Surgery for retroperitoneal and pelvic lymph node metastases of colorectal cancer

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ABSTRACT | *AIM: to evaluate the effect of surgery for metastases in retroperitoneal and pelvic lymph nodes on overall and disease-free survival.*
PATIENTS AND METHODS: the analysis included 30 patients with retroperitoneal lymph node metastases of colorectal cancer. Synchronous metastases to the retroperitoneal lymph nodes, were diagnosed in 21/30 (70%).
RESULTS: the median overall and disease-free survival in patients who underwent lymphodissection was 32 and 13 months, respectively. Recurrence occurred in 14/30 (47%) patients. One-, two-, three-year disease-free survival was 61 ± 11%, 20 ± 11%, 0%; general 95 ± 4%, 74 ± 14%, 37 ± 19%, relatively. The median disease-free survival in the group with isolated retroperitoneal lymph node lesion was 14 (9–29) months and 10 (6–18) months in the group with retroperitoneal lymph node metastases in combination with synchronous liver lesion. One-and three-year disease-free survival was the same in the groups and was 58 ± 15% and 0%, p = 0.2. The univariate analysis did not reveal any factors related to overall and disease-free survival.
CONCLUSION: in a selected group of patients with colorectal cancer, with lesions of retroperitoneal lymph nodes, including resectable metastases to the other organs, surgery can be justified, since it is accompanied by a relatively low rate of complications. However, the small cohort requires further study.

KEYWORDS: *rectal cancer, surgery, colorectal cancer, lymph node metastases, retroperitoneal lymph node metastases, metastases of colorectal cancer, lymphodissection, paraaortic lymph node metastases, lymphadenectomy*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

INTRODUCTION

The expansion of indications for surgical treatment in patients with distant metastases of colorectal cancer, with isolated lesions of the liver, lungs, and peritoneum led to an increase in 5-year survival to 30%, which is not achievable with systemic chemotherapy [1–3]. Metastases to retroperitoneal lymph nodes are classified as distant metastases (M1) of colorectal cancer with an unfavorable prognosis. Isolated lesions of retroperitoneal lymph nodes are rare: in 1–2% of cases [4–6]. The main method of treatment for these patients, most often, is systemic chemotherapy. However, active surgical tactics, as shown in the study by Min, B. S. et al., in patients with isolated retroperitoneal and pelvic lymph node lesions, the median overall survival is increased to 34 months, compared to 14 months with chemotherapy [5]. Also in the study by Choi, P. W. et al. it was shown that after performing lymphodissection for metastases to retroperitoneal lymph nodes the 5-year overall survival rate was 53.4% compared to 12.0% in the group without paraaortic lymphodissection, *p* = 0.045. [4]. Moreover, in patients with retroperitoneal lymph node metastases combined with lesions of the other organs that underwent radical surgery, the 5-year survival rate was 56% [4]. Similar results are demonstrated by the study of Kim et al., the median of disease-free and overall survival is greater in patients with lymphodissection, compared with chemotherapy (71 months vs.

39 months, P = 0.017 and 77 months vs. 62 months, P = 0.055, respectively) [7].

Since there are relatively few publications in the literature devoted to the surgical treatment of patients with metastatically affected retroperitoneal lymph nodes, our experience may be of some interest.

PATIENTS AND METHODS

A retrospective analysis of the results of treatment of patients operated for retroperitoneal lymph node metastases from January 2016 to October 2019 was performed. Out of 39 selected patients with a morphologically confirmed diagnosis of retroperitoneal lymph node metastases, 1 patient with a neuroendocrine tumor, 1 patient with non — colorectal cancer metastases, and 7 patients who also had carcinomatosis were excluded. Thus, the study included 30 patients with retroperitoneal and pelvic lymph nodes lesion (Table 1).

Diagnostic Program
Before making a decision on the possibility of surgical treatment, all patients underwent CT of the chest, CT/MRI of the abdominal and pelvic organs with intravenous contrast. The indication for surgical treatment was the potential for R0 removal of all metastases detected at the diagnostic stage. If neoadjuvant treatment was necessary, surgery was performed in the second stage.

