Comparative analysis of synchronous and staged resections in patients with metastatic colorectal cancer

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Summary

Surgical treatment of metastatic colorectal cancer remains the only method that improves overall 5-year survival. For the moment the issue of feasibility and effectiveness of synchronous operative interventions application in metastatic liver lesion in patients with SMCLC remains challenging.

Results of 98 MCLC patients treatment with synchronous liver lesion that received synchronous (group A, n=40) and staged (group B, n=58) liver resections in the Department of Abdominal and Retroperitoneum Tumors of the National Institute of Cancer of the Ministry of Health Care of Ukraine in the period from 2008 till 2012.

Overall 3-year survival in the group of patients with synchronous resections (group A) was 42 %/ and in the group B 55 % (p=0.22). Overall level of post-operative complications in the groups A and B after surgical stages finishing did not differ statistically, being 30 % and 35.7 % in the groups A (n=40) and B (n=28), respectively (p=0.83). Shorter operative intervention duration was registered in the group A – (316.3±10.3) min, whereas in the group B it was (484.1±18.3) min (p<0.001). Patients after staged resection stayed in in-patient clinic for a longer time– 23.3±0.8 bed-days, when synchronous resections provided with shorter recovery terms in post-operative period – 10.2±0.4 bed-days (p<0.001).

Analysis of our research indicated necessity of the development of differentiated approach in SMCLC surgical treatment. Subsequent research should be directed towards study of prognosis factors and criteria for patients' selection for surgical treatment groups, assessment of economic effect, and patients' life quality.

Key words: synchronous metastatic colorectal cancer, synchronous and staged resections.

Introduction

Colorectal cancer (CRC) holds forth place in the structure of cancer morbidity and second place among the causes of cancer lethality over the world. In 40-50% of patients with CRC metastatic liver lesion is diagnosed, in half of then - of systemic character [9, 10]. Metastatic liver lesion in CLC is unfavourable prognostic factor, and median survival of such patients does not exceed 12 months [23].

Surgical treatment remains the only method that improves overall 5-year survival, which indices according to different authors' data reach 25–58 % [9, 24]. Optimal approach to surgical treatment tactics of the patients with synchronous metastatic colorectal cancer (SMCLC) remains controversial. Traditionally, surgical treatment of SMCLC patients assumes staged resections when primary tumor is removed at initial stage with subsequent delayed liver tumor resection [25]. During recent years in some research centers positive shift towards synchronous primary tumor resections in patients with SMCLC was noted [12]. However, patients' treatment comparative results after synchronous and staged resections are insufficiently presented, and post-surgical complications indices according to the data of various authors vary significantly. Therefore, until today, issue of feasibility and effectiveness of synchronous operative interventions application in metastatic liver lesion in patients with SMCLC remains challenging.

Aim of the study: to carry out comparative analysis of immediate and long-term outcomes of synchronous and staged surgical treatment of patients with SMCLC.

Material and methods

Results of 98 MCLC patients treatment with synchronous liver lesion that received medical treatment in the Department of Abdominal and Retroperitoneum Tumors of the National Institute of Cancer of the Ministry of Health Care of Ukraine in the period from 2008 till 2012 are analyzed. To provide comparative analysis the following patients groups were selected: patients with SMCLC, who underwent synchronous resections of primary colon tumor and liver (group A) – 40 patients (40.8 %); patients with SMCLC, in whom delayed liver resections took place 3-6 months after primary tumor resection (group B) – 58 patients (59.2%). All patients in the Group A after single-stage resections received 6 polychemotherapy (PCT) courses as adjuvant regimen according to standard schemes – FOLFOX(XELOX)/FOLFIRI; in the group B all the patients were indicated with analogous PCT courses after first (3-4 courses) and after second (3-4 courses) surgical stages. Patients' characteristics are presented in the Table.

