COMPARATIVE ANALYSES BETWEEN THE EARLY POSTOPERATIVE RESULTS AFTER MAJOR LIVER RESECTIONS OF COLORECTAL AND NONCOLORECTAL CANCER LIVER METASTASES

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ABSTRACT

Background: Liver resections (LR) are an obligatory element in the multimodal treatment scheme of colorectal cancer liver metastases (CRCLM). Nowadays still there are debates about the benefit of any aggressive surgical approach in noncolorectal cancer liver metastases (NCRCLM) because many authors report desperately high rates of early specific post-resection complications (SPRC) followed by unsatisfactory long term results.

Aim: Comparative analyses between the SPRC after major liver resections (MLR), i.e. ≥ 2 segments of CRCLM and NCRCLM for confirming or denying the hypothesis of higher risk in the group of NCRLM.

Material and methods: A total of 331 MLR of benign and malignant tumors were performed between 01.01.2007 – 31.12.2014 in the Clinic of Liver, Biliary, Pancreatic and General Surgery, Tokuda Hospital Sofia. Radical resections received 143 CRCLM patients and 58 NCRCLM patients, both synchronous and metachronous. The design of the study was "a single center" and "retrospective". The perioperative data of these 201 patients were analyzed and finally 59 cases of CRCLM (Group 1) and 36 cases of NCRCLM (Group 2) were included in the study. All the metastases were metachronous and no significant differences in demography, comorbidity, liver function, ASA group, neoadjuvant chemotherapy and surgery specificity were detected between the two groups. Cases that were indicated for MLR were those under 65 years of age, with preserved liver function, without serious pulmonary and cardiac concomitant diseases, and estimated as ASA group ≤ III. Data about SPRC were collected and analyzed. Results: The entire early postoperative mortality rate was 3.2% (3 fatal outcomes) - 1/59 (1.7%) in group 1 and 2/36 (5.5%) in group 2. The cause of death was liver failure, sepsis and pulmonary embolism. The rate of SPRC was significantly higher in group 2, affecting 16/36 patients (44.4%) while only 18 out of all the 59 patients (30.5%) in group 1 suffered specific complications. However only 5.1% and 8.3% of the SPRC necessitated reoperations in group 1 and group 2 respectfully. The comparative analysis denied any prognostic value for the early SPRC played by the time of metastases detection, adjuvant chemotherapy, the duration of liver resection procedure and the necessity of blood transfusion. Conclusions: Both mortality and specific morbidity after MLR affected patients with ≥3 comorbid conditions which proved to be the only predictive factor for SPRC. SPRC were more frequent in group 2 (NCRCLM) but the great majority of them were solved by conservative measures, less often by interventional procedure and reoperations were indicated very rarely.

Keywords: *Colorectal cancer liver metastases (CRCLM); noncolorectal cancer liver metastases (NCRCLM); major liver resection (MLR); specific post-resection complications (SPRC)*

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BACKGROUND

Ekberg formulated the contraindications for colorectal cancer liver metastases (CRCLM) resections in 1986: (a) more than 4 lesions; (b) extrahepatic involvement, incl. periportal lymph node metastases; (c) impossibility of resection margin of at least 1 cm [9]. Since that year Ekberg's criteria have been accepted as the "golden standard" in the treatment of CRCLM and those of neuroendocrine tumors (NET). [1,5,7,10,12,20,21]. There is an "evidence based" benefit for those patients concerning long-term survival rates, decreased tumor toxicity, improvement of hepatocyte function, the immune competence and increasing the chance of chemotherapy response [1,5,7,10,12,19,20]. Nowadays still there are debates about the benefit of any aggressive surgical approach in noncolorectal cancer liver metastases (NCRCLM) because many authors report desperately high rates of early specific post-resection complications (SPRC) followed by unsatisfactory disease free survival (DFS) and over-all survival (OS) [3,6,15,17,19].

AIM OF THE STUDY

Comparative analyses between the SPRC after major liver resections (MLR), i.e. ≥ 2 segments of CRCLM and NCRCLM for confirming or denying the hypothesis of higher risk in the group of NCRCLM.

MATERIAL AND METHODS

A total of 331 MLR of benign and malignant tumors were performed between 01.01.2007 – 31.12.2014 in the Clinic of Liver, Biliary, Pancreatic and General Surgery, Tokuda Hospital Sofia (Table.1). Radical resections received 143 CRCLM patients and 58 NCRCLM patients, both synchronous and metachronous. The design of the study was "a single center" and "retrospective". The perioperative data of these 201 patients were analyzed and finally 59 cases of CRCLM (Group 1) and 36 cases of NCRCLM (Group 2) were included in the study. All the metastases were metachronous and no significant differences in demography, comorbidity, liver function ASA group, neoadjuvant chemotherapy and surgery specificity were detected between the groups.

