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Twenty-year experience in liver surgery in metastatic colorectal patients: a case series study in Ukraine

Anton Burlaka, MD, PhD[a,*], Anton Ryzhov, PhD[g], Yurii Ostapenko, MD, PhD[c], Natalia Bankovska, MD, PhD[d], Kostiantyn Kopchak, MD, PhD[e], Vitalii Zvirych, MD, PhD[a], Tetiana Golovko, MD, PhD[b], Andriy Shypko, MD, PhD[f], Andrii Lukashenko, MD, PhD[f]

Background: For the last three decades, the world surgical community successfully adopted different surgical strategies for colorectal cancer (CRC) patients with liver metastases (LM), however, we are still seeing the evolution of treatment guidelines. The purpose of the study was to analyze a 20-year evolution of CRC patients with LM being treated in a specialized state Ukrainian oncological center.

Materials and methods: The retrospective analysis of 1118 CRC patient cases using prospectively collected patient data from the National Cancer Institute registry. The time ranges between 2000–2010 and 2011–2022 and the LM manifestation – metachronous (M0)/synchronous (M1) were the two main grouping criteria.

Results: The overall survival 5-year survival of patients who had surgery between 2000–2011 and 2012–2022 was 51.3 and 58.2% ($P = 0.61$) for the M0 cohort and 22.6 and 34.7% at M1 ($P = 0.002$), respectively. The results of the multivariate analysis in 1118 cases revealed that liver re-resection and regional lymph node dissection ≥ D2 were associated with better overall survival [hazard ratio (95% CI) = 0.76 (0.58–0.99) $P = 0.04$] in the M0 cohort and receiving at least 15 courses of chemotherapy had better recurrence-free survival rates [hazard ratio (95% CI) = 0.97 (0.95–0.99), $P = 0.03$] for both M0 and M1.

Conclusions: It was shown the improvement of the oncological prognosis for CRC patients with synchronous LM who were treated after 2012. The adaptation of world experience algorithms and the surgical strategy evolution have become the root cause of the above.

Keywords: case series, colorectal cancer, liver metastases, liver resection, parenchyma sparing

Introduction

One of the top five malignant neoplasms in terms of frequency of diagnosis in Ukraine is CRC. And nearly 18 000 new people are diagnosed with it each year among the adult population[1]. According to medical records, LM are diagnosed in more than half of CRC patients for the period of 'anamnesis morbi,' and in 95% of cases it leads to cancer-specific death[2–4].

For a long time, the number and size of metastatic lesions of CRC in the liver were considered as a 'guideline' for resection[5,6]. However, the evolution of oncology has made it possible to implement more extreme approaches in liver surgery[7,8]. Until now the debates between advocates of two main strategies in CRC patient's liver resection (LR) are ongoing[9]. One of which is the two-stage LR, which was successfully adapted by the international surgical community[10]. In contrast, the first-choice strategy in the world for CRC metastases removal remains one-stage parenchymal-sparing surgery[11]. The adaptation of intraparenchymal 1–2 order vessel skeletonization and intraoperative ultrasound guidance significantly increased the precision of resection and thereby resectability[12]. In contrast, two-stage anatomical liver surgery increased resectability by augmenting the future liver remnant and in cases of bilobar LM these two strategies routinely accompany each other. Hepatobiliary surgeons worldwide have adopted laparoscopic minor wedge resections and left lateral sectionectomies after the Louisville Laparoscopic Liver Resection conference[13]. Whereupon the last

HIGHLIGHTS

- The aim of this work was to analyze a 20-year period of colorectal cancer (CRC) patients with liver metastases (LM) treatment who have undergone it in a specialized state Ukrainian oncological center.
- Parenchymal-sparing liver surgery implementation associated with a better long-term oncological prognosis.
- Receiving of more the 15 courses chemotherapy (CTx) improved recurrence-free survival rates.

Departments of [a]Colorectal Cancer, [b]Radiology, [c]Minimally Invasive Surgery, [d]Science, [e]HPB, National Cancer Institute, [f]National Cancer Institute and [g]Department of Cancer Control, National Cancer Registry of Ukraine, Kyiv, Ukraine

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**Corresponding Author. Address: Colorectal Cancer Department of NCI, Lomonosova, Kyiv 03022, Ukraine. Tel: +380 678 002 748. E-mail address: nir.burlaka@gmail.com (B. Anton).*

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Table 1

General characteristics of patients[a]