Surgical Technique
The technique of lymphodissection for retroperitoneal lymph node lesions included: removal of tissues paraaortically, paracavally, and in the aortocaval interval from the level of the left renal vein to bifurcation of the aorta. When retroperitoneal lymph nodes were affected above the renal vessels, lymphodissection reached the level of the ventral trunk. In case of the iliac lymph nodes lesion, lymphodissection was performed along the iliac vessels. The surgery was considered radical if all macroscopic manifestations of the disease were removed. If there was a synchronous primary tumor and/or synchronous liver metastases, they were removed simultaneously. If retroperitoneal lymph nodes grew into the main vessels, their resection was performed with subsequent reconstruction. Patients were monitored according to a standard schedule with mandatory CT scans of the chest, abdomen, and pelvis at each visit.

Statistical Analysis
The data was described as a median (min — max) with an abnormal distribution. Survival was assessed using the Kaplan-Meier curve. The univariate analysis was performed using proportional Cox-regression. The differences were considered statistically significant if the first type error was less than 5%. Statistical data processing was carried out using the Statistica 13.3 program (Tibco, the USA).

RESULTS

Colorectal cancer with synchronous metastases to retroperitoneal lymph nodes was diagnosed in 21/30 (70%) cases. The median time before the appearance of metachronous metastases in retroperitoneal lymph nodes was 18 (3–63) months. In metachronous metastases 4/9 patients had isolated retroperitoneal lymph node lesion, and 5/9 patients had synchronous liver lesion, which was an indication for performing simultaneous surgery. In all cases, the volume of liver surgery was represented by atypical resection. With the rectal tumor, an isolated lesion of site 1 was observed in 13/20 patients, of whom the suprarenal site was involved in 1/13 observation, the infrarenal site — in 4/13 and the iliac site — in 8/13 observations. In case of the tumor site in the left half of the colon, an isolated lesion of site 1 was observed in 5/8 patients, of whom the suprarenal site was involved in 2/5 observations and the infrarenal site — in 3/5 ones.

Two lesion sites with the rectal tumor were detected in 7/20 patients: a combination of infrarenal and ileal — in 4/7, infrarenal and suprarenal — in 2/7, suprarenal and ileal — in 1/7 patients. When the tumor site was in the colon, infrarenal and ileal lesions were observed in 2/4 patients, infrarenal and suprarenal — in 2/4 patients. The lesion of all the three sites was observed in 1/30 case, with the tumor site in the right half of the colon.

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Table 1. *Characteristics of patients with colorectal cancer metastases to retroperitoneal lymph nodes*

No of patients	30
Sex	
Male	17 (57.0%)
Female	13 (43.0%)
The median age	62 (26-78)
Tumor site	
Right half	2 (7.0%)
Left half	8 (26.0%)
Rectum	20 (67.0%)
Disease stage	
III	6 (20.0%)
IV	24 (80.0%)
Time of appearance of metastases in the lymph nodes	
Synchronous	21 (70.0%)
Metachronous	9 (30.0%)
Disease-free survival for metachronous metastases (months)	18 (3-63)
Number of lymph nodes examined	5 (1-39)
Number of metastatic lymph nodes	3 (1-29)
The largest size of lymph nodes according to morphological study, cm	4,5 (1,5-10)
The lesion sites	
Suprarenal	9 (30.0%)
Infrarenal	18 (60.0%)
Iliac	15 (50.0%)
Number of affected areas	
1	18 (60.0%)
2	11 (37.0%)
3	1 (3.0%)
One lesion site	
Suprarenal	3 (10.0%)
Infrarenal	7 (23.0%)
Iliac	8 (28.0%)
Two lesion sites	
Infrarenal + Iliac	6 (20.0%)
Infrarenal + Suprarenal	4 (13.0%)
Suprarenal + Iliac	1 (3.0%)
Paraaortic lymph nodes between the upper edge of the ventral trunk and the lower edge of the left renal vein	9 (30.0%)
Paraaortic lymph nodes between the lower edge of the left renal vein and the upper edge of the lower mesenteric artery	10 (33.0%)
Paraaortic lymph nodes between the upper edge of the lower mesenteric artery and the bifurcation of the aorta	15 (50.0%)
Lymph nodes at the level of:	
Aortic bifurcations	6 (20.0%)
Lymph nodes in the area of:	
Left iliac vessels	4 (13.0%)
Bifurcations of the left iliac vessels	3 (10.0%)
The left internal iliac vessels	–
The left external iliac vessels	1 (3.0%)
The right iliac vessels	4 (13.0%)
Bifurcations of the right iliac vessels	4 (13.0%)
The right internal iliac vessels	1 (3.0%)
External right iliac vessels	1 (3%)
Radical surgery for primary tumors	
R0	18 (60.0%)
R1	12 (40.0%)