Table. Clinical characteristics of SMCRC patients receiving synchronous and staged resections (n = 98)

Clinical characteristics	Liver resections			p value
	synchronous, group A	staged, group B		
Patients number (n)	40	58		
Mean age±SEM, years	61,1±1,5	62,8±0,9		0,33
Gender (males and females), (%)	22(55)/18(45)	26(44,8)/32(55,2)		0,43
Metastatic lesion degree by Gennariat the moment of establishing diagnosis, n(%)				
I stage	13 (32.5)	11 (18.9)		0.84
II stage	10 (25)	19 (32.7)		0.14
III stage	17 (42.5)	28 (48.4)		0.14
Intestine resection type, n (%)				
colon	11(27.5)	36(62.1)		<0.001
rectum	29(72.5)	22(37.9)		0.4
Liver resection type, n (%)				
≤3 segments	31(77.5)	23(39.6)		0.34
>3 segments	9(22.5)	5(8.6)		0.42
Multivisceral resections	2(5)	–		
at first resection stage	–	2(3.4)		
at second resection stage	–	6(10.3)		
Mean operations duration±SEM, (min)	316.3±10.3	484.1±18.3		<0.001
Meanin-patientclinicstayduration ±SEM,(days)	10.2±0.4	23.3±0.8		<0.001
CLC localization, n(%)				
ascending	4(10)	14(24.1)		0.03
transverse	1(2.5)	3(5.2)		0.62
descending	1(2.5)	6(10.3)		0.2
sigmoid	5(12.5)	13(22.4)		0.98
rectosigmoid	2(5)	1(1.8)		1.0
rectum	27(67.5)	21(36.2)		0.47
Progressing on PCT background during 1-st treatment year, n(%)	12(30)	30(57.1)		0.008
Post-operative complications, n(%)	(n=40)	Istage* (n=58)	II stage** (n=30)	
anastomosis dehiscence	2(5)	–	–	
outflow of bile	1(2.5)	–	1(3.6)	
wound infection	3(7.5)	1(1.7)	4(17.8)	
intraperitoneal abscess	2(5)	–	2(7.2)	
liver insufficiency	2(5)	–	2(7.2)	
colon fistula	1(2.5)	–	–	
pneumonia	–	1(1.7)	1(3.6)	
others	1(2.5)	1(1.7)	–	*0,61
Total	12(30)	3(5.2)	10(35.7)	*0,66/**0,83
Without complications	28(70)	55(94.8)	18(64.3)	
Post-operative lethality, n(%)	2(5)	–		0.47

Notes.* – groupAversus group Bat I stage of surgical treatment

** – groupAversus group Bat II stage of surgical treatment

Metastatic lesion degree was determined according to classification of Gennari and co-authors, 1982. Pre-operative diagnostics scope: ultrasound examination, fibrogastroscopy, fibrocolonoscopy, irrigoscopy, transanal ultrasound examination (US), spiral computer tomography (SCT) with i/v enhancement, ECG, echocardiography, virological examination of viral hepatitises markers, tumor markers complex, ultrasound Doppler fluorometry, and needle biopsy for cytological diagnosis verification. Vascular liver anatomy in all cases was explored according to the results of SCT angioreconstruction. Functional liver reserves were assessed according to Child-Pugh scale. At planning of operative intervention volume on liver international liver resection classification (Brisbane, 2000) was applied. Liver foci response to PCT was assessed according to RECIST 1.1 criteria. Statistical analysis of the obtained data was provided with software STATISTICA 6.0. Non-parametric values are presented by median and interquartile range, for comparison Mann-Whitney test was applied. Categorical values were compared using chi-square test. Values that were presented as Mean±SEM, $p<0.05$ were considered statistically reliable.

