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ORIGINAL ARTICLE

Intraoperative indocyanine green lymphography during lymph node dissection in patients with colorectal cancer liver metastases

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Abstract

Purpose of the study. To evaluate the diagnostic performance of intraoperative fluorescence lymphography in patients with colorectal liver metastases (CLM).

Patients and methods. The study included 55 patients with CLM who underwent intraoperative fluorescence lymphography with indocyanine green (ICG) during laparotomy to guide hepatic hilum lymph node dissection (LND) and liver resection. The first three fluorescent lymph nodes (LNs), defined as sentinel lymph nodes (SLNs), were identified within 30–45 minutes after peritumoral ICG injection. LND was performed with excision and labeling of SLNs and all fluorescent LNs detected during the observation period, as well as lymph nodes from stations 12, 13, and 8, regardless of fluorescence. Liver resection was subsequently performed.

Results. In six of 55 patients (10.9 %), no SLNs were visualized. These patients underwent LND with removal of lymph nodes from stations 12, 8, and 13; histopathological examination revealed no LN metastases in this subgroup. In the remaining patients (89.1 %, *n* = 49), SLN fluorescence was observed. Histopathological analysis demonstrated lymphogenous metastases in 11 of 55 patients (20.0 %). In four of these 11 patients (36.3 %), selective LND based solely on preoperative imaging and intraoperative assessment would have failed to identify and remove metastatic LNs. The sensitivity of ICG lymphography was 100 %: in all 11 patients with nodal metastases, at least one SLN (SLN No1, No2, or No3) was involved. In two cases (18.2 %), metastatic involvement was detected only in SLN No3, with SLN No1 and SLN No2 being negative. Only one of the 11 patients (9.1 %) had additional metastatic LNs beyond the SLN basin; in this patient, all three SLNs were metastatic.

Conclusion. Hepatic hilum LN metastases were detected in one in five patients with CLM. Reliable preoperative or intraoperative identification of metastatic hilar LNs remains challenging. ICG-guided SLN mapping enables more precise lymph node dissection. Further studies are required to determine whether this approach improves long-term oncological outcomes after liver resection for CLM.

Keywords:
colorectal cancer, liver metastases, lymph node metastases, extrahepatic colorectal cancer metastases, sentinel lymph nodes, fluorescent lymphography

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Compliance with ethical standards: the study followed the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was conducted in accordance with the ethical principles outlined in the World Medical Association Declaration of Helsinki (1964, revised 2013). The research protocol was approved by the Ethics Committee of the N.N. Blokhin National Medical Research Center of Oncology (extract from meeting protocol No. 12 dated 26.10.2023). Informed consent was obtained from all participants in the study.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Интраоперационная лимфография с индоцианином зеленым при лимфодиссекции у больных с метастазами колоректального рака в печени

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Аннотация

Цель исследования. Изучить диагностические возможности интраоперационной флуоресцентной лимфографии при метастазах колоректального рака (КРР) в печени.
Пациенты и методы. В работу включены 55 пациентов с метастазами КРР в печени, которым за период с 2023 по 2025 г. во время лапаротомии при планировании лимфодиссекции ворот печени с последующей резекцией печени была применена флуоресцентная лимфография с индоцианином зеленым (ИЦЗ-лимфография). В течение 30–45 мин от перитуморального введения ИЦЗ под капсулу печени определяли первые три прокрашенных лимфатических узла (ЛУ) – сторожевые лимфатические узлы (СЛУ). Осуществляли лимфодиссекцию (ЛД) с удалением и маркировкой СЛУ и всех прокрашенных за время наблюдения ЛУ, а также ЛУ 12, 13 и 8 групп вне зависимости от наличия прокрашивания. Далее осуществляли резекцию печени.
Результаты. У шести пациентов (10,9 %) не выявлено ни одного СЛУ. Этим пациентам выполнена ЛД с удалением ЛУ 12, 8, 13 групп, метастазов в ЛУ в этой группе не было. В остальных случаях (89,1 %, *n* = 49) отмечено накопление ИЦЗ в ЛУ. Поражение ЛУ по данным морфологического исследования отмечено у 11 пациентов из 55 (20,0 %). У четырех из этих одиннадцати (36,3 %) при выполнении селективной ЛД, осуществленной с учетом данных предоперационного обследования и интраоперационной ревизии, пораженные ЛУ не были бы распознаны и удалены. Чувствительность ИЦЗ-лимфографии составила 100 %: у всех 11 пациентов с положительными ЛУ был поражен хотя бы один СЛУ (№ 1, № 2 или № 3). В двух случаях (18,1 %) вовлечение ЛУ было выявлено только при изучении всех трех СЛУ без поражения СЛУ № 1 или № 2. Только у одного пациента из 11 (9,1 %) с положительными ЛУ был дополнительно поражен ЛУ вне СЛУ, при этом все три СЛУ у этого пациента были также поражены.
Заключение. Лимфогенное метастазирование в ворота печени выявлено у каждого пятого пациента с колоректальными печеночными метастазами. Достоверно определить наличие и локализацию метастатических узлов ворот печени до или во время операции сложно. ИЦЗ-лимфография с диссекцией СЛУ позволяет выполнить ЛД более прецизионно. Необходимо изучить, улучшит ли такая тактика отдаленные результаты лечения после резекции печени по поводу метастазов КРР.