No of patients	30
Morphology of metastases in retroperitoneal lymph nodes	
Adenocarcinoma	26 (87%)
Mucosal adenocarcinoma	3 (10%)
Ring-cell cancer	1 (3%)
Neoadjuvant chemotherapy	
Yes	6 (20.0%)
No	24 (80.0%)
Resection of blood vessels	
Yes	2 (7.0%)
No	28 (93.0%)
Simultaneous surgeries on the liver	
Yes	12 (40.0%)
No	18 (60.0%)
The number of operations in the anamnesis	
0	20 (67.0%)
1	7 (23.0%)
2	3 (10.0%)

Neoadjuvant chemotherapy in patients with synchronous metastases of colorectal cancer to retroperitoneal lymph nodes was performed in 1 patient, the remaining 19 patients abstained from neoadjuvant chemotherapy due to a symptomatic primary tumor. In patients with metachronous lesions of retroperitoneal lymph nodes, neoadjuvant chemotherapy was performed in 5/9 patients. The median postoperative day of hospital stay was 15 (7–28) days. The postoperative period in 2/30 (7%) patients was complicated by a hematoma in the site of lymphodissection, which required urgent repeated surgery. The median follow-up after lymphodissection for retroperitoneal lymph node metastases was 12 (1–38) months. The median overall and disease-free survival was 32 and 13 months, respectively (Figure 1).

In 2 out of 30 observations, lymphodissection was associated with resection and prosthetics of vessels, in 1 observation lymphodissection was combined with resection of the lower horizontal branch of the duodenum with a section of the aorta for 5 cm, followed by its prosthetics with a synthetic prosthesis (Fig. 2, 3, 4), in the other
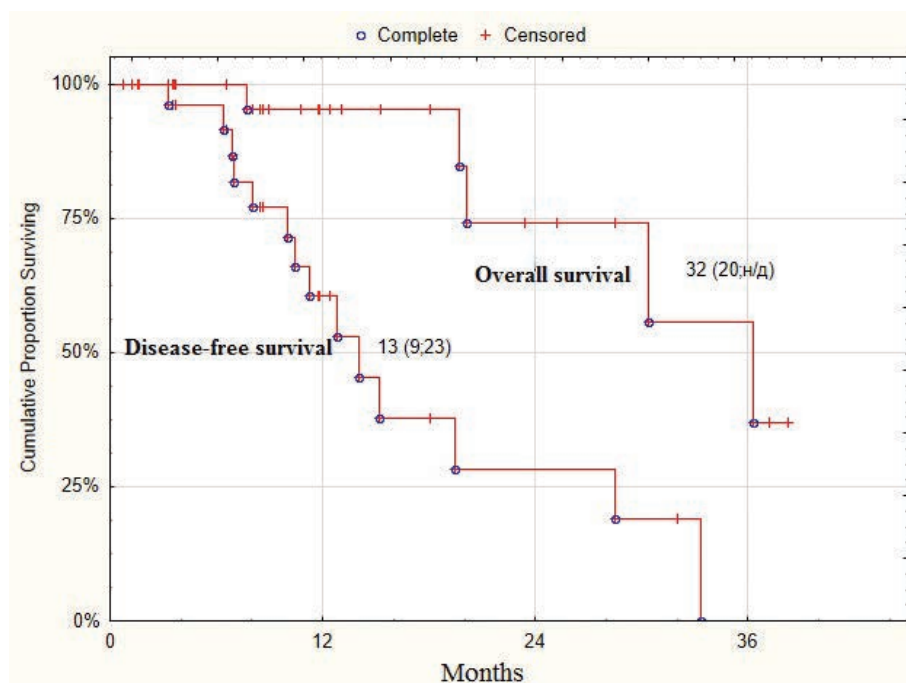