Indicators	Total ($N=1118$)	Metachronous LM (M0) ($n=515$)		Synchronous LM (M1) ($n=603$)	
Time lines	**2000–2022**	**2000–2011**	**2012–2022**	**2000–2011**	**2012–2022**
Age [mean (SD)]	66 (13)	65 (12)	67 (10)	64 (11)	66 (12)
Male sex	526 (47)	27 (2.4)	225 (20.1)	33 (3.0)	241 (21.6)
Primary tumor status, AJCC, sixth					
pT1–pT3	684 (61.2)	36 (6.9)	288 (55.9)	66 (10.9)	294 (48.8)
pT4	434 (38.8)	13 (2.5)	221 (42.9)	18 (3.0)	182 (30.2)
Status of regional lymph nodes					
pN0	671 (60.0)	32 (6.2)	298 (57.9)	35 (5.8)	306 (50.7)
pN1–pN2	447 (40.0)	17 (3.3)	168 (32.6)	49 (8.1)	213 (35.3)
Primary tumor location					
Right colon	117 (10.5)	9 (1.7)	44 (8.5)	11 (1.8)	53 (8.8)
Left colon	1001 (89.5)	40 (7.7)	422 (81.9)	73 (12.1)	466 (77.3)
Metastasis spread characteristic					
Bilobar metastases	274 (24.5)	4 (0.7)	117 (22.7)	8 (1.3)	145 (24)
Extrahepatic disease	36 (3.2)	1 (0.2)	19 (3.7)	3 (0.5)	13 (2.2)
Lung metastases	184 (16.5)	8 (1.5)	69 (13.4)	13 (2.2)	92 (15.3)

[a]Unless otherwise stated, numbers are represented as *n* (%).
AJCC, American Joint Committee on Cancer; LM, liver metastases.

meta-analysis demonstrates favor of a laparoscopic approach over open LR for reducing postoperative complications, and hospital stay, and improving survival[14]. In parallel, the evolution of the surgery of the primary CRC tumor took place, by taking into account anatomical, embryological, and oncological aspects[15–17]. And the CTx optimization in combination with target and immunotherapy directed to controlling the 'waves' of tumor progression was done[18].

The above-described evidence-based medicine evolution has had its impact on the treatment approaches for patients with CRC in Ukraine. Therefore, the purpose of this study was to analyze a 20-year period of CRC patients with LM treatment who have undergone it in a specialized state Ukrainian oncological center.

Materials and methods

A retrospective single-centre consecutive analysis of 1118 CRC patients, who received surgical treatment for primary tumor and metastatic liver lesion between 1 January 2000 and 1 July 2022 has been performed in the state clinic of National Cancer Institute (Kyiv). The time ranges between 2000–2010 and 2011–2022 and the LM manifestation – metachronous/synchronous (M0/M1) were the grouping criteria. The manuscript is written in line with the PROCESS 2020 criteria[19]. The Ministry of Health of Ukraine sponsored the study, but had no role in the design, data gathering, data analyses, or writing of the manuscript (registered in www.researchregistry.com, no. 1480). The study protocol has been approved by the Regional Ethical Committee of National Cancer Institute, Kyiv (ID 76 of 15.01.2015). The authors gathered and analyzed the data from The National Cancer Registry of Ukraine and wrote the manuscript.

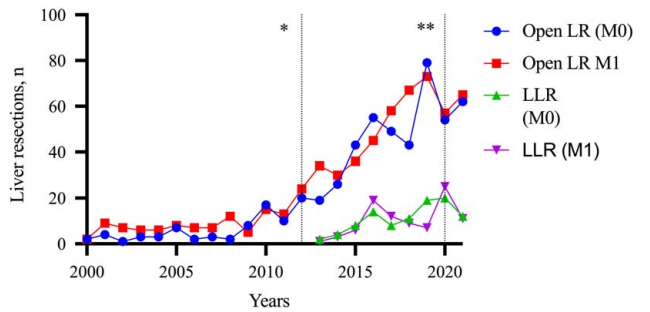

Figure 1. The experience curve of open and LLRs in patients with colorectal cancer. *Performed more than 50 open interventions per year. **Performed more than 35 LLR per year. LLR, laparoscopic liver resection; LR, liver resection.

The preoperative patient management optimization was standardized from 2009 with ERAS protocols implementation[20]. Patients received CTx accordingly to the Ukrainian guidelines from 2000 till 2011 and as recommended by the multidisciplinary team meeting from 2012 till present time. Since 2000, adjuvant CTx in Ukraine has included the Mayo regimen and monotherapy with fluorofur, while capecitabine regimen started from 2005. From 2007 doublet regimens based on oxaliplatin and irinotecan have been included in the Ukrainian guidelines. Subsequent to 2010 and 2012, the state and local guidelines have included CTx with anti–vascular endothelial growth factor and anti–epidermal growth factor receptor–based regimens. Triplet regimens has been used after 2016.