Ключевые слова:
рак толстой кишки, метастазы в печени, метастазы в лимфатических узлах, внепеченочные метастазы колоректального рака, сторожевые лимфатические узлы, флуоресцентная лимфография

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INTRADUCTION

Liver metastases develop in 50 % of patients with CRC [1]. Liver resection in such cases is the priority treatment method. The incidence of hepatic hilum lymph node (LN) involvement in resectable colorectal liver metastases (CLM) can reach up to 14–20 %, and the prognosis in this case is generally unfavorable [2–4]. In certain patient groups, hepatic hilum LN involvement can be as high as 40 % [5].

An article by René Adam showed that long-term survival following liver resection for CLM is possible even in the presence of extrahepatic metastases, such as metastases to the LNs or peritoneal metastases[6]. In a study by Wakai T. et al. among CRC patients with metastatic liver and LN involvement, a five-year overall survival (OS) rate of 29 % was noted [7]. In a study by Patyutko Iu.I. et al., the combination of resection and chemotherapy in a group of patients with CLM and hepatic hilum LN involvement resulted in a five-year OS of 21.9 % [8]. The presence of long-term survival following resection and systemic therapy justifies performing the surgical stage after appropriate patient selection [9]. In the study by Mahuron K. M. et al., liver resection and lymph node dissection (LND) of its hilum in combination with successfully conducted systemic therapy reached excellent long-term results – the median OS in the group of patients with CRC liver metastases and LN involvement reached 54 months [10].

At the same time, the question of performing systematic versus selective LND of the hepatic hilum during liver resection for CRC metastases remains controversial. Routine preoperative diagnostic methods generally have low diagnostic capabilities in interpreting lymphogenic metastases [5, 11]. Proponents of systematic LND point to the inaccuracy of preoperative diagnosis and intraoperative assessment – with selective LND, many patients are left with unremoved lymphogenic metastases. The operation in this case is non-radical [3, 4, 12].

Considering the difficulties in determining the necessity of LND and choosing its extent, searches are underway for methods to identify affected LNs, including through morphological examination of sentinel lymph nodes (SLN). Fluorescence lymphography using indocyanine green (ICG) has found application in identifying SLNs with subsequent histopathological examination in ovarian cancer [13], breast cancer [14], melanoma [15], lung cancer [16], and endometrial cancer [17]. There are studies on identifying SLNs in biliary tract cancer [18], as well as in various pathologies involving the liver, including in patients with CLM [19].

It should be noted that lymphatic drainage from the liver is complex, and involvement of specific LNs depends on the location of the tumor node within the liver [20, 21]. This complexity of lymphatic drainage from the liver further underscores the relevance of searching for methods to determine the advisability ad extent of LND for CLM, including through SLN identification [18, 19].

Purpose of the study was to evaluate the diagnostic performance of intraoperative fluorescence lymphography in patients with CLM.

PATIENTS AND METHODS

The study included patients with CLM who underwent ICG lymphography in 2023–2025 prior to planned liver resection with preliminary lymph node dissection (LND) of the hepatic hilum. Exclusion criteria were: absence of informed consent for the study, allergy to iodine-containing drugs, and a history of prior liver resection (patients who had undergone liver resection previously were not included).

Before surgery, the following steps were performed: magnetic resonance imaging (MRI) and/or contrast-enhanced computed tomography (CT) of the abdomen and contrast-enhanced CT of the chest. The interpretation of hepatic hilum lymph node (LN) status by a radiologist was recorded. Levels of tumor markers CEA and CA 19–9 were determined.

After laparotomy, abdominal exploration was performed, including assessment of LNs in the hepatic hilum area, along the common hepatic artery, left gastric artery, behind the pancreatic head, along the lesser curvature of the stomach, and retroperitoneal LNs.