Figure 1. *Overall and disease-free survival of patients with colorectal cancer metastases to retroperitoneal lymph nodes*

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observation — at the level of aortic bifurcation with aortoiliac prosthetics (Fig. 5, 6).

Recurrences occurred in 14/30 (47%) patients. Metastases in retroperitoneal lymph nodes occurred in 6/30 (20%), in the lungs — in 3/30 (10%), in the liver — in 3/30 (10%), in the brain — in 1/30 (3%), in the soft tissues — in 1/30 (3%), recurrence in the pelvic cavity — in 1/30 (3%), in two cases the recurrence site is unknown. One -, two -, three-year disease-free survival was 61 ± 11%, 20 ± 11%, 0%, accordingly. After the surgery, 5/30 (17%) patients died from disease progression
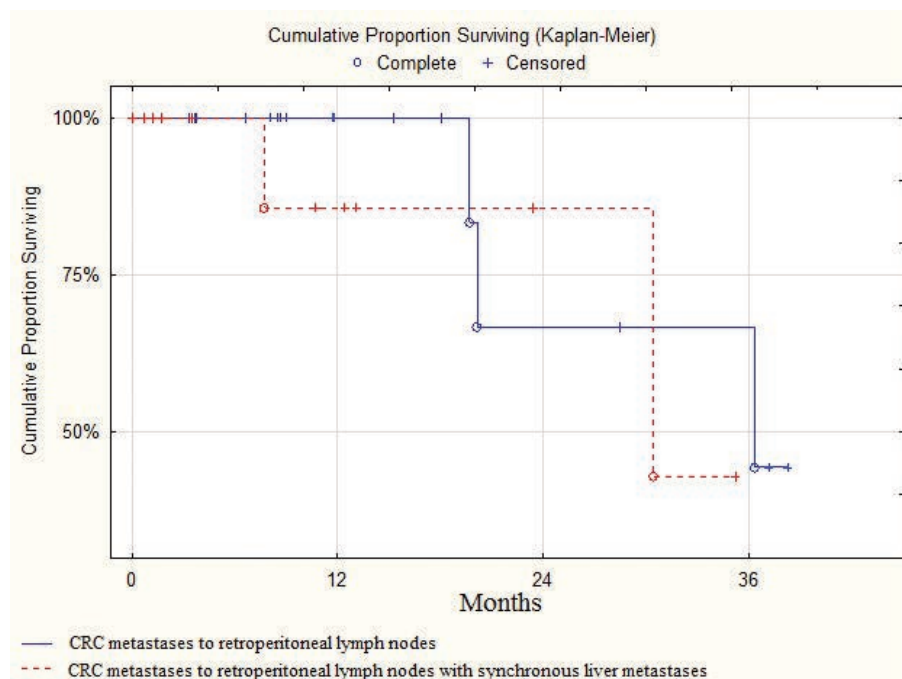