Surgical aspects

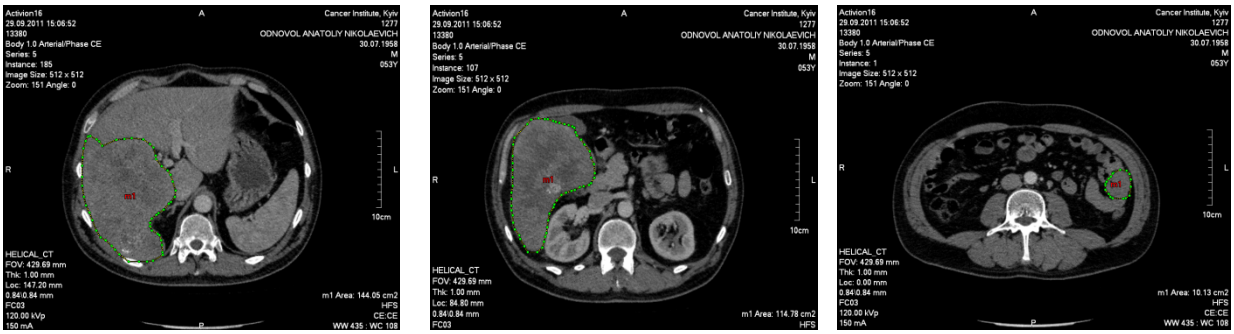
Principal moment in the work was compliance to major oncologic principles: radicality (mandatory operation fulfillment in R0-resection volume) across with application of organ-preserving procedures. Planning and preparation for such surgeries was practicable due to precise SCT evidences on determination of metastases number, dimensions, and also tumor location and interrelations with major vascular structures. Vascular anatomy exploration and, in fact, full value visualization of right hepatic vein, determination of presence or absence of additional hepatic veins (postero-inferior hepatic vein Makuuchi) allowed us to realize organ-preserving operations in mesohepatectomy volume (Sgs 4, 5, 8,); right anterior liver section resections (Sgs 5, 8). In such surgeries right posterior liver section is preserved (Sgs 6–7) with single, usually, venous drainage (of right hepatic vein). Intra-operational

ultrasound examination data allowed detecting invasion of one of the metastases into right hepatic vein in patient with 3 metastases in Sgs 4, 5, 8. Mesohepatectomy (Sgs 4, 5, 8,) with segmentectomy of Sg 1 was implemented, with right hepatic vein transsection and preservation of venous drainage from right posterior section (Sgs 6, 7) by postero-inferior hepatic vein of 1.2-1.3 cm diameter. Parenchyma transsection in all cases was implemented through healthy tissues (not less than 1.2 cm from tumor border). At histological examination of operative material microscopic signs of malignant growth along the resection border were not detected.

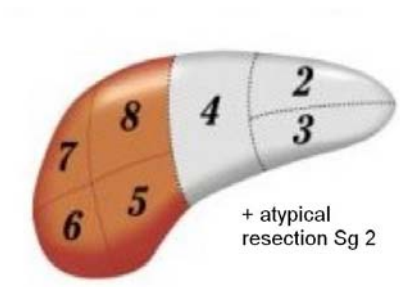
Segmentecomies, hemihepatectomies and extended hemihepatectomies (right- and left-sided) were performed according to generally accepted procedures with maintenance of the following action algorithm (Fig. 1):

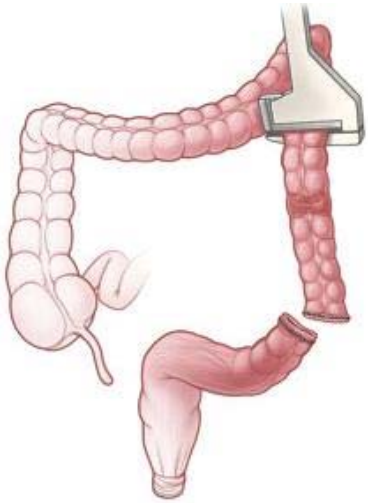
- Subcostal bilateral assess was performed supplemented with supermedian laparotomy (Calne).
- Liver mobilization.
- Intra-operational liver ultrasound examination – refinement of quantitative and qualitative liver tumor characteristics, its intra-organ topography.
- Separation of hepatoduodenal ligament elements – cholecystectomy, vessels identification responsible for afferent blood supply to remaining and removable part of liver parenchyma.
- Hepatic veins separation in caval hilus.
- Selection of liver resection plane and trajectory – intermittent short-time cross-clamping of arterial and portal system afferent vessels. Determination of resection borders by ischemia lines.
- Ligation of artery, portal vein and hepatic vein of removable liver part.
- Liver parenchyma separation – monopolar or bipolar coagulation method, application of ultrasound cavitator-aspirator, water-jet dissector, instrumental “crush” of parenchyma.