After exploration, 1 ml of a prepared solution consisting of 25 mg ICG and 20 ml of water for injection was injected subcapsularly into the liver, peritumorally. The ICG solution was injected around the periphery of the node(s). For metastases larger than 3 cm in diameter, the agent was injected from two maximally distant positions; for nodes larger than 5 cm – from three positions. In cases of bilobar involvement, the largest and, when possible, the most distant metastases (up to 3 nodes) were injected. To expand the infiltration field around a single node, the needle direction was changed without additional puncture of the liver capsule. The puncture site was sutured or coagulated to prevent agent leakage. A total of no more than 4 ml of the ICG solution was injected.

After injection, the accumulation of ICG in the lymphatic apparatus of the liver and bile ducts was observed using an infrared camera with a peak wavelength of 805 nm for excitation and 830 nm for detection.

Time points for studying ICG spread through the lymphatic apparatus were 1, 3, 5, 10, 15, 30, and 45 minutes after injection. During this time, LND and liver mobilization were not performed. Limited dissection of adhesions interfering with objective assessment of LNs and observation of agent accumulation was allowed. If three

sentinel LNs (SLNs) were identified within 30 minutes, observation at 45 minutes was not performed.

LNs accumulating ICG, depending on the time interval at which their fluorescent staining was noted, were marked as SLN № 1, № 2, № 3 after lymph node dissection. Lymph node dissection was performed with removal and marking of SLNs and all stained LNs. LNs from stations 12, 13, and 8, and LNs suspicious for metastatic involvement – those with firm consistency, round shape regardless of size, or larger than 1 cm in short axis – were also removed and marked. Subsequently, liver resection was performed when technically feasible and oncologically justified.

The surgical protocol recorded characteristics of the removed LNs, including SLNs, such as location, size, consistency, shape, presence of infiltration of surrounding tissues. The clinician's interpretation (metastatic, suspicious for involvement, lymphadenopathy without signs of metastatic LN involvement, unchanged LNs without signs of involvement). Numerical parameters were presented indicating the median and the 1st and 3rd quartiles.

The diagnostic potential of ICG lymphography with subsequent SLN assessment, as well as preoperative diagnostic methods and intraoperative exploration, in predicting hepatic hilum LN status was studied. Sensitivity was defined as the ratio of the number of patients with correctly predicted metastatic LN involvement to the total number of patients with lymphogenic metastases identified by morphological examination. Specificity was defined as the ratio of the number of patients with correctly predicted absence of lymphogenic metastases to the number of patients without LN metastases according to morphological examination.

RESULTS

A total of 55 patients were included in this study. All patients underwent laparotomy, lymphography with ICG followed by lymph node dissection.

Some patients (32.7 %, *n* = 18) were operated on for liver metastases from rectal cancer. Liver metastases from colon cancer were operated on in 67.3 % of cases (*n* = 37).

Synchronous liver metastases (detected simultaneously with the primary tumor) were found in 34 patients (61.8 %). Of these, in 18 patients (52.9 %), the bowel was resected earlier as the first stage. In 47.1 % of cases with synchronous involvement (*n* = 16), the decision was made to operate on the liver first.

Metachronous liver metastases (detected after the primary tumor surgery) were found in 21 patients (38.2 %). In half of the cases, these were patients older than 58 years; men and women were equally represented. Preoperative parameters are presented in Table 1.

The majority of patients (85.5 %, n=47) received preoperative chemotherapy, most commonly oxaliplatin-based regimens (93.6 %, *n* = 44/47). The median number of chemotherapy cycles was 8 (range 4–28). Disease progression was noted in four patients (7.2 %), stable disease in twenty-five (45.5 %), partial response in seventeen patients (31 %), and complete response (RECIST) in one patient (1.8 %).

Table 1. Patient characteristics before surgery

Parameter		Value
Gender	Male, *n* (%)	29 (52.7 %)
	Female, *n* (%)	26 (47.3 %)
Age, median (first – third quartile), years		58 (34 – 73)
Body Mass Index, median (first – third quartile)		27.12 (22.7–30.55)
Preoperative therapy	Chemotherapy, *n* (%)	47 (85.5 %)
	None, *n* (%)	8 (14.5 %)
Size of the largest liver metastasis according to imaging, median (first – third quartile), mm		61.85 (7–123)
Signs of lymph node involvement according to preoperative imaging	None, *n* (%)	42 (76.3 %)
	Lymphadenopathy, *n* (%)	7 (12.7 %)
	Suspicion, *n* (%)	3 (5.5 %)
	Confirmed involvement, *n* (%)	3 (5.5 %)
CA 19-9 level before surgery, median (first – third quartile), U/ml		8.53 (2–21.9)
CEA before surgery, median (first – third quartile), ng/ml		5.615 (2.4–22)

Signs of LN involvement according to preoperative diagnostics were noted in three patients (5.5 %), and in another three patients (5.5 %) there was suspicion of metastatic LNs.