Figure 2. *Overall survival of patients with isolated CRC metastases to retroperitoneal lymph nodes in patients with retroperitoneal lymph node metastases and synchronous liver lesion*
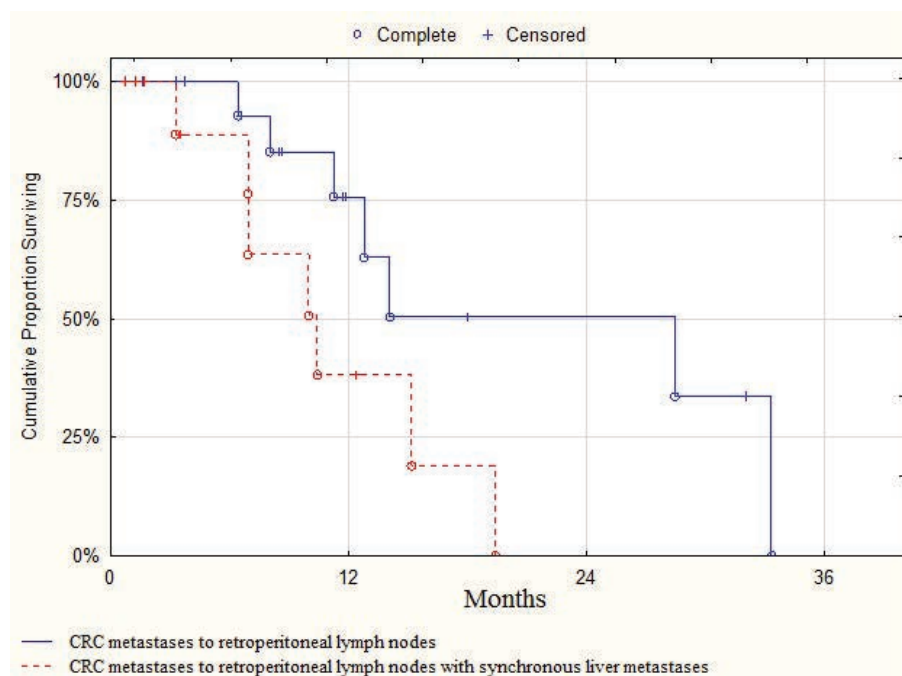

Figure 3. *Disease-free survival of patients with isolated CRC metastases to retroperitoneal lymph nodes and patients with metastases to retroperitoneal lymph nodes in combination with synchronous liver lesion*

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Table 2. *Univariate Cox regression analysis of disease-free and overall survival*

Factors	Survival			
	Disease-free OR (95% CI)	p	Overall OR (95% CI)	p
Sex Female/Male	1,1 (0,4–3,3)	0,9	2,3 (0,4–14)	0,4
Age	1 (0,95–1,1)	0,8	1,18 (0,95–1,47)	0,1

Tumor site
  Right half
  Left half
  Rectum
	1,7 (0,2–14)
	1,5 (0,4–5,7)
	1
		0,6
		0,5
			–
			3 (0,2–52)
			1
				–
				0,5

Disease stage III/IV	0,8 (0,2–2,6)	0,7	2,2 (0,4–14)	0,4
Time of appearance of metastases in the lymph nodes Metachronous/Synchronous	1 (0,3–3,1)	0,95	1,7 (0,3–10)	0,6
Number of metastatically affected lymph nodes	1,1 (0,9–1,2)	0,4	1 (0,9–1,2)	0,6
The largest size of lymph nodes according to morphology, cm	0,96 (0,7–1,2)	0,7	1,3 (0,8–1,95)	0,3
Number of lesion sites 2/1	1 (0,3–3,4)	0,98	1,7 (0,2–13)	0,6

One lesion site
  Infrarenal
  Iliac
  Over 1 site
	1,3 (0,3–5,7)
	0,5 (0,1–2,1)
	1
		0,7
		0,3
			3,6 (0,3–41)
			–
			1
				0,3
				–

Radical surgery for primary tumors R0/R1	0,4 (0,1–1,3)	0,15	0,7 (0,1–4)	0,7
Neoadjuvant chemotherapy No/Yes	0,9 (0,3–3)	0,8	–	–
Number of surgeries in the anamnesis 1/2	0,2 (0,03–1,7)	0,14	–	–
Resection of blood vessels No/Yes	0,6 (0,13–3)	0,6	0,5 (0,04–5,3)	0,5
One-stage liver surgery No/Yes	0,4 (0,14–1,3)	0,14	0,4 (0,07–3,4)	0,5

during dynamic follow-up. One -, two -, three-year overall survival was 95 ± 4%, 74 ± 14%, 37 ± 19%, accordingly. The overall and disease-free survival of patients with isolated lymph node lesion and in combination with synchronous liver lesion was analyzed separately. Overall one-and three-year survival in the group with isolated lesion was 83% ± 15 and 44% ± 22, in the group with synchronous liver metastases — 86% ± 13 and 43% ± 8, respectively, *p* = 0.2 (Fig. 2).