Inclusion criteria comprise CRC patients with morphologically approved adenocarcinoma with at least 1 LM, who completed the surgical treatment of primary tumor and liver/lung metastases. Exclusion criteria included patients carriers of more than 5 resectable lung metastases, and/or unresectable peritoneal carcinomatosis.

Surgical techniques included anatomical-oriented, parenchyma sparing LR, radiofrequency ablation (RFA), electrochemical treatment, cryotherapy. All the surgical procedures in the time range beetween 2000 and 2011 were performed by consultant hepato-pancreatico-biliary (HPB) surgeons skilled in the technique in use. In the period between 2012 and 2022 LRs were performed by four surgeons trained in HPB surgery and experienced in open liver surgery (≥ 50 resections), laparoscopic

Table 2

Characteristics of surgical treatment[a]

Indicators	Metachronous LM (M0)		Synchronous LM (M1)	
Time lines	**2000–2011**	**2012–2022**	**2000–2011**	**2012–2022**
Total operations performed	49 (9.5)	466 (90.5)	84 (13.9)	519 (86.1)
LRs				
Anatomical	24 (4.7)	43 (8.3)	44 (7.3)	214 (35.5)
Nonanatomical	19 (3.7)	25 (4.8)	25 (4.1)	31 (2.7)
Parenchymal-sparing	–	2	–	256 (22.8)
RFA	4 (0.8)	5 (1.0)	8 (1.3)	18 (3.0)
Electrochemiolysis	1 (0.2)	7 (1.4)	1 (0.2)	–
Cryodestruction	1 (0.2)	–	6 (1.0)	–
Major LR	–	38 (7.4)	–	41 (6.8)
Re-resections of the liver	–	69 (13.4)	–	91 (15.1)
Simultaneous surgery	–	–	2 (0.3)	163 (27.1)
Laparoscopic colon surgery	–	283 (55)	–	323 (53.6)
Lymph node dissection				
D1	49 (9.5)	–	84 (13.9)	–
D2 and higher	–	466 (90.5)	–	519 (86.1)
LLR	–	116 (24.8)	–	95 (18.3)
Major LLR	–	24 (5.2)	–	18 (3.5)
Lung resections	16 (3.1)	105 (20.4)	8 (1.3)	55 (10.6)
CTx (courses) (mean ± SD)	4.6 ± 0.6	8.5 ± 0.4	3.8 ± 0.4	9.7 ± 0.4
No CTx	13 (2.5)	77 (15)	20 (3.3)	65 (10.8)
CTx + radiation therapy	13 (2.5)	123 (23.9)	18 (3.0)	94 (15.6)
Overall	515		603	

[a]Unless otherwise stated, numbers are represented as *n* (%).

CTx, chemotherapy; LLR, laparoscopic liver resection; LM, liver metastases; LR, liver resection; RFA, radiofrequency ablation.

interventions were performed by two surgeons who also completed a laparoscopic and open HPB training programs and experienced more than 25 laparoscopic liver resections (LLRs). The complete removal of at least 1 Couinaud's segment containing the tumor burden together with the related portal vein and the corresponding hepatic territory was defined as the anatomical LR. Whereas the resections of the metastatic lesion with a margin of at least 1 cm, whenever possible, without regarding the segmental anatomy of the liver were recognized as nonanatomical. All parenchyma sparing surgical LRs included crash-clamping or cavitron ultrasonic surgical aspirator with resection margin size of at least1 mm. In possible cases a tactic of 'vascular detachment' has been used. Ischemia technique included classical Pringle maneuver (20 min – ischemia, 5 min – reperfusion). All parenchyma sparing LRs were accompanied by intraoperative ultrasound navigation.

Complication data were collected from the medical record. Major complications were defined either as requiring intensive care unit stay, treatment by an interventional radiologist, or reoperation, or as resulting in death.

Primary outcome was measured by analyzing of overall survival (OS) and recurrence-free survival (RFS) rates after liver surgery. Follow-up was done every 4 months for the first 3 years and then every 6 months for the next 2 years and then every 12 months per year in the time range between 2011 and 2022.