Lymphography with ICG was performed after laparotomy. ICG injection was administered via a single puncture in 22 cases (40 %), via two punctures in 27 patients (49.1 %), and via three punctures in 6 patients (10.9 %). In six patients (10.9 %), no ICG accumulation was observed in any LN within the 45-minute observation period. It should be noted that in this patient group, subsequent morphological examination did not reveal any metastatic LNs. In the remaining patients (89.1 %, *n* = 49), at least one SLN was identified; 11 of them had LN metastases. The median time for the appearance of staining in the first sentinel lymph node (SLN No1) was 3 minutes (1st – 3rd quartile: 1–5 minutes).

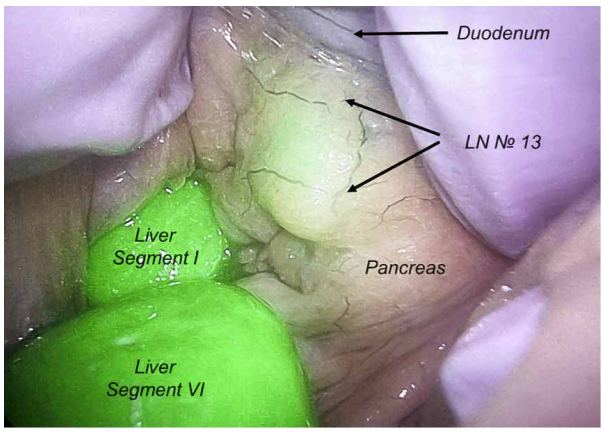

Fig. 1. Uptake of indocyanine green by a station 13 lymph node. LN №13 – Station 13 lymph node

Figure 1 shows ICG accumulation in a LN of station 13 (SLN No2) at the 5th minute after peritumoral injection of the agent into the fifth and fourth liver segments, 1 ml each, resulting in a total of 2 ml injected from two puncture sites, forming three infiltration zones. According to preoperative imaging, LNs in the liver hilum were interpreted as non-involved. Intraoperative examination revealed LNs ranging from 0.5 to 10.0 mm in length, soft, flattened, and appearing visually and palpably non-involved. A total of 6 LNs were removed. Pathomorphological examination revealed metastatic involvement of SLN No2. The remaining LNs were free of metastases.

In half of the cases (56.4 %), the liver metastases exhibited bilobar spread. In one-third of the patients (30.9 %, *n* = 17), signs of metastatic lymph node involvement or suspicion of lymphogenic metastases were noted during surgical exploration. The planned liver resection volume could not be performed in four patients (7.3 %) due to more extensive disease. The remaining patients (92.7 %, *n* = 51) underwent curative-intent liver resection (Table 2).

Table 2. Intraoperative patient characteristics

Parameter		Value
Affected Liver Lobe	Right, *n* (%)	19 (34.5 %)
	Left, *n* (%)	5 (9.1 %)
	Bilobar involvement, *n* (%)	31 (56.4 %)
LN Involvement or Suspicion of Involvement During Exploration	Yes, *n* (%)	17 (30.9 %)
	No, *n* (%)	38 (69.1 %)
Liver Resection Volume	Major liver resection, *n* (%)	17 (30.9 %)
	Limited liver resection, *n* (%)	32 (58.1 %)
	Central resection, *n* (%)	2 (3.7 %)
	Exploratory laparotomy, *n* (%)	4 (7.3 %)
Successful Lymphography (Presence of at Least One SLN)	Yes, LNs involved, *n* (%)	11 (20 %)
	Yes, but no involved LNs, *n* (%)	38 (69.1 %)
	No SLN, *n* (%)	6 (10.9 %)
Operative Time, median (1^{st}–3^{rd} quartile), minutes		270 (210–330)
Blood Loss, median (1^{st}–3^{rd} quartile), milliliters		300 (100–800)

Note: LN – lymph node, SLN – sentinel lymph node.

Hemiphepatectomies were performed on 17 patients (30.9 %). Limited liver resections were predominant (61.8 %, *n* = 34), including two cases of segment IV–V resections. The median operative time was 270 (210–330) minutes, and the median blood loss was 300 (100–800) ml.

Intraoperative red blood cell transfusion was required in one case – a patient with 3000 ml blood loss. No intraoperative complications related to ICG administration were observed.