- Hemostasis of liver wound (argon coagulation, hemostatic preparations “Tachocomb”, “Surgicel”).
- Pneumo-hydro test for bile ducts impermeability.



a





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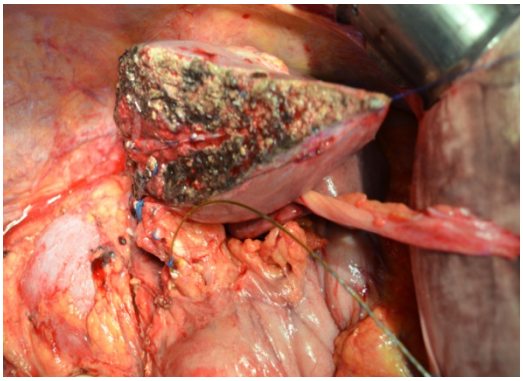

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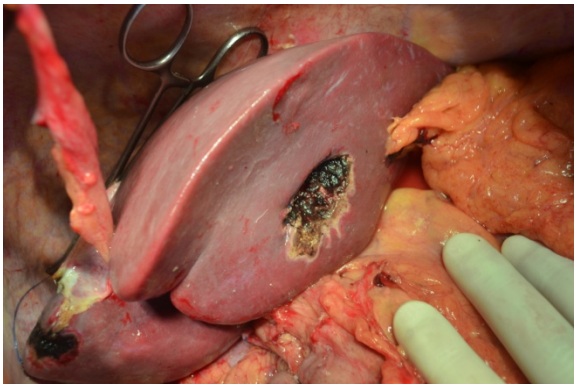

e

f

Fig. 1 Clinical example (patient K.),synchronousmultivisceral resection of the sigmoid colon with right hemihepatectomy and atypical resection of Sg 2
a) results of SCT: liverlesionSg 6,7,8,tumor of sigmoid colonb) operationsscheme
b) operation scheme
c,d) surgical field after right hemihepatectomy (Sg 5,6,7,8) and atypical resection of metastatic lesions Sg 2
e,f) right lobe of the liver with metastases and sigmoid colon with a primary tumor.

Lymphodissection in all operations foresees separation of hepatoduodenal ligament elements with removal of cellular tissue and lymph nodes of N 12 group, and also at metastatic lesion suspected – of lymph nodes N 8a, N 8p and N 13 (according to Japanese stomach carcinoma classification, 3rd edition). According to literature data at present time research on efficiency of paraaortal lymphodissection and also of celiac trunk are ongoing. In this connection at evident signs of lymph nodes tumorous lesion we perform lymphodissection of groups N9 and N 16. Combined operations were fulfilled in standard manner – after resectability determination first we performed liver resection (“clean” stage) and afterwards – colon resection. Atypical liver resections were performed at detection of metastases

with dimensions up to 3-3.5 cm in diameter with subcapsular location, or at "borderline" localization – in the absence of invasion into large intrahepatic vascular structures according to intra-operational US data.