The basic steps in the liver resection were: (a) intraoperative exploration incl. ultrasound; (b) „in-flow control" – a selective clampage was preferred, less often intermittent Pringle's manouvre. Total vascular exclusion was performed when suspected blood loss was over 1000 ml; (c) gentle and precise parenchyma dissection using CUSA knife; (d) reliable definitive hemostasis and biliostasis on the resection surface; (e) prophylaxis of postoperative biliary hypertension by external biliary drainage, usually a cystic duct drainage installed; (f) adequate drainage of the peritoneal cavity.

The definitions of the International Study Group of Liver Surgery (ISGLS) about the liver resection volume and the local and general SPRC were used. [16]. All the data were analyzed statistically with the help of variation and alternative analyses, t-value and Fisher's exact test. Statistically significant differences were considered for $P<0.05$.

RESULTS

The demographic data were statistically similar (Table. 2). Only one female patient from Group 2 was 72 years of age but the lack of significant comorbidity, the normal range of laboratory tests, the good performance status and the ASA II made us undertake a radical surgical procedure. All the rest of the patients were < 65 years of age.

Comorbodity was "remarkable" in both groups affecting 2/3 of all cases with a slight but not statistically significant prevalence in the NCRCLM group – 72.2% vs 66.1% (Table.3).

The detailed analysis of comorbidity as „type" and „severity" proved that all the patients but one had ≤ 3 cormobid conditions of the

Table. 1. Indications for radical MLR and multi-organ resections in Tokuda Hospital (2007-2014)

Basic Diagnosis	*No of cases*	*%*	*Male*	*female*
1. Colorectal Liver Metastases	**143**	**43,20%**	**91**	**52**
2. Noncolorectal Liver Metastases	**58**	**17,52%**	**29**	**29**
2.1. Gastric cancer liver metastases – synchronous and metachronous	25	7.55%	16	9
2.2. Pancreatic cancer liver metastases – synchronous and metachronous	21	6.34%	8	13
2.3. Other malignant tumor metastases – breast cancer, GIST, common bile duct, gall bladder, ovarial cancer	8	2,42%	2	6
2.4. NET liver metastases - synchronous and metachronous	4	1,21%	3	1
3. Primary liver cancer (hepatocellular cancer - 29; cholangicarcinoma - 13)	42	12,69%	23	19
4. Benign liver tumors	33	9,97%	11	22
5. Hydatid liver disease	36	10,88%	22	14
6. Liver abscesses	12	3,63%	6	6
7. Liver cysts	7	2,11%	2	5
Total	**331**	**100,00%**	**184**	**147**

Table. 2. Sex and age distribution of patients from group 1 and group 2

Criterion	Group 1 (CRLM)	Group 2 (NCRLM)	„p“
Median age	56.22 +/- 6.876 год.	54.31 +/- 5.326 год.	p>0.05
Sex (male/female)	29(49.2%) / 30 (50.8%)	17 (47.2%) / 19 (52.8%)	p>0.05

Table. 3. Distribution of patients from group 1 and group 2 according to comorbidity (CoM)

			Group	
			Group 1 CRCLM	*Group 2 NCRLM*
	without CoM	No. of patients	20	10
		% in the group	33,9%	27,8%
	With CoM	No. of patients	39	26
		% in the group	**66,1%**	**72,2%**
Total		No. of patients	59	36
		% total	100.0%	100.0%

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Table 4. Distribution of patients from group 1 and group 2 according to the number of comorbid conditions

number of comorbid conditions	*Group 1 (CRCLM)*	*Group 2 (NCRCLM)*
0 (no comorbidity)	20 (33,9%)	10 (27,8%)
1 comorbid condition	16 (27,1%)	12 (33,3%)
2 comorbid conditions	12 (20,3%)	11 (30,6%)
3 comorbid conditions	9 (15,3%)	3 (8.4%)
4 comorbid conditions	2 (3,4%)	0 (0%)
5 comorbid conditions	0 (0%)	0 (0%)
Total	59 (100.0%)	36 (100.0%)

Table. 5. Early specific postresection complications (SPRC) after MLR of CRCLM and NCRCLM

*Complications – code**	*Group 1 (CRCLM)*	*Group 2 (NCRCLM)*
Code 0	41 (69,5%)	20 (55,6%)
Code 1	10 (16,9%)	10 (27,8%)
Code 2	5 (8,5%)	3 (8,3%)
Code 3	3 (5,1%)	3 (8,3%)
Total	**59** (100.0%)	**36** (100.0%)

** Code for the „type of complication": 0 – no SPRC registered; 1 – SPRC, treated conservatively; 2 – SPCR, treated by an interventional procedure (percutaneous drainage under US guide; pig-tail catheter; drainage of a pleural effusion); 3 – SPRC necessitating reoperation*

following (table.4): (a) cardio-vascular; (b) pulmonary; (c) anemia; (d) diabetes; (e) others.

The lab tests showed mild but not severe deviations in RBC and Hb, blood sugar, albumin, ASAT, ALAT, bilirubin, coagulation. Preoperative conservative measures (blood and plasma transfusions, hepatocyte protectors, vitK, Insulin, others) aimed corrections. We have never undertaken MLR in cases of serious liver function disturbances – total bilirubin > 21 μmol/l, ASAT and ALAT > 80 UI/l, INR > 1,35 and APTT > 35 sec. All patients from the study were ASA ≤ 3.