Characteristics of the follow up are presented in Table 3. Complications developed in 12 patients (21.8 %). Post-hepatectomy liver failure (*n* = 4) predominated and was noted only among patients who underwent major liver resection. Other complications included bile leakage (*n* = 3) and lymphorrhea (*n* = 3). Complications of Clavien-Dindo grade III or higher occurred in 5 cases (9.1 %). One patient experienced bleeding from the LND site, which required re-laparotomy. Post-hepatectomy liver failure led to death in three patients (mortality – 5.4 %).

Among patients in whom at least one SLN was identified (*n* = 49), lymphogenic metastases were not found based on morphological examination in 38 patients. As noted earlier, among patients without SLN staining (*n* = 6), no lymph node metastases were detected either. Among all patients (*n* = 55) included in the study, histopathological examination revealed lymphogenic metastases in 11 cases (20.0 %). The characteristics of patients with lymphogenic metastases are presented below (Table 4). It is important to note that of the 11 patients with morphologically confirmed metastatic LNs, only two (18.2 %) had their involvement indicated by preoperative examination.

In the group of patients with involved LNs, 4 to 21 LNs were removed during lymph node dissection. The median, 1st and 3rd quartiles of removed LNs were 7 (6–13). The median ratio of involved to removed LNs was 0.14 (0.07–0.225).

In the group with lymphogenic metastases, staining of the first LN (SLN 1) occurred at a median of 3 minutes (1–5 minutes). In seven patients (63.6 %), LNs from station 12 were stained in the first step: 12A in three patients, 12B in three patients, and in one case SLN 1 was a cystic LN (12C). In two cases, station 8 LNs were the first to accumulate the agent. In two cases, simultaneous staining of several LN groups occurred at the first step, in both cases involving station 13 LNs and hepatoduodenal ligament LNs (station 12A and 12C, respectively). SLN 1 was metastatic in four patients.

SLN 2 was also identified in all 11 patients with involved LNs, with a median staining time of 5 minutes (1^{st}-3^{rd} quartile: 5–15 minutes). Station 12 LNs accumulated ICG at the second stage in two cases (12A and 12P, one each). Station 8 LNs were stained at the second stage in three patients. In three cases, SLN 2 were station 13 LNs. Station 11 LNs, as well as station 3 LNs, were noted as SLN 2 in one case each. Interestingly, in one patient, station 12A and 8 LNs stained simultaneously during the second observation stage – and the 12A LN was metastatic. Perhaps, by studying lymphatic drainage with a shorter time interval between control points in this patient, it would have been possible to differentiate these LN groups into SLN 2 and SLN 3. Note that formally, SLN 3 was not identified in this patient – no further ICG accumulation was observed. Involvement of SLN 2

Table 3. Postoperative period characteristics

Parameter	Value
Complications, *n* (%)	12 (21.8 %)
Bile Leakage, *n* (%)	3 (5.4 %)
Post-hepatectomy Liver Failure, *n* (%)	4 (7.3 %)
Lymphorrhea, *n* (%)	3 (5.4 %)
Bleeding from LND Site, *n* (%)	1 (1.8 %)
Complications ≥ Grade III, *n* (%)	5 (9 %)
Mortality, *n* (%)	3 (5.4 %)
Number of Involved LNs in N+ Group, median (1^{st}–3^{rd} quartile)	1 (1–1)
Number of Removed LNs in N+ Group, median (1^{st}–3^{rd} quartile)	7 (6–13)
Ratio of Involved to Removed LNs in N+ Group, median (1^{st}–3^{rd} quartile)	0.14 (0.07–0.225)
Number of Removed LNs in the Entire Group, median (1^{st}–3^{rd} quartile)	6 (4–9)

Note: LN – lymph node, LND – lymph node dissection, N+ – lymph node positive.