The median disease-free survival between the groups did not differ statistically and was 14 (9–29) months in the group with isolated retroperitoneal lymph node lesion and 10 (6–18) months in the group with retroperitoneal lymph node metastases in combination with synchronous liver lesion. One-and three-year disease-free survival was the same in the groups and was 58% ± 15 and 0%, *p* = 0.2. The univariate analysis of disease-free and overall survival did not reveal significant factors affecting survival due to a small number of observations (Table 2).

DISCUSSION

The treatment of lymphogenous disseminated forms of colorectal cancer in general is the prerogative of chemical therapists. The effectiveness of surgical treatment in these patients has not been determined. In comparison with metastases to the liver, lungs, or peritoneum, isolated lesions of retroperitoneal lymph nodes are very rare and are most often combined with distant metastases

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Figure 4. *Metastasis to the paraaortic lymph node with sprouting into the lower horizontal branch of the duodenum*

Figure 5. *Removed specimen. Lymph node growing into the abdominal aorta and the duodenum*

to the other organs [4, 8]. In the study by Shibata, D. et al., it was shown that the median overall survival in patients with surgical treatment was 40 months, with exploratory laparotomy — 3 months. However, the author does not specify the prevalence of cancer and the reasons for failure in exploratory laparotomy, which may provide better results due to a systematic selection error [6]. In fact, the lesion of retroperitoneal lymph nodes is more often combined with metastases to the other organs. In the study by Gagniere, J et al., the overall survival rate for lymphodissection with resection of other organs is comparable to the survival rate for isolated lesions [8].
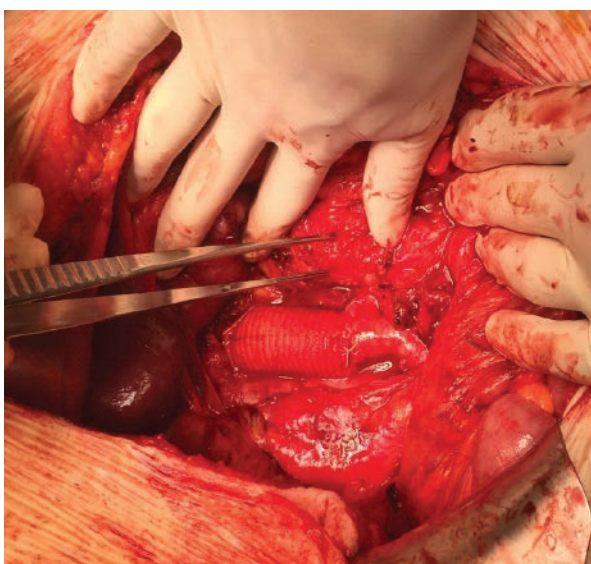
A number of authors cite the fact that lymph nodes grow into the aorta or inferior vena cava [9–11]. In this situation they performed a lymph node dissection with resection of the portion of the vessel and its prosthetics. Given the isolated observations associated with resection of the aorta or inferior vena cava, it is difficult to judge the advantage of combined resections in such patients. However, in our opinion, resection of the main vessels is justified in such patients, since it can potentially increase the life expectancy. In our study, the disease-free survival of these patients was 13 and 14 months, and the overall survival was 20 and 29 months, respectively.