Results

During indicated period of time for all patients of group A (n=40) radical synchronous colon resections and liver resections for SMCLC were fulfilled. In the group B at the first stage palliative surgical interventions for primary tumor were performed. Disease progression during first year in the groups A and B was registered in 12 (30 %) and 30 (57.1 %) of patients, respectively (p=0.008). Therefore, we managed to perform isolated liver resection only in 28 patients of group B (Table 1). According to the data of final pathohistological conclusion in all patients R0 resection was confirmed.

By single-factor analysis reliable difference in study groups was not detected, overall survival median was 30 months in the group A and 36 months in the group B. Overall 3-year survival (Fig. 2) in the group of patients with synchronous resections (group A) was 42 %, and in the group B - 55 % (p=0.22). At resection type comparison is necessary to mention that in the group A larger part (72.5%) of patients was operated for colon cancer, whereas in the group B this index was 27.5 %, (p<0.001). Statistically reliable difference in liver resection volume was not registered: ≤ 3 segments were removed in 77.5 % and 39.6 % in the groups A and B, respectively (p=0.43).

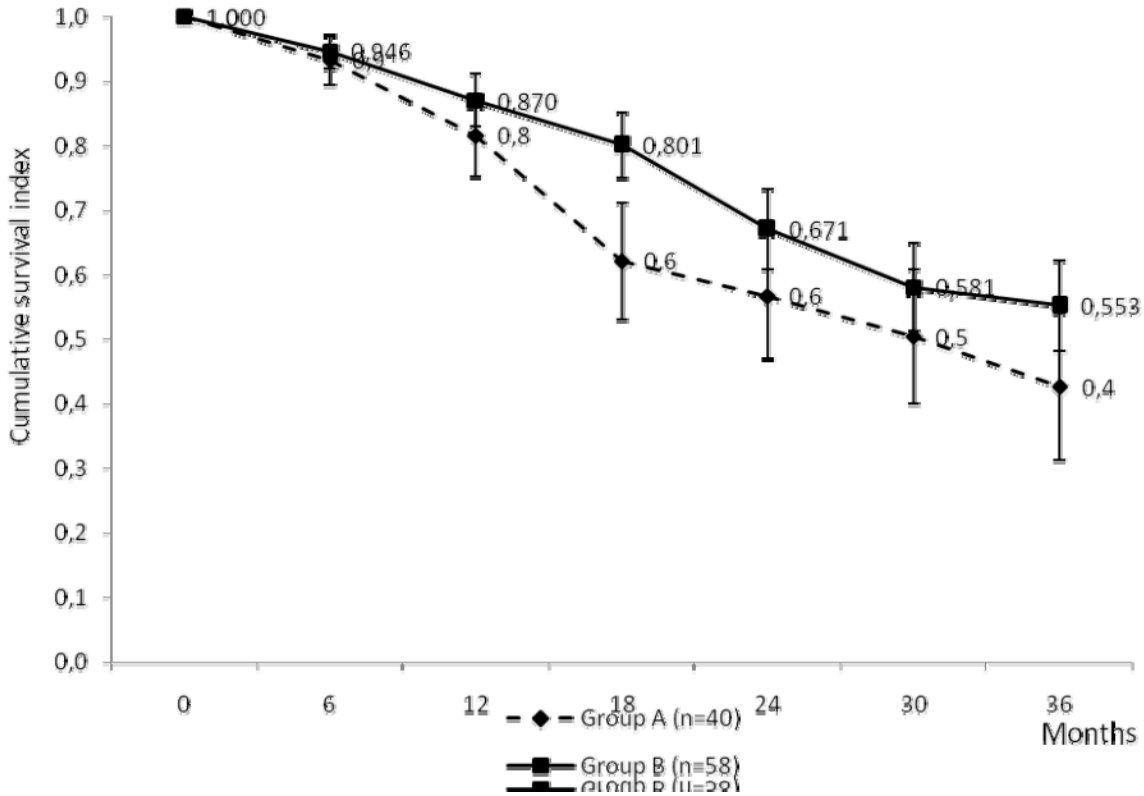

Figure 2. Overall 3-year survival of patients with SMCLC in the groups (p=0.22).