Statistical analysis

Descriptive data are presented with means, SDs, medians, interquartile ranges, numbers, and percentages. Categorical variables were compared using the χ^2 or Fisher exact test when applicable. Survival analyses done using Kaplan–Meier method, the log-rank test and Cox proportional hazards regression to compare outcomes between groups. Differences between median values compared using Mann–Whitney *U*-test. For comparison between two groups with categorical variables the two-sided Fisher's exact test used. *P*-value less than 0.05 considered statistically significant. To identify predictors of survival, univariable and multivariable analyses were done using the log-rank test and the Cox proportional hazards model. Statistical analyses performed using Prism 9.0.

Results

A total of 1118 patients with CRC have been operated between 1 January 2000 and 1 July 2022, all patients completed the surgical program according to the standards of that time. Cohorts with synchronous (M1) and metachronous (M0) LM included 603 and 515 patients, respectively. Distribution by sex, age, primary tumor localization, regional, and distant metastases spreading are represented and stratified according to the time ranges of between 2000–2011 and 2012–2022 (Table 1).

In 61.2% primary tumors did not penetrate the surface of visceral peritoneum (pT1–pT3) and in 60% regional lymph nodes had negative status. The vast majority of primary tumors (89.5%) were the left colon cancers.

Bilobular metastases were seen in 23.5 and 25.4% of cases in cohorts metachronous and synchronous LM, respectively ($P = 0.93$). Extrahepatic intra-abdominal spread of the metastatic was in 3.2% of the cases. In addition, 16.5% of patients had synchronous metastatic lung lesions.

Open liver surgeries exceeded 50 per year in 2012, although the maximum surgical activity was recorded in 2019 (152 resections per year) (Fig. 1). The first LLR was done in 2012 and the most of them ($n = 35$) were done in 2020. A separate analysis was performed by decades: 2000–2011 and 2012–2022, taking into account the fact that the center was low-volume in terms of the number of open LR performed up until 2011. A total of 133 procedures were carried out between 2000 and 2011 (11.8%), 111 of which (9.9%) were resections, 12 (1.2%) were RFA, 7 (0.6%) were cryodestructions, and two (0.2%) patients underwent electrochemolysis therapy. The majority of resections were done between the years of 2012 and 2022, with 466 (90.5%) of them being for synchronous metastatic lesions and 519 (86.1%) for metachronous ones.

The number of LR increased exponentially between 2011 and 2020, reaching a peak of over 100 in 2017 – 20% of which were laparoscopic procedures. The overall number of LLR from 2012 to the analysis's time was 211 (21.4%). The majority of LLR were performed according to the principles of parenchymal-sparing surgery, anatomical major LRs were successfully performed in 24 (5.2%) and 18 (3.5%) patients with metachronous and synchronous LM. The analysis also took into account 160 re-resections, 79 big resections, and 642 (57.4%) parenchymal-sparing resections that were carried out between 2014 and 2022. In the cohort of M1 patients, the strategy of simultaneous resections of primary tumors and metastases in the liver was adapted in 165 (27.1%) of the cases. Until 2011, regional lymph node dissection was performed in the D1 volume (9.5 and 13.9%), starting from 2012, D2 and D3 dissection types have been performed.

Laparoscopic surgery of the primary colon and rectal tumors was implemented in 2014, and as of the analysis, 606 laparoscopic interventions had been registered, accounting for 61.5% of all operations in the surgical department. Lung resections due to metastatic disease were performed in 16.4% of patients. Surgical treatment without CTx was registered in 17.5 and 14.1% of cases, respectively, at metachronous and synchronous group. The number of the CTx courses that the patients received after 2012 was higher (8.5 ± 0.4 vs. 4.6 ± 0.6 for M0 and 9.7 ± 0.4 vs. 3.8 ± 0.4 for M1) in comparison with the time range between 2000 and 2011 (Table 2).

The OS at 1-, 3-, 5-, 10-, and 20-year survival rates were 98.6, 78, 57.1, 28.5, and 14.6%, respectively, for the metachronous cohort and 93.3, 58, 30.5, 17.5, and 8.6% for synchronous ($P < 0.0001$) (Fig. 2). The 5-year OS rate in the cohort of patients who received only surgical treatment and both CTx with surgery was 61.2 and 56.2% ($P = 0.43$) in the metachronous cohort and 16.5 and 31.5% ($P = 0.006$) in patients with synchronous LM. The OS 5-year survival of patients who had surgery between 2000–2011 and 2012–2022 was 51.3 and 58.2% ($P = 0.61$) for the M0 cohort and 22.6 and 34.7% at M1 ($P = 0.002$), respectively. The OS 5-year survival rate depending on the embryonic distribution was 54.2 and 57.3% for patients in the M0 cohort with tumors located in the right and left colon, respectively ($P = 0.67$). Whereas for CRC patients with M1, 5-year OS was 23.7 and 31.4%, respectively in right and left colon cohort ($P = 0.14$).

