CLINICO-PATHOLOGICAL PROGNOSTIC FACTORS IN HEMATOGENOUSLY DISSEMINATED COLORECTAL CANCER

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ABSTRACT

Background: Ekberg's criteria for liver resections (LR) of colorectal cancer liver metastases (CRCLM) have been accepted as a "dogma" and the procedure – as a "gold standard" since 1986. There are many well-known predictive factors for the early and long-term results in this field of surgery. However, some of them are still a matter of debate.

Aim: Study on the possible prognostic value of some clinical-pathological factors for the early and late results after major LR ($\geq$ 2 segments) of CRCLM.

Material and methods: A total of 143 radical (R0) major LR ($\geq$ 2 segments) of synchronous and metachronous CRCLM were performed between 01.01.20007 – 31.12.2014 in the Clinic of Liver, Biliary, Pancreatic and General Surgery, Tokuda Hospital Sofia. The design of the study was "a single center" and "retrospective". We analyzed the data with possible predictive value - demography, comorbidity, liver function, ASA group, neoadjuvant chemotherapy, type and characteristics of the surgical procedure, pathological data (T,N,G,H) and time of detection of metastases (synchronous or metachronous). The early postoperative morbidity and mortality rates were compared with these factors looking for correlation. The long-term follow-up period was $\geq$ 12 months for 86 patients (60.1%).

Results: The early postoperative mortality rate was 2.8% (4 cases) for the whole series. The specific morbidity rates were significantly higher in patients above 65 years of age, with $\geq$ 3 comorbid conditions, multivisceral resections in cases of synchronous metastases and atypical (non-anatomical) LR. The majority of CRCLM cases were $\geq$ T2, N (+) positive and G2-3. Unfavorable prognostic factors were the detection of metachronous lesions earlier than 12 months after a curative previous resection especially on the basis of adequate chemotherapy.

Conclusions: The knowledge on prognostic factors in patients with CRCLM as well as on indications and contraindications helps the correct preoperative judgment on choosing the right and appropriate type and volume of surgical procedures.

Keywords: *colorectal cancer (CRC); colorectal cancer liver metastases (CRCLM); liver resection (LR); major liver resection (MLR) specific post-resection complications (SPRC)*

BACKGROUND

Ekberg's criteria for liver resections (LR) of colorectal cancer liver metastases (CRCLM) have been accepted as a "dogma" and the procedure itself - as a "golden standard" since 1986 [11]. The good long-term results are the logical consequence not only of the progress in LR surgery but also of the invention and

usage of highly effective chemotherapeutic drugs for CRC [2,5,6,8,9,11,13,15]. There are many well studied predictive factors for the early postoperative results, disease free survival (DFS) and overall survival (OS) after resection procedures of CRCLM. However some of them are still a matter of debate. In this course of issues it is very important for a surgeon to have profound knowledge in the next three aspects: (a) judgment of the resectability in every particular case of CRCLM based on the main principles of oncology; (b) avoiding major liver resection (MLR), i.e. „senseless surgical aggression" when there are high perioperative risks for specific post-resection complications (SPRC); (c) defining the right multimodal approach – time appointment of methods, one- or two-stage surgery, liver metastases or primary tumor removal as the first?

AIM

To study the possible prognostic value of some clinic-pathological factors for the early and late results after MLR (≥ 2 segments) of CRCLM.

MATERIAL AND METHODS

A total of 143 radical (R0) MLR (≥ 2 segments) of synchronous and metachronous CRCLM were performed between January, 1 2007 – December, 31 2014 in the Clinic of Liver, Biliary, Pancreatic and General Surgery, Tokuda Hospital Sofia. The design of the study was "a single center" and "retrospective". Patients with excision biopsy in multiple residual metastases as well as patients with very small enucleations and/or wedge resections were excluded because of very low risk for SPRC. Patients were divided in two groups according to the volume of the procedure – only LR or LR as a part of a multiple organ resection. Group 1 included 110 cases (76,9%) with a LR alone which had been performed in two situations: (1) metachronous CRCLM after a previous curative (radical) resection of the large intestine; (2) synchronous CRCLM judged as indicated for a two-step procedure – primary tumor removal as the first step and LR after that. Group 2 consisted of all the rest 33 patients (23.1%) with synchronous CRCLM who received a one-step procedure – primary tumor removal plus LR.

We analyzed 2 categories of factors. The first category included factors with a possible predictive value for the early results – demography, comorbidity, liver function, ASA group, neoadjuvant chemotherapy, type and characteristics of the surgical procedure (LR alone or as a part of a multiple organ resection); anatomical or atypical (non-anatomical) LR. Chemotherapy again, pathological characteristics (T,N,G,H) and the time of detection of metastases (synchronous or metachronous) were included in the second category, which was of quite possible predictive value for the remote results. The early postoperative morbidity and mortality rates were compared with the first category of factors looking for correlation. The long-term follow-up period was ≥ 12 months for 86 patients (60.1%). So the DFS and OS data were compared to the second category of factors.