Table 4. Characteristics of patients with identified lymphogenic metastases

Parameter	Patient Number										
	1	2	3	4	5	6	7	8	9	10	11
Affected Liver Segments	3, 4, 7, 8	4, 5, 6, 8	3, 5, 6, 7, 8	2, 3, 4, 5, 8	2, 3, 6, 7, 8	4, 5, 6, 7, 8	4, 5, 6	2, 4, 5, 6, 7, 8	7, 8	8	4, 5, 8
LNs per MRI/CT	no mts	no mts	no mts	no mts	mts	no mts	no mts	no mts	no mts	no mts	no mts
SLN 1, min	5	3	3	1	1	7	3	1	1	1	10
Group	8	12b, 13	12a	12a	8	12b	12b	12c, 13	12b	12c	12a
Surgeon's Interpretation	mts	susp	susp	susp	mts	no mts	susp	susp	no mts	no mts	no mts
Morphology	mts	mts	no mts	no mts	mts	mts*	no mts	no mts	no mts	no mts	no mts
SLN 2, min	30	25	5	5	5	15	5	2	3	15	5
Group	12a	3	8	8	11	12p	13	12a, 8	13	13	8
Surgeon's Interpretation	susp	no mts	susp	susp	no mts	no mts	no mts	susp	no mts	susp	mts
Morphology	mts	no mts	no mts	no mts	no mts	no mts	mts*	mts	mts**	mts	mts
SLN 3, min	30		8	7	5	-	10	-	5	8	-
SLN 3, group	12b	-	12b	12p	9,7	-	16	-	8	12b	-
Interpretation	susp	-	no mts	susp	no mts	-	no mts	-	no mts	no mts	-
Morphology	mts	-	mts**	mts	no mts	-	no mts	-	no mts	no mts	-
LNs with Metastases	4	1	1	1	1	1	2	1	1	1	1
Removed LNs	7	11	6	5	14	13	6	21	11	4	7
LNR	0.57	0.09	0.16	0.20	0.07	0.07	0.33	0.05	0.09	0.25	0.14
Sensitivity											
SLN 1: 36.4 %, *n* = 4	True Positives	True Positives	False Negatives	False Negatives	True Positives	True Positives	False Negatives	False Negatives	False Negatives	False Negatives	False Negatives
SLN 1-2: 81.8 %, *n* = 9	True Positives	True Positives	False Negatives	False Negatives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives
SLN 1-3: 100.0%, *n* = 11	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives	True Positives

* In two patients (Patients 6 and 7), lymph node metastases were identified only during lymph node dissection with subsequent morphological examination, with no indication of involvement/suspicion of involvement based on MRI/CT or surgical exploration; ** In another two patients (Patients 3 and 9), suspicions of lymphogenic metastases were raised based on exploration, but the groups of metastatic lymph nodes indicated during exploration and those identified by morphological examination differed. Abbreviations: LN – lymph node; SLN – Sentinel lymph node; mts – metastasis; susp – suspicious for metastasis; LNR – Lymph node ratio (ratio of metastatic to removed lymph nodes).

was noted in six patients, including one in combination with involvement of SLN 1.

Staining of LNs at the third stage (SLN 3) occurred in seven patients with a median time of 30 minutes (5–30 minutes). In four cases, station 12 LNs were stained (12B in three cases, 12P in one). Station 8 and station 16 LNs accumulated contrast at the third stage in one case each. In another patient, simultaneous accumulation of ICG in station 7 and station 9 LNs was noted. Involvement of SLN 3 was found in three patients, with only one of them having involvement of both SLN 1 and SLN 2.

Note that when using the first three stained LNs as SLNs, the sensitivity of the method was 100 %. It is also important that after systematic LND, only in one case was a non-SLN involved (9.1 %), while metastases were found in all three SLNs.

We compared data from imaging methods and surgical exploration with morphological examination results in the entire group.

The majority of patients underwent MRI preoperatively (94.5 %, *n* = 52/55). In two patients, MRI raised suspicion of metastases in station 12 LNs, and in another one – in station 8 LNs. None of these patients had involved LNs confirmed by morphology. MRI convincingly indicated metastases in station 12 LNs in three patients; however, one patient had no LN metastases, one patient had involvement of a station 8 LN without involvement of station 12, and in one patient the indication of hepatoduodenal ligament LN involvement was confirmed.

CT was performed in 14 patients (24.4 %), with three patients (5.4 %) undergoing CT alone, without MRI. Suspicion of metastases in station 8 and 12 LNs was raised in one case, and convincing indication of metastases in station 12 LNs was obtained in two other patients. None of them had lymphogenic metastases confirmed by histology.

Previously, in Table 1, it was indicated that suspicion or convincing indication of involvement of hepatic hilum LNs (any station) based on any imaging method (CT and/or MRI) was noted in six patients (10.9 %). The interpretation was correct in only two cases (33.3 %), in the other four cases the result was a false positive. The sensitivity of the method was 18.2 %, specificity was 90.9 %.

During intraoperative exploration, suspicion of metastases in hepatic hilum LNs (any location) was raised in 17 patients, but only in half of them (52.9 %, *n* = 9) were metastatic LNs of the hepatic hilum confirmed by morphological examination. Both the sensitivity and specificity of intraoperative exploration in determining hepatic hilum LN status were 81.8 %. It is worth emphasizing that, despite the fact that in 9 out of 11 cases the prediction of involvement of any hepatic hilum LNs was correct based on exploration data, the location of the suspected involved LNs in two patients (Patients 3 and 9) (Table 4) was not confirmed by morphological results. With selective lymphadenectomy performed based on exploration data, unrecognized involved LNs in these two patients would also not have been removed, as in two other cases (Patients 6 and 7) (Table 4), where exploration did not suggest involvement of hepatic hilum LNs.