The results of multivariate analysis revealed that the spread of the primary tumor beyond the serosal membrane, synchronous manifestation of metastatic disease in the liver, simultaneous metastatic lesions of the lungs and liver, and extrahepatic intra-abdominal spread had a negative impact on OS. Whereas liver re-resection and regional lymph node dissection $\geq$D2 were associated with better OS in the M0 cohort. Moreover, the rate of RFS was significantly lower in the cohorts of patients with regional lymph node involvement and extrahepatic intra-abdominal spread of metastases, while better RFS rates in both M0 and M1 have been observed in the cohort who received at least 15 CTx courses.

Meanwhile, the number of CTx courses, the status of the R1v resection margin, the simultaneous surgical strategy did not affect the OS rate, nor did the LLRs affect the RFS (Table 3).

Discussion

The history of the treatment of CRC patients is an example of the influence of technical progress on the strategy paradigm. Therefore, the stages of the 20-year evolution of liver surgery for its metastatic lesions were examined as part of a retrospective investigation of 1118 individuals with CRC in Ukrainian state center. The results of this analysis confirm the importance of using a parenchymal-sparing surgical strategy, which increases the chances of repeated re-resections of the liver, since such a strategy is associated with better OS rates. More than 40% of CRC

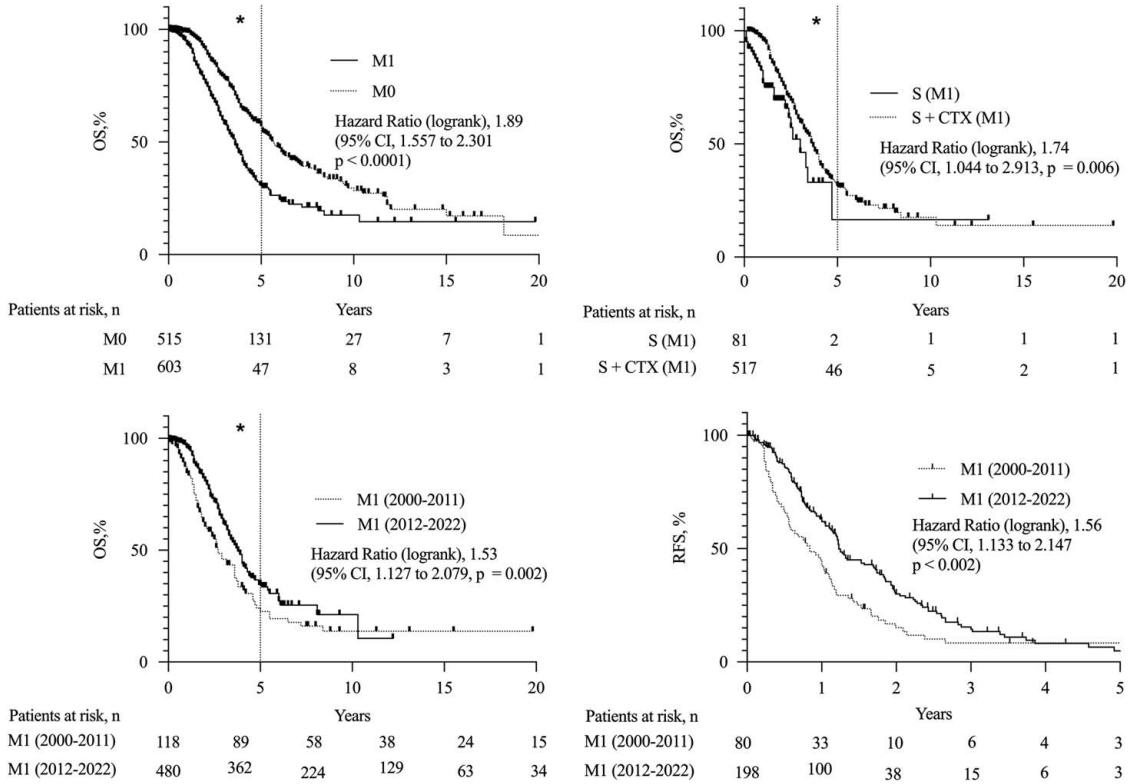

Figure 2. The overall survival (OS) and recurrence-free survival (RFS) of 1118 patients with colorectal cancer. Where 'M0' and 'M1' are patients with metachronous and synchronous liver metastasis, respectively; 'S(M1)' – cohort of patients with synchronous metastasis who received only surgical treatment; 'S + CTx (M1)' – cohort of patients with synchronous metastasis who received surgical treatment and CTx; 'M1 (2000–2011)' and 'M1 (2012–2022)' – cohorts of patients with synchronous metastasis who were treated in the corresponding time intervals. *A vertical dashed line in the graph represents the 5-year survival rate.