Despite extensive trauma, these surgeries are quite bearable and safe. According to Choi et al., the overall incidence of complications in comparison of patients without lymphodissection and patients with simultaneous removal of the tumor and lymphodissection was 20.8% versus 27.8%, respectively, but no statistical differences were
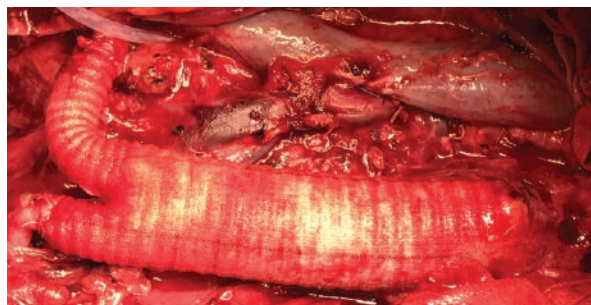

Figure 6. *Performed lymphodissection with prosthetic section of the abdominal aorta for 5 cm*

Figure 7. *Performed lymph node dissection with aortoiliac prosthesis*

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Figure 8. *Removed specimen. Group of metastatic lymph nodes growing into the lower segment of the abdominal aorta at the bifurcation level of the common iliac arteries*

obtained, p = 0.324 [4]. None of these studies [4, 5, 8] showed any fatal outcomes.

Another issue is the role of chemotherapy in the combined treatment of such patients. Is the neoadjuvant chemotherapy for retroperitoneal lymph node metastases necessary? How many courses of the neoadjuvant chemotherapy are necessary in the presence of removable retroperitoneal lymph nodes according to objective methods of examination? Is lymphodissection necessary for isolated retroperitoneal lymph node lesions in the absence of a response to the neoadjuvant chemotherapy? In the studies by Gagniere J. et al., Shibata D. et al., in some patients with synchronous retroperitoneal lymph node involvement, the neoadjuvant treatment was not performed, and those patients were treated only in the adjuvant mode [6, 8]. According to the univariate analysis, the neoadjuvant chemotherapy did not affect disease-free and overall survival [8]. In our study, neoadjuvant chemotherapy also had no effect on overall or disease-free survival.

However, given the small number of observations in all studies, it is not possible to answer these questions.

The limitation of publications is due to the retrospective nature of the data. It is worth noting that in the postoperative period, chemotherapy based on fluoropyrimidines and oxaliplatin was performed as the first line. It is not possible to evaluate subsequent lines of chemotherapy.

CONCLUSION

In a selected group of patients with colorectal cancer, with lesions of retroperitoneal lymph nodes, including resectable metastases to the other organs, surgical treatment can be undertaken, since it is accompanied by a relatively low rate of complications.

However, the small number of observations requires further study of this issue.

AUTHORS CONTRIBUTION
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REFERENCES

1. Nordlinger B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet*. 2008;371(9617):1007–16.

2. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. *Ann Thorac Surg*. 2007;84(1):324–38.

3. Esquivel J, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Ann Surg Oncol*. 2007;14(1):128–33.

4. Choi PW, et al. Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels. *J Surg Oncol*. 2010;101(1):66–71.

5. Min BS, et al. Isolated paraaortic lymph-node recurrence after the curative resection of colorectal carcinoma. *J Surg Oncol*. 2008;97(2):136–40.

6. Shibata D, et al. Surgical management of isolated retroperitoneal recurrences of colorectal carcinoma. *Dis Colon Rectum*. 2002;45(6):795–801.

7. Kim YI, et al. Management of isolated para-aortic lymph node recurrence after surgery for colorectal cancer. *Annals of surgical treatment and research.,* 2020;98(3):130–138.

8. Gagniere J, et al. Retroperitoneal nodal metastases from colorectal cancer: Curable metastases with radical retroperitoneal lymphadenectomy in selected patients. *Eur J Surg Oncol*. 2015;41(6):731–7.

9. Hashimoto M, et al. Resection of paraaortic lymph node metastasis of colon cancer with graft replacement. *Hepatogastroenterology*. 2003;50(51):709–10.

10. Tsarkov P.V., et al. *En bloc* resection of abdominal aorta and paraaortic lymph node metastasis of sigmoid cancer. *Tech Coloproctol*. 2007;11(4):346–9.

11. Torchua N.R. et al. Multidisciplinary approach in the treatment of patients with recurrent colorectal cancer and involvement of the main vessels. *Annals of surgery*. 2017;3:173–180. (in Russ.).