DISCUSSION

Liver resection for CRC metastases is a standard approach, yet the role of hepatic hilar lymph node dissection (LND) is frequently debated. One argument in favor of LND for CRC liver metastases is the high incidence of involvement of stations 8, 12, and 13 lymph nodes, which can reach 14–20 % [2–4]. This was confirmed in our study – in one out of every five patients (20 %, *n* = 11/55) who underwent liver resection with LND, lymphogenic metastases were identified upon morphological examination of the resected specimen.

Extrahepatic metastases in CRC, including metastatic involvement of hepatic hilar LNs, worsen the prognosis. However, performing surgery with removal of all detectable disease manifestations in combination with systemic therapy allows for long-term survival in 20 % of patients with CLM and lymph node involvement [8, 10]. Advances in systemic therapy for metastatic CRC have led to expanded indications for liver resection, including in cases with additional extrahepatic metastases. In the ESMO clinical guidelines, metastases to hepatic hilar lymph nodes are no longer a contraindication to resection [9].

However, the question of LND of the hepatic hilum and its extent remains controversial. In their study, Pindak D. compared the results of systematic versus selective LND during liver resection for CLM. Systematic LND was defined as dissection removing LNs from stations 12, 8, and 9. Selective LND involved removal of LNs suspicious for metastasis. The authors noted that performing systematic LND did not significantly increase the complication rate compared to selective LND (13.63 % vs. 8.69 %, *p* = 0.36). Patients with metastatic LNs had worse long-term outcomes, with a median OS of 29.6 months compared to 66.97 months in patients without lymph node involvement (*p* = 0.0001). On one hand, the authors noted a higher detection rate of LN metastases with systematic versus selective LND (11.11 % vs. 3.7 %). In other words, in some patients undergoing selective LND, involved LNs might not have been recognized and removed. However, the difference in detection rate of involved LNs was not statistically significant (*p* = 0.4), and the authors themselves attributed the difference in diagnosing LNs metastases to some patient selection – during a certain time period, clinically detectable metastases in

hepatic hilar LNs were a contraindication to continuing the operation. Indeed, in the cited work, only one patient in the selective LND group with involved LNs underwent liver resection. Furthermore, in the group of patients without LNs involvement (n = 74), systematic LND did not affect OS (HR 1.17; 95 % CI 0.6–2.11, p = 0.6). In the overall patient group (n = 81), there was also no difference in the risk of death (HR 0.90; 95 % CI 0.52–1.58, p = 0.7), with median OS being about 5 years in both groups. The authors concluded that LND is relatively safe but does not affect prognosis [24].

The study by Hess G. et al. similarly showed that systematic LND did not improve overall (p = 0.959) or disease-free survival, p = 0.076. Moreover, more extensive LND led to increased postoperative complications (p = 0.0023). According to the authors, performing LND is justified when metastases are suspected preoperatively or during surgery [4].

Proponents of systematic LND point to the inaccuracy of preoperative diagnosis and intraoperative exploration in determining the status of hepatic hilar LNs. In the study by Rau C., 76 patients with CRC liver metastases underwent liver resection combined with LND removing LNs from stations 12, 8, and 13. Lymph node metastases were found histologically in 20 % of cases. The authors note that in more than a quarter of patients (27 %), LNs involvement was detected only based on the results of systematic LND. Preoperative CT and intraoperative exploration did not raise suspicion of LNs involvement in these patients [3]. In the previously cited work by Hess G. et al., it was also noted that preoperative diagnostics were not sufficiently accurate in determining LNs metastases; in 18.5 % of patients, metastatic LNs were detected only by LND with subsequent morphological examination. The authors concluded that LND improves staging, but systematic LND did not impact long-term outcomes [4].

In controversial cases, PET/CT can be used. Its sensitivity in detecting metastases in hepatic hilar LNs exceeds 90 %, which is higher than CT/MRI (93.5 % vs. 64.5 %, respectively, p = 0.011), but the method is not routine [11].