Table 3

Univariate and multivariate analyses of prognostic factors for OS and RFS

	OS			RFS		
	Univariable	Multivariable Cox regression analysis		Univariable	Multivariable Cox regression analysis	
Variables	*P*	Hazard ratio (95% CI)	*P*	*P*	Hazard ratio (95% CI)	*P*
Sex (female)	< 0.001	0.86 (0.71–1.1)	0.14	0.09	1.22 (0.92–1.62)	0.15
Surgery alone	0.19	1.4 (0.94–2.1)	0.07	0.59	0.79 (0.38–1.43)	0.47
CTx ≥ 15 cycles (M0 and M1)	0.61	1.4 (0.65–2.7)	0.14	0.002	0.97 (0.95–0.99)	0.03
Parenchyma sparing surgery	0.01	1.2 (0.81–1.8)	0.33	0.44	1.95 (0.98–3.88)	0.06
Primary tumor (right sided)	0.09	1.1 (0.73–1.7)	0.61	0.11	0.78 (0.43–1.37)	0.39
AJCC (pT4)	0.004	1.3 (1.0–1.5)	0.04	0.08	1.09 (0.85–1.39)	0.48
Lymph nodes involvement (pN2)	0.005	1.0 (0.88–1.2)	0.81	< 0.001	1.82 (1.14–3.12)	0.02
Primary tumor (recti)	0.06	1.0 (0.76–1.5)	0.79	0.47	1.12 (0.75–1.483)	0.72
LM (M1)	< 0.001	1.8 (1.4–2.2)	< 0.001	0.21	1.01 (0.75–1.35)	0.94
Extrahepatic disease	< 0.001	3.4 (1.4–7.0)	0.003	< 0.001	1.03 (1.01–1.04)	0.002
Bilobar metastases	0.34	0.92 (0.58–1.4)	0.68	0.17	1.08 (0.01–0.08)	0.9
Liver re-resections	0.01	0.55 (0.31–0.90)	0.03	0.76	1.14 (0.58–2.03)	0.68
Lung metastases (present)	0.02	0.64 (0.48–0.83)	0.001	< 0.001	1.02 (0.68–1.46)	0.94
Regional lymph node dissection (≥ D2) for M0 cohort	< 0.001	0.76 (0.58–0.99)	0.04	0.07	1.12 (0.93–1.35)	0.21
R1 vascular detachment	0.67	0.96 (0.47–1.8)	0.91	0.61	1.53 (0.71–2.88)	0.22
Simultaneous surgery (M1 cohort)	0.09	1.3 (0.75–2.2)	0.34	0.21	0.77 (0.35–1.49)	0.48
LLR	0.89	0.90 (0.58–1.3)	0.61	0.78	1.23 (0.74–2.01)	0.36

AJCC, American Joint Committee on Cancer; CTx, chemotherapy; LLR, laparoscopic liver resection; LM, liver metastases; OS, overall survival; RFS, recurrence-free survival.

patients experience recurring waves of localized metastatic liver damage after the surgical program is over[21]. This requires the use of seond-line CTx and re-resection. Also, the improvement of CTx over the last decade in Ukrainian guidelines has provided the shift in the recurrence-free survival due to the improvement of resectability. And parenchymal-sparing surgery allows for an individualized application of the surgical method with minimal risks of falling into the 'drop-out' group due to tumor progression and improves the liver re-resection perspective[22].

The era of the anatomically oriented LR did not demonstrate advantages in the treatment of metastatic CRC disease, this analysis confirmed that the 5-year OS of patients who were operated on in the time range between 2000–2011 and 2012–2022 for the M1 cohort was 22.6% (anatomical resections) and 34.7% (parenchymal-sparing–oriented method) ($P = 0.002$). Also this approach contradicts the model of progression and metastasizing of CRC[23]. Molecular studies have shown the simultaneous and not interdependent presence of very early lymphatic and hematologic tumor spread the dissemination of CRC cells from the primary tumor at I–II stages of the disease[24]. That is why contemporary multidisciplinary teams should strive to develop an individualized treatment strategy taking into account the duration and frequency of CTx and the optimal time for resection. In our opinion, the latter should be planned with foresight, because in half of the cases, the success of the surgical program does not depend on the first resection of the liver. The diffusion of micrometastases and the dormant state of CRC cells are currently the main arguments against performing a wide resection margin liver surgery for these patients[25].