RESULTS

The mean age in both groups was 63.7 years (range 40-82 years) with a prevalence of those under 65 years of age - 82 cases (57.3%) and 51 cases (42,7%) were > 65 years of age. LR of CRCLM as one- or two-stage procedure was performed as an exception in patients above 70 years of age, who were only 2.8% from all cases (4 patients). The male/female ratio was 1.7/1 (91 men/52 women).

The comorbidity data were an interesting issue because of the age structure of our groups. Comorbid conditions were registered in 108 patients (75.5%). Cardio-vascular disorders (high blood pressure and ischemic heart disease), anemia and diabetes were the most common ones. Pulmonary (chronic obstructive bronchitis and asthma) and other diseases were diagnosed much more rarely. There was no patient with 5

concomitant diseases and only 13 of them (9.1%) had 4 comorbidities.

Biochemical blood tests found unimportant deviations in blood glucose, serum albumin, cholestatic and cytolytic enzymes and coagulation. We routinely performed pre-resection preparation with hepatoprotective agents, correction and substitution. Obligatory conditions before performing MLR of synchronous or metachronous CRCLM were Hb>100 g/L, total bilirubin<21 μmol/l, ASAT and ALAT <80 UI/l, INR<1,35 and APTT<35 sec. All the 143 patients from our study were ASA group ≤ 3.

The mean time of detection of metachronous CRCLM was 11.7 months (range 5-46 months) after previous curative large intestine resection.

Anatomical MLR accounted for 54.5% of all surgeries, predominantly in group 1 - 64.5% of all procedures. The synchronous metastases were mainly removed atypically (Table. 1).

The mean procedure duration was 3.68 hours (3-7 hours) in group 1 and 4.58 hours (3-8 hours) in group 2 (p<0.05). Approximately half of the patients needed blood transfusion - 51/110 (46.4%) and 17/33 (51.5%) from group 1 and group 2 respectively. Substitution with ≥ 2 RBC packages was necessary in only 16 cases (11.2%).

Pathological diagnosis and staging was possible in 125 cases because the remaining 18 patients from group 1 had received the previous procedure in other hospitals and the T,N,G-data were insufficient. Most cases were T2-3 (80,4%), N(+) positive (90,4%) and G2,3 (64,0%) demonstrated on table 2. Twelve biopsies had a negative N-status which is not casuistic according to our experience and according to literature data. However we didn't find prevalence of locally advanced cancer, i.e. T4 in metastatic diseases.

The early postoperative mortality rate was 2.8% (4 cases) for the whole series - 2/110 (1.8%) in group 1 and 2/33 (6.06%) in group 2. The fatal outcome was caused by acute liver failure (2 cases), sepsis with MODS and MOF (1 case) and pulmonary embolism (1 case).

The specific morbidity rate (table.3) was significantly higher in group 2 affecting 13/33 patients (39.4%) while in group 1 only 36/110 (32.7%). Conservative treatment succeeded in 29 of the complicated cases and the number of interventional procedures was 14, presented by US guided drainage of perihepatic fluid collections, ERCP + stent in the common bile duct, management of abdominal drainages in cases of pathologic secretion, pleural drainage in cases of effusions, etc. Reoperations received 6 patients (4,2% from the whole serie). None of the reoperated patients had a fatal outcome.

An analysis and comparison of data showed that SPRC were more common in patients above 65 years of age, with ≥ 3 comorbid conditions, after multivisceral resections of synchronous liver metastases (group 2) and after atypical (non-anatomical) MLR. The procedure duration and the blood transfusion didn't have any prognostic value. In this item an explanation is a must: only 11.2% of the operated patients were substituted with ≥ 2 RBC units.

Eighty six cases (60.1%) were followed up for a period of more than 12 months. Recurrent liver metastatic disease was diagnosed in 52 of them (60.5% of the followed up) and extrahepatic involvement (lungs, bones) affected 6 patients (7.0%). An early recurrence (< 6 months after a previous radical procedure) was detected in 21 patients (24.4%). Significantly unfavorable prognostic factors were the synchronous liver lesions or the metachronous ones which appeared ≤ 8 months after a previous radical intestinal resection on the bases of adequate chemotherapy."T","N" and "G" categories did not demonstrate correlation to the recurrence rates in our material.