Patients after staged resection stayed in in-patient clinic for a longer time– 23.3±0.8 bed-days, whereas synchronous resections provided with shorter recovery terms in post-operative period – 10.2±0.4 bed-days ($p<0.001$). Shorter operative intervention duration was registered in the group A – (316.3±10.3) min, whereas in the group B it was (484.1±18.3) min ($p<0.001$).

Post-operative lethality index (5 %) was higher in the group A. Lethality cause was progressive liver insufficiency. Post-operative lethality in the group B was not registered. Overall level of post-operative complications in the groups A and B after surgical stages finishing did not differ statistically, being 30 % and 35.7 % in the groups A (n=40) and B (n=28), respectively (p=0.83). It should be mentioned that post-operative complications level during study period was reduced significantly in both groups. In such a way, starting from 2008, after recruiting by 10 patients in every

group post-operative complications level was 50 % and 40 % for the groups A and B, respectively. By the moment of completing the analysis in 2012 the index was 26 % and 27.5 % that is demonstrated graphically on learning curve (Fig. 3).

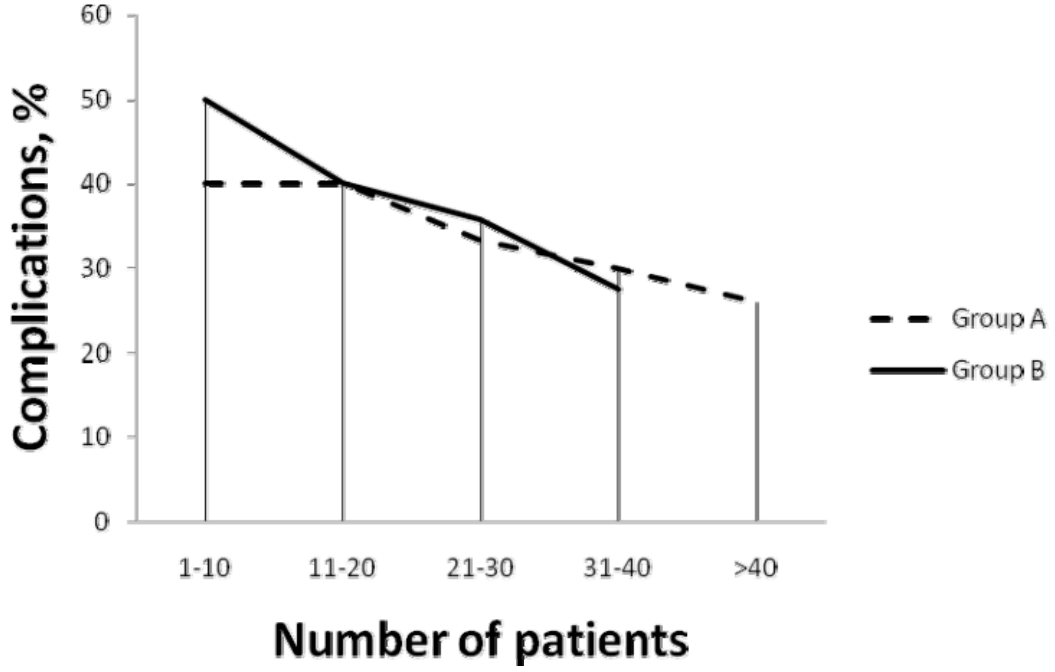

Figure 3. Complications level index at synchronous and staged resections in patients with SMCLC.

Treatment results discussion

For the moment it has been proved that radical surgical removal of all tumor foci reliable improves life-time of patients with MCLC [13]. Treatment strategy for given patients' category supposes complex approach, considering numerous prognostic factors, among them are: clinical disease manifestation, localization of primary tumor and metastases in liver, presence of synchronous or metachronous metastases, somatic patient's status and concomitant diseases; possibility of combined treatment provision. One of the major tasks challenged to surgeon and anesthesiologist is securing of combined operative intervention safety.