The use of intraoperative ultrasound navigation during liver surgery, preservation of parenchyma in the right venous core, elements of vascular skeletonization, and research into the pathological effects of ischemia–reperfusion problems first emerged at the National Cancer Institute in 2012 and were finally standardized in 2015[26–28]. Until that moment, the center's surgeons followed the principles of anatomical-oriented or nonanatomical resections and used the strategy of two-stage LR for bilobar metastases, which was accompanied by a higher level of complications and worse oncological results. Our state center was able to consistently raise survival rates for one of the most challenging metastatic cancers by using the capabilities of parenchymal-sparing LRs and LLRs. We believe that such a strategy should be implemented within the framework of state programs. Unfortunately, according to the latest Ukrainian CRC statistical offices data, every year one third patients do not survive 12 months and only 69.4% of all patients received anticancer treatment (35.1% surgical and 34.3% combined)[29].

Current improvement of laparoscopic technologies and energery systems can be used to improve surgical strategy, as was recently demonstrated in the context of the randomized trial, which enables reliable reduction of the level of postoperative complications and cost with parity in terms of oncological effect[30]. In addition, a team of Japanese surgeons demonstrates the prospects for the development of liver surgery through ICG visualization of resection margins, according to their preliminary results, it allows to reduce the risks of liver dysfunction and improve the radicalism of the operation[31]. The latter has the potential to improve both liver surgery and oncological prognosis. The obtained results of our study and literature data demonstrate the importance of a wider implementation of LLRs strategy within the framework of a randomized study in Ukrainian high-volume centers.

Conclusions

The improvement of the oncological prognosis for CRC patients with synchronous LM who were treated after 2012 has been shown. The adaptation of world experience algorithms and the surgical strategy evolution have become the root cause of the above. Important surgical prognostic factors for better OS rates include standardizing regional lymph node removal, liver re-resections and parenchyma sparing surgery implementation.

Receiving of more the 15 courses CTx improved recurrence-free survival rates.

Strengths

The strength of the study follows the multivariate analysis of 1118 CRC patients conducted, who were treated during last two decades in a specialized center.

Limitations

Recurrence-free data was obtained fom 976 patients, which could affect the results of multivisceral resection. We also understand the low quality of the observation results for the time range 2000–2012 due to equipment problems. Moreover, diagnostic radiological algorithms and intraoperative ultrasound technologies have been adopted from 2014 which have the huge impact on the oncological results.

Ethical approval

Ethical approval for this study was obtained from the NCI Ethics Service committee (Project ID 76 of 15.01.2015).

Consent

Not required.

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Author contribution

A.B.: Main idea, design, paper writing, paper translation. A.R.: Statistical analysis, software. A.L.: Supervision and idea. All other co-authors: Study concept.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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References