DISCUSSION

A surgical resection is the main treatment option for patients with CRCLM that leads to a mean survival period of 24-42 months and

Table. 1. Anatomical vs atypical LR of metachronous (group1) and synchronous (group 2) CRCLM

Characteristics of liver resection (LR)			Metastases type – resection type		
			Group 1	Group 2	
			LR only	liver + intestinal resection	**Total**
	Anatomical	Number	**71**	**7**	**78**
		% in the group	64,5%	21,2%	54,5%
	Atypical	Number	**39**	**26**	**65**
		% in the group	35,5%	78,8%	45,5%
Total		Number	**110**	**33**	**143**
		% from all	76,9%	23,1%	100%
		% total	100%	100%	100%

Table. 2. T, N u G-categories in patients with CRCLM

Category	Stage	No of cases (%)
T	*T1*	*0 (0%)*
	T2	***33 (26,4%)***
	T3	***68 (54,4%)***
	T4	*24 (19,2%)*
N	*(-) negative*	*12 (9,6%)*
	(+) positive	***113 (90,4%)***
G	*G1*	*21(16,8%)*
	G2	***38 (30,4%)***
	G3	***42 (33,6%)***
	G4	*24 (19,2%)*

Table. 3. Specific post-resection complications after resection of metachronous (group 1) and synchronous (group2) CRCLM

Complications – code*	Group 1	Group 2
Code 0	74 (67,3%)	20 (60,6%)
Code 1	19 (17,3%)	10 (30,3%)
Code 2	12 (10,9%)	2 (6,1%)
Code 3	5 (4,5%)	1 (3,0%)
Total	**110** (100.0%)	**33** (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

a 3- and 5-year survival rates of 50% and 35% respectively [8,9]. Chemotherapy alone can reach less than 10% 5-year survival [7]. A considerable contribution to the improvement of long-term results (DFS, OS) was given by the progress in drug development [1,3,4,13]. The introduction of monoclonal antibodies against vascular endothelial growth factor (bevacizumab = VEGF antibodies) in last decade amended significantly the local cancer control and slowed down the progression and metastasizing [12,15].

The main issues before undertaking resection of CRCLM are the following six ones: (1) What's the general condition of the patient, i.e. is he/she able to stand and survive a major surgery; (2) Is there a possibility for R0-resection; (3) Will be there sufficient residual liver parenchyma or the so- called "future liver remnant" (FLR); (4) Is there a possibility for preserving at least two liver segments with adequate blood in-flow and out-flow as well as adequate biliary drainage; (5) What are the biological characteristics of the tumor itself (is it more or less aggressive) which justifies aggressive surgical approach with expected long-term benefit; (6) Is the surgical team experienced enough [11].

A very important corner-stone is the FLR specificity [2]. A FLR must be ≥ 25% of the pre-surgery volume in patients with "healthy liver", ≥ 40 % in cases of steatosis, fibrosis, concomitant diabetes and after aggressive chemotherapy and > 50% in cirrhotics [11].

About 30% of patients with synchronous/metachronous CRCLM have only hepatic involvement at the time of establishing the diagnosis [16]. Less than 25% of these 30% are candidates for LR since the rest of cases present with bilobar multiple lesions (H3) and/or major blood vessels infiltration and/or impossibility for R0 procedure which would preserve at least two anatomical segments [6]. Neoadjuvant chemotherapy leads to down-sizing and down-staging in 15-30% of unresectable cases making them resectable. In our series there are no such data because the great majority of unresectable

cases get their consultations as out-patients without admitting to hospital. At the same time many "unresectable" patients who have received chemotherapy seek a consultation at another surgeon with the hope to be promised an operation.

„Early recurrence" is one of the main problems affecting patients who have undergone LR of CRCLM. In 2014 R.Adam et al. reported their series including 6025 CRCLM patients who had received radical procedures since 1998 till 2009 [5]. Recurrence was diagnosed in 2734 cases (45.4%) and 639 of them (10.6%) were early recurrences, i.e. less than 6 months after a previous LR. T3-4, synchromous LM, „simple metastasectomy" (resection margin of 0 mm!) and intraoperative radio frequency thermo-ablation were proven as risk factors for early recurrence while the response to chemotherapy could significantly reduce that risk. The 5-year survival rate of early recurrent cases was 26.9% while of late recurrent cases it reached 49.4%.

We diagnosed 24.4% early recurrences among the 86 followed-up cases in our series. A profound analysis of the operative protocols and other medical reports concerning pathology staging and chemotherapy demonstrated the importance of advanced T as a risk factor for early recurrence. But no cases of resection margin < 1.0 cm were found in the files so it was impossible for us to estimate it as a risk factor.

CONCLUSIONS
The knowledge on prognostic factors for early and late postoperative results in patients with MLR of CRCLM (as a single procedure or as a part of multimodal treatment) helps the correct preoperative judgment on: (1) the type and volume of the planned procedure; (2) the risk of specific post-resection complication; (3) the expected long-term results. Thus the oncologic basis of surgery is respected.

Risk factors for SPRC include patient's age above 65 years, the presence of more than 3

comorbid conditions, a multivisceral resection and a non-anatomical (atypical) LR.

Unfortunately, we registered high absolute number (52) and relative share (60.5%) of recurrent liver metastases in our series. Significant prognostic factors were synchronous metastases and the development of metachronous lesions less than 8 months after a previous curative intestinal resection especially in the background of chemotherapy.

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