition to surgical salvage (**20**). Current results support the concept that radical LNR resection can be potentially curative and improve survival in selected patients.

Additionally, in patients who presented with further recurrence (after LNR resection), a longer time interval between primary lesion and LNR resections as well as exclusively intra-abdominal disease were associated with better prognosis. The presence of synchronous liver metastases or other metastasis sites were not associated with poorer prognosis, as long as they were resectable. Good prognosis factors found in current study are in accordance with previously reported results (**11,20**), and might help to better identify candidates with a slowly spreading, controlled disease and favorable tumor behavior. Patients with these factors could therefore particularly benefit from LNR resection. Tumors responding to chemotherapy might matter more than the metastatic status per se in the decision to undergo LNR resection.

Current results raise several points. First, recurrence and survival in this series seem to tend to towards results observed after surgical resection of hepatic and pulmonary metastases whenever possible (**24-26**), with 5-year disease-free survival reaching 30% in patients who managed to undergo complete surgical resection of all recurrences. The encouraging results of curative resection of liver and pulmonary metastasis have compelled to reappraise admitted paradigm and to define the concept of oligometastatic disease (**27**). Indeed, in selected patients, complete resection of metastases with curative intent may improve survival. Other similar reports also showed improved outcomes following LNR resection, suggesting that LNR should be considered as a separate metastatic site (in accordance with the concept of oligometastatic disease) and, therefore, should be treated with curative intent in selected patients. However, standardized therapeutic management of LNR has yet to be described and preliminary results (such as this report) are valuable in order to define further high-evidence studies.

Other therapeutic options, such as chemotherapy (**28**) and radiotherapy (alone or combined), are not considered curative (**29**); chemotherapy should be used in order to control the disease (and allow for better patient selection). Among other modalities that must be defined, the type of proposed surgical resection should be discussed; in current analysis, limited resection focused on highly suspicious lymph nodes (after CT-scan, MRI and PET-scan) was performed in all patients. Other authors have recently suggested extended lymphadenectomy in order to achieve clearance (**15**),

yielding interesting results. Currently, there is no compelling evidence in favor of one or the other therapeutic management; we have also recently completed a complete resection of LNR as a two-stage strategy, (supra-mesocolic and inframesocolic LNR, respectively) without further recurrence after 13 months in a patient who has not been included in this study. Also, current protocol with resection of LNR (not a complete lymphadenectomy) might have led to the lack of significance regarding LNR number on recurrence. Consequently, the extent and timing of LNR resection must be investigated in further studies. Early recurrences (<6 months after LNR resection) were found in 36% of patients included, indicating that selection criteria still require improvement.

Obviously, current analysis presents several limitations. Conclusions are difficult to draw due to the study's retrospective nature and the small number of patients. Patients were selected without standardized assessment (all patients received at some point different modalities of radio-chemotherapy). There is no control group. Also, some authors might suggest that retroperitoneal and intraperitoneal LNR (as LNR in hepatic pedicle or celiac axis) should be differently managed **(15)**; in the described protocol, localization was not discriminant as long as complete resection was achievable. Yet, when compared to patients with LNR treated without surgery that were reported in literature, this report suggests that an association of complete surgical resection (potentially associated with other metastatic sites resection), chemotherapy and radiotherapy should be considered as a treatment

modality in with curative intent in patients with LNR from CRC. Further studies are required to confirm these points.

In conclusion, in selected patients with controlled disease after chemotherapy, colorectal LNR resection should be considered in therapeutic management as a curative modality. LNR surgery can be associated with chemotherapy, radiotherapy as well as other metastatic sites resection. Further studies (mainly randomized control trials) should be designed in order to describe optimal protocol.

COMPLIANCE WITH ETHICAL STANDARDS:

Conflict of Interest: None.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

TABLE

Table.1: Patients' characteristics based on further recurrence.

Patient characteristics	Overall (n=18)	No recurrence after LNR resection (n=4)	Early recurrence (≤6months) after LNR resection (n=5)	Late recurrence (≥6months) after LNR resection (n=9)
Gender: male	10 (56%)	0 (0%)	4 (80%)	6 (67%)
Mean age (years) (range)	58 (30.7-73.4)	51.6 (38.1-69.5)	61.3 (53.7-68.7)	58.9 (30.6-73.4)
Left-sided primary colorectal lesion.	14 (78%)	4 (100%)	5 (100%)	7 (78%)
T3/T4 status	16 (89%)	4 (100%)	4 (80%)	8 (89%)
N+ status	15 (83%)	4 (100%)	3 (60%))	8 (89%)
Synchronous metastasis	8 (50%)	4 (100%)	1 (20%)	3 (33%)
Mean time between primary and LNR resections (months) (range)	31.6 (4.1-73)	48.8 (29-73)	27.1 (8.1-45)	24.9 (4.1-48.8)
Adjuvant treatment	15 (83%)	4 (100%)	3 (60%)	7 (78%)

(radiotherapy, chemotherapy)				
Multisite recurrence	5 (28%)	0 (0%)	1 (20%)	4 (44%)
Extra-abdominal recurrence	6 (33%)	0 (0%)	3 (60%)	3 (33%)
Mean overall survival (range) (months)	41.6 (10.4-95.2) 78% alive	49.8 (36.9-80) 100% alive	38.9 (10.4-95.2) 80% alive	51.3 (31.4-89.2) 66% alive
Mean Disease free-survival (range) (months)	22.5 (2.1-80)	49.8 (36.9-80)	3.6 (2.1-4.5)	12.2 (6.5-27.9)

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FIGURE

Figure.1: Overall and Recurrence free survival after resection of lymph node recurrence.