[1] Archambault AN, Su YR, Jeon J, *et al*. Cumulative burden of colorectal cancer-associated genetic variants is more strongly associated with early-onset vs late-onset cancer. Gastroenterology 2020;158:1274–86.
[2] Kaminski MF, Robertson DJ, Senore C, *et al*. Optimizing the quality of colorectal cancer screening worldwide. Gastroenterology 2020;158:404–17.
[3] Pretzsch E, Bösch F, Neumann J, *et al*. Mechanisms of metastasis in colorectal cancer and metastatic organotropism: hematogenous versus peritoneal spread. J Oncol 2019;2019:7407190.
[4] Chen J, Zheng Y, Wang H, *et al*. Cause of death among patients with colorectal cancer: a population-based study in the United States. Aging 2020;12:22927–48.
[5] Nordlinger B, Quilichini MA, Parc R, *et al*. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. Ann Surg 1987;205:256–63.
[6] Azoulay D, Adam R, Castaing D, *et al*. Mehrzeitige Leberresektionen bei colorectalen Lebermetastasen. Das Paul Brousse-Konzept [Multistage liver resections in colorectal liver metastases. The Paul Brousse concept]. Chirurg 2001;72:765–9.
[7] Nieuwenhuizen S, Puijk RS, van den Bemd B, *et al*. Resectability and ablatability criteria for the treatment of liver only colorectal metastases: multidisciplinary consensus document from the COLLISION Trial Group. Cancers (Basel) 2020;12:1779.
[8] Santibañes E, de Ardiles V, Alvarez F, *et al*. Extreme Hepatic Surgery and Other strategies: increasing Resectability in Colorectal Liver Metastases. Springer; 2017.
[9] Botea F, Bârcu A, Kraft A, *et al*. Parenchyma-sparing liver resection or regenerative liver surgery: which way to go? Medicina 2022;58:1422.
[10] Moris D, Ronnekleiv-Kelly S, Kostakis ID, *et al*. Operative results and oncologic outcomes of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH) in patients with unresectable colorectal liver metastases: a systematic review and meta-analysis. World J Surg 2018;42:806–15.
[11] Kalil JA, Poirier J, Becker B, *et al*. Laparoscopic parenchymal-sparing hepatectomy: the new maximally minimal invasive surgery of the liver-a systematic review and meta-analysis. J Gastrointest Surg 2019;23:860–9.
[12] Del Fabbro D, Galvanin J, Torzilli G. R1vasc surgery for colorectal liver metastases. Minerva Surg 2022;77:441–7.
[13] Buell JF, Cherqui D, Geller DA, *et al*. World Consensus Conference on Laparoscopic Surgery. The International Position on Laparoscopic Liver Surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825–30.
[14] Syn NL, Kabir T, Koh YX, *et al*. Survival advantage of laparoscopic versus open resection for colorectal liver metastases: a meta-analysis of individual patient data from randomized trials and propensity-score matched studies. Ann Surg 2020;272:253–65.
[15] Kobayashi H, West NP. CME versus D3 dissection for colon cancer. Clin Colon Rectal Surg 2020;33:344–8.
[16] West NP, Hohenberger W, Weber K, *et al*. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol 2010;28:272–8.
[17] Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479–82.
[18] National Comprehensive Cancer Network. Colon cancer (Version 1.2022). Accessed 4 October 2022. https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
[19] Agha RA, Sohrabi C, Mathew G, *et al*. The PROCESS 2020 Guideline: updating Consensus Preferred Reporting of Case Series in Surgery (PROCESS) Guidelines. Int J Surg 2020;84:231–5.
[20] Lassen K, Soop M, Nygren J, *et al*. Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery: enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009;144:961–9.

[21] Battula N, Tsapralis D, Mayer D, *et al*. Repeat liver resection for recurrent colorectal metastases: a single-centre, 13-year experience. HPB (Oxford) 2014;16:157–63.
[22] Torzilli G, Adam R, Viganò L, *et al*. Surgery of colorectal liver metastases: pushing the limits. Liver Cancer 2016;6:80–9.
[23] Ramser M, Warschkow R, Viehl CT, *et al*. The simultaneous presence of isolated tumour cells and bone marrow micrometastases in stage I and II colon cancer-challenging the theory of a chronological pathway of tumour cell dissemination. World J Surg 2022;46:680–9.
[24] Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014;383:1490–502.
[25] Heinz MC, Peters NA, Oost KC, *et al*. Liver colonization by colorectal cancer metastases requires YAP-controlled plasticity at the micrometastatic stage. Cancer Res 2022;82:1953–68.
[26] Burlaka AA, Paliichuk AV, Iatsyna OI, *et al*. Colorectal cancer liver metastases within the central and peripheral segments: parenchymal sparing surgery adaptation. Ann Med Surg 2020;58:8–13.
[27] Burlaka AA, Gogo-Abite A, Paliichuk AV, *et al*. Systematic extended posterior right sectionectomy with simultaneous resection of the dorsal part of segment 1 and middle hepatic vein detachment. Clin Case Rep 2021;9:e04803.
[28] Burlaka AP, Ganusevich II, Vovk AV, *et al*. Colorectal cancer and mitochondrial dysfunctions of the adjunct adipose tissues: a case study. Biomed Res Int 2018;2018:2169036.
[29] Fedorenko Z, Michailovich Yu, Goulak L, *et al*. Cancer in Ukraine, 2019–2020. Incidence, mortality, prevalence and other relevant statistics. Bulletin of the National Cancer Registry of Ukraine; 2022. Accessed 12 September 2022. http://ncru.inf.ua/publications/BULL_22/index_e.htm.
[30] Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, *et al*. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. Ann Surg 2018;267:199–207.
[31] Funamizu N, Ozaki T, Mishima K, *et al*. Evaluation of accuracy of laparoscopic liver mono-segmentectomy using the Glissonian approach with indocyanine green fluorescence negative staining by comparing estimated and actual resection volumes: a single-center retrospective cohort study. J Hepatobiliary Pancreat Sci 2021;28:1060–8.