In our study, as noted above, after systematic LND with removal of LNs from stations 8, 12, and 13, as well as all nodes stained during observation outside these stations, morphological examination revealed LN involvement in 11 out of 55 patients (20 %). In one-third of the patients (two out of six) in whom CT and/or MRI indicated suspicion or involvement of hepatic hilar LNs, this involvement was indeed present. On the other hand, absence of hilar LNs involvement was indicated by MRI/CT in 49 cases, but in 9 patients they were involved. Thus, in the group of patients with involved LN (n = 11), only in two patients (18.2 %) did preoperative examination methods allow prediction of this involvement, confirming the low sensitivity of routine preoperative radiological methods in determining lymphogenic metastasis. However, we note the acceptable specificity of preoperative examination in assessing LNs status (90.9 %).

In the aforementioned work by Rau C. et al., a high frequency (up to 20 %) of hepatic hilar LNs involvement is noted based on morphological examination after performed LND. Moreover, in 27 % of cases, intraoperative exploration did not suggest lymphogenic metastases [3].

According to the results of the present work, in one-third of patients (30.9 %, n = 17/55), exploration revealed either convincing signs of metastatic involvement of hepatic hilar LNs, or lymphogenic metastases were suspected. In nine patients, LNs metastases were morphologically confirmed, showing acceptable sensitivity (81.8 %) and specificity (81.8 %) of exploration in predicting the detection of LNs from stations 8, 12, and 13. However, only in seven of them did the location of the involved nodes according to exploration and morphological examination coincide. Only adherence to the protocol of the present work – performing at least systematic LND with removal of stations 12, 8, and 13 nodes in all patients with careful labeling of the removed specimens – allowed detection of these metastases and establishment of their topographic location. Thus, in four out of eleven patients (36.4 %) with morphologically confirmed lymphogenic metastases, LNs involvement with precise localization was not established during exploration; in these patients, involved nodes were detected only during morphological examination after systematic LND. It is noteworthy that in these four patients, radiological diagnostic methods were negative for LNs metastases.

Positive results of using SLN identification methods with ICG are known for various oncological diseases [13–17]. However, studies on SLN in liver resection are few. We note the successful application of ICG lymphography in determining lymphatic drainage from the affected part of the liver in biliary cancer in most patients (12/20) in the study by Zhang Y. et al. The proposed method allowed performing LND with removal of a larger number of nodes (7 vs. 3.5, $p < 0.001$), and the ratio of involved to removed LNs was also higher in the experimental group (75.0 % vs. 33.3 %, $p < 0.001$). In other words, the proposed method allowed for more precise LND in intrahepatic cholangiocarcinoma [18]. The study by Ruzzenente A. et al. describes a method for determining SLN and the main lymphatic drainage pathway from the liver in primary and metastatic liver cancer, as well as biliary cancer, using ICG lymphography. Despite generally positive results, attention is drawn to the small number of patients with CRC liver metastases

(*n* = 2) and the absence of LN staining in one of them. Also, note that patients with CLM underwent limited lymphadenectomy with removal of 1 LN in one case and three LNs in another, which does not exclude the presence of lymphogenic metastases in non-removed nodes. At the same time, none of the patients had involved nodes in the studied specimens, which does not allow judgment on the feasibility of the method for CLM [19].

In our study, the method was applied to a significant pool of patients with CLM (*n* = 55), with SLNs identified in 49 (89.1 %) and LNs metastases in 20.0 %. Comparison of the results of preoperative MRI/CT, exploration data, and morphological findings demonstrated the unreliability of radiological and clinical signs in interpreting the status of hepatic hilar LNs in CRC with liver involvement. At the same time, the sensitivity of ICG lymphography in determining SLNs in patients with involved hepatic hilar LNs was 100 % (11 out of 11), but only when using the first three stained lymph nodes as sentinel nodes.

The results obtained in this study can be used to perform more accurate LND in patients with CLM. The necessity of removing the first three LNs accumulating ICG to achieve 100 % sensitivity of lymphography is explained by the complexity of lymphatic drainage from the liver, as indicated in several studies [18, 20, 21]. On the other hand, as our experience shows, in the majority of patients (90.9 %) with involved hepatic hilar LNs, removal of precisely the first three stained nodes is sufficient, since in 10 out of 11 patients, lymphogenic metastases were limited to SLNs 1–3.

CONCLUSION

Lymphogenic metastases of the hepatic hilum are detected in 20 % of cases in patients with CML. However, preoperative diagnostic methods and intraoperative exploration do not allow for confident assessment of lymph node status or precise localization of involved LNs. When planning liver resection in patients with CLM, the use of ICG lymphography with removal of at least three SLNs is feasible to achieve more selective and accurate LND of the hepatic hilum. It is advisable to evaluate the impact of LND, performed with consideration of ICG lymphography findings on long-term outcomes in patients with resectable CLM.

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