The median period of detection of metachronous NCRCLM was 11.7 months (6-37 months) after previous curable pancreatic resections, 11.0 months (7-18 months) after gastrectomy and 28.1 months (24-39 months) after surgery on other types of cancer. Adjuvant chemotherapy was received by 53 CRCLM patients (89.8%) and 30 NCRCLM patients (83.3%).

Anatomical LR accounted for 55.8% in the whole series - 33/59 (55.9%) in group 1 and 20/36 (55.6%) in group 2. The median surgical procedure duration was 4.02 hours (3-7 hours) in group 1 and 4.58 hours (3-7 hours) in group 2. Blood transfusion needed 25 of the 59 CRCLM patients (42.8%) and 16 of the 36 NCRCLM patients (44.4%). The mean transfused quantity was 0.81 RBC packs (concentrate unit) per patient.

The entire early postoperative mortality rate was 3.2% (3 fatal outcomes) - 1/59 (1.7%) in

group 1 and 2/36 (5.5%) in group 2. The cause of death was liver failure, sepsis and pulmonary embolism.

The rate of SPRC was significantly higher in group 2, affecting 16/36 patients (44.4%). Only 18 out of all the 59 patients (30.5%) in group 1 suffered specific complications. However only 5.1% and 8.3% of the SPRC necessitated reoperations in group 1 and group 2 respectfully (table.5).

Correlation analysis showed that none of the listed below proved to be a risk factor for postoperative morbidity and mortality, i.e. age, time of detection of metachronous lesions, duration of surgery and the blood loss quantity. The presence of more than 3 comorbid conditions was the only risk factor for higher morbidity and mortality rates.

DISCUSSION

During the last three decades liver resection surgery in oncology is more and more aggressive especially in the so called „marginal curable cases". Results permanently get better and better due to improved surgical technique, methods of anesthesia, hepatocyte protection and intensive postoperative care. Morbidity in experienced centers is less than 25% (in some series even 5-6%), while mortality rate trends 0% [10,11,13,14]. To our opinion an explanation is necessary about those data. Probably some of those data are speculative because not all the authors define the "liver resection volume" and "major liver resection" (MLR) in their reports. Thus one and the same study includes MLR together with wedge resections, simple tumorectomies, enucleations, even biopsies. MLR such as right or left hemihepatectomies and trisectionectomies show a morbidity rate between 11% and 34% [8,18].

The benefit of multivisceral resections of synchronous NCRCLM including gastrectomy or pancreatic resection plus metastasectomy or MLR is still a matter of debate according to some authors and a certain issue of according to others [3,6,15,17,19]. The attitude towards hepatic metastasectomy or MLR of metachronous metastases of gastric, pancreatic, gynecological and urological cancer, sarcomas, melanomas, others is almost the same [3,6,17,19].

MLR are contraindicated in the great majority of patients because of multiplicity and/or bilobar involvement (H2, H3) as well as a peritoneal dissemination exists in many of the gastric or pancreatic carcinomas [17]. Studies show a desperately high recurrence incidence of resected metachronous NCRCLM which varies from 63.6% to 91.0% [17].

It was on the "107er Congrés Français de Chirurgie", Paris, Arnette, 2005 when R.Adam and L.Chiche presented a report titled „Chirurgie des métastases hépatiques de cancers non colo-rectaux non endocrine" [4]. The authors emphasized on the fact that they had found less than 80 articles in English treating the problems of the surgical treatment of NCRCLM. R.Adam and L.Chiche analyzed the reported data as well as their own institutional experience and concluded about the "incorrectness and laps" of many of the studies, i.e. including less than 20 cases, different primary cancer site, different histology, biology and tumor aggressiveness.

In 2006 the same authors published a retrospective analysis of 1492 patients with NCRCLM who had received surgery in 41 French hospitals [3]. The approach was differentiated according to the type and primary tumor site, the time of detection and some demographic data. However, the study of R.Adam et al. is more or less epidemiological and aimed at the cancer population in general than at the individual patient. The "risk model" proposed by the authors helps the judgment of an eventual benefit for the patient's long term survival which advocates an aggressive surgical approach. Our study was focused on the early postoperative results (morbidity and mortality rates) aiming an "individual approach based algorithm" for cases of NCRCLM.

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CONCLUSIONS

Aggressive MLR of metachronous and synchronous CRCLM and NCRCLM have oncologic justification in selected patients. As "selected patients" we define those who are under 65 years of age, with preserved liver function, without serious pulmonary and cardiac concomitant diseases, and estimated as ASA group ≤ III. The time of metastases detection, adjuvant chemotherapy, duration of liver resection procedure and the necessity of blood transfusion didn't play statistically significant predictive value.

Both mortality and specific morbidity affected patients with ≥3 comorbid conditions which proved to be the only predictive factor for SPRC. SPRC were more frequent in the NCRCLM group 2 but the great majority of them were solved by conservative measures, less often by interventional procedure and reoperations were indicated very rarely.

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