Post-operative complications level at synchronous approach depends on volume of colon and liver resection. Increase in this index is possible, when performing synchronous resections of primary colon tumors and more than 3 liver segments that was indicated by meta-analysis results [26] and our research. In several studies the possibility of single-step hemihepatectomy with colon resection due to SMCLC was demonstrated [16, 17–20]. The authors also revealed correlation between increase of post-operative complications level and mortality. Complication frequency at synchronous resections with right- or left-sided hemihepatectomy according to different authors data is 5–48 %, whereas after extended hemihepatectomies – 33–55 %. For this reason the majority of extended hemihepatectomies due to SMCLC is recommended to perform in postponed manner that reduce complications development risk to 16–47 % [14, 15].

In our study in the group A single-step intestine resections with hemihepatectomy were performed (n=6). And it is worth mentioning that basic mass of post-operative complications was in these patients.

Major aim of the present research was study and analysis of primary clinical data in patient with MCLC with synchronous metastasis into liver to optimize surgical strategy of their treatment. At present stage the analysis has not shown statistically reliable differences in the level of post-operative complications in the groups of synchronous and staged treatment. However, synchronous resections secured shorter duration of patients stay in in-patient clinic and accordingly, fewer expenses for such patients' therapy. However, the obtained results did not reveal improvement of long-term outcomes in the group of patients with synchronous resection. This may be explained by forced "patients selection" in the group of patients with staged approach (group B). The patients received PCT after first surgical approach, and in case of progression the delayed liver resection stage was not performed. At that in the group A all the patients were subject to synchronous surgical intervention without possibility to assess sensitivity to system therapy and accordingly, without possibility

of patients selection. In this way R. Adam and co-authors in their study conclude that difference in terms of PCT prescription before liver resection stage in patients with SMCLC may be the cause of higher disease recurrences index in single-step resections group. During 3 observation years in patients with SMCLC after combined treatment disease recurrences developed more often in the group with synchronous resections, making 85% from all patients of this group comparing to 63.6% at staged resections (p=0.002) [16].

C.Y. Hao and co-authors demonstrated that median survival of patients with SMCLC without surgical treatment was from 6 to 12 months, and at chemotherapy application (fluoropyrimidines, oxaliplatin or irinotecan) this index increased to 19 months. During recent years new chemotherapeutic and biological agents, and also approaches in systemic cancer therapy were developed; however analysis completed by J. Shindoh and co-authors demonstrated that the level of objective therapeutic effect did not exceed 47 % [27]. The latest can be the explanation of the differences in progression terms in patients groups.

Major advantage of single-step surgical interventions in patients with SMCLC is the possibility to remove all tumor foci at one step that reduces risk of disease dissemination development, and enables to avoid repeated post-operative immunosuppression [16]. Besides this single operation improves patient's quality of life and reduces treatment cost that is also confirmed by our data. It is worth to mention that radical removal of primary tumor and distant metastases provides with better conditions for systemic PCT in patients with IV stage of CLC. From the other side, tumor micrometastases, being not detected with currently available examination method at the stage of primary surgical intervention, could influence treatment results.

Currently the majority of research works are aimed at study of possibility of disease progressing control, regimens and methods of drug therapy, and systemic therapy toxicity control for safety liver resection securing.

Conclusion

Analysis of our research indicates necessity of the development of differentiated approach in SMCLC surgical treatment. Synchronous resections performed by experienced specialists in patients with SMCLC are safe at resection of ≤3 liver segments, provide with better economic result. Analysis of long-term outcomes did not demonstrate advantages in overall 3-year survival in studied patients groups. Subsequent research should be directed towards study of prognosis factors and criteria for patients' selection for surgical treatment groups, assessment of economic effect, and patients' life quality.

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