Chemotherapy does not impair parenchymal saving surgery for the treatment of colorectal liver metastases

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BACKGROUND

Parenchymal sparing surgery (PSS) is a concept for treating colorectal liver metastases (CRLM) by minimising healthy liver (HL) sacrifice. Not only minor but all types of hepatectomies can be included provided the retrieved HL is minimal. As chemotherapy is expected to increase morbidity-mortality after extended hepatectomies, we studied its compatibility with PSS.

PATIENTS AND METHODS

Patients operated on for CRLM between January 2003 and May 2015 were retrospectively identified from our prospectively-maintained database (Base FOI, Medlog™). For each patient, only the first liver surgery performed at our centre was considered in the interest of homogeneity. Re-hepatectomies will be separately reported in a follow-up publication.

THERAPEUTIC CONCEPT

In 2000, we were among the first teams to adopt the use of intra-operative ablation (IOA). In April 2012, we published the first prospective study (ARF2003, NTC 00210106) establishing the efficacy and safety of IOA for CRLM, just before the CLOCC study report.

In 2013, we confirmed the CARe (Combined ablation and resection) concept through an international collaboration (New-York, Liverpool, Aarhus). The current study duration covers this period during which our team performed PSS as a standard.

Tumourectomies were favoured for superficial lesions whereas IOA was used for deep and solitary lesions. Non-anatomical hepatectomies were favoured and one-stage surgeries were always discussed and preferred before deciding to opt for a two-stage surgery. Use of portal vein obliteration (PVO) by embolization (by the radiologist) or by ligature plus alcoholisation (during the surgery) were minimalised, when PHLF was considered to be a threat. Lesions in close contact with hepatic veins were treated by IOA under vascular exclusion without the need for a venous resection and reconstruction. Extensive hepatectomies were performed only to retrieve a large tumoural burden, never on a prophylactic basis to cure potent but invisible micrometasases. Low amounts of normal parenchyma and not the absolute volume of the specimen need to be taken into account while defining PSS i.e. a right hepatectomy can be a PSS procedure if numerous metastases and few normal parenchyma are present.

The decision to perform surgery always involved a multidisciplinary team decision (initiated in 1999 by our group) including surgeons, oncologists, radiologists, radiotherapists, etc.

RESULTS

Table 1. Patients's clinico-pathological characteristics (n=387)

Variable	No. of patients	%
Median age, years	63.8	
Sex		
Female	162	41.9
Male	225	58.1
Body mass index		
Median, Kg/m²	25.2	
≥ 25 Kg/m²	202	52.2
including ≥ 30 Kg/m²	*53*	*13.7*
Primary tumour site		
Colon	309	79.8
Rectum	78	20.2
Hepatic metastases		
Synchronous	239	61.8
Metachronous	148	38.2
Primarily resectable	191	49.4
Initially unresectable	196	50.6

Table 2. Postoperative complications according to Dindo-Clavien system and liver-related morbidiy

Variable	No. of patients	%
Postoperative complications		
No	182	47.0
Yes	205	53.0
Grade I	42	10.6
Grade II	85	22.0
Grade IIIA	25	6.5
Grade IIIB	22	5.7
Grade IVA	10	2.6
Grade IVB	11	2.8
Grade V (death)	10	2.6
Minor complications	127	32.8
Major complications*	78	20.2
Liver-related complications		
No	315	81.4
Yes	64	16.5
Haemorrhage	9	2.3
Biliary complications	24	6.2
Liver failure**	37	9.6
Grade 1	28	7.2
Grade 2	5	1.3
Grade 3	4	1.1
Median duration of hospitalisation, days	10	

*Major complications: grade ≥ 3
**According to ISGLS score

Table 3. Risks factors of major post-operative complications

N/%	Minor complication Grade < 3 (N = 309)	Major Complication Grade ≥ 3 (N = 78)	All patients (N = 387)	p, uni variate analysis	p, multi variate analysis	Odd ratio OR [95% CI]
BMI						
•< 25 Kg/m²	143 (77.3)	42 (22.7)	185			
•> 25 Kg/m²	166 (82.2)	36 (17.8)	202			
Pre-operative chemotherapy						
•No chemotherapy	32 (82.1)	7 (17.9)	39			
•With irinotecan	111 (79.3)	29 (20.7)	140			
•With oxaliplatine	94 (80.3)	23 (19.7)	117			
•Oxaliplatine and Irinotecan	72 (79.1)	19 (20.9)	91	p = 0.97		
Pre-operative targeted therapy						
•No	142	31	173			
•Yes						
Anti-VEGF	113	34	147	p = 0.50		
Anti-EGFR	56	14	70			
Initial resecability						
•Primarily resectable	158 (82.7)	33 (17.3)	191			
•Initially unresectable	151 (77.0)	45 (23.0)	196	p = 0.16		
Resection extension						
•Minor resection	207 (79.9)	52 (20.1)	259			
•Major resection	102 (79.7)	26 (20.3)	128	p = 0.96		
Resection technique						
•Surgery alone	165 (82.5)	35 (17.5)	200			
•IOA alone	40 (80.0)	10 (20.0)	50			
•Combination	104 (75.9)	33 (24.1)	137	p = 0.33		
PVO*						
•No	287 (82.2)	62 (17.8)	349			
•Yes	22 (57.9)	16 (42.1)	38	p < 0.001	p < 0.001	5.11 [2.35-11.10]
Two-stage hepatectomy						
•Yes	11 (55.0)	9 (45.0)	20			
•No	292 (81.8)	65 (18.2)	357		Not introduced	
•Cancelled	6 (60.0)	4 (40.0)	10	p < 0.01		
Extra-hepatic surgery						
•Yes	70 (59.8)	47 (40.2)	117			
•No	239 (88.5)	31 (11.5)	270	p < 0.001	0.045	2.68 [1.02-7.03]
Septic procedure						
•Yes	52 (55.9)	41 (44.1)	93			
•No	257 (87.4)	37 (12.6)	294	p < 0.001	0.038	2.82 [1.06-7.51]

*Portal vein obstruction

Table 4. Post-operative hepatic failure: patients' characteristics and surgery procedures

	Hepatic failure Grade A N = 28	Hepatic failure Grade B N = 5	Hepatic failure Grade C N = 4
Preoperative chemotherapy			
Oxaliplatine	9	2	1
Irinotecan	13	2	0
Both	6	1	3
Median number of oxaliplatine	8	9	8
Median number of irinotecan	12	15	16
Preoperative used of Bevacizumab	14	1	2
Resection technique			
Surgery alone	9	4	2
IOA	1	1	1
Combination	18	0	1
Resection extension			
Major	20	4	1
Minor	8	1	3
PVO*			
Yes	5	1	0
No	23	4	4
Post-operative complications			
Minor complication	20	3	0
Major complication	8	2	4 (death)

*Portal vein obstruction

Risks factors of major post-operative complications

In univariate analysis, PVO, two-stage hepatectomy, extra-hepatic surgery and contaminating surgery were significant risks factors for major complications.

For multivariate analysis, two-stage hepatectomy was excluded due to an association with PVO. In multivariate analysis, PVO, extra-hepatic surgery and contaminating surgery were each independently associated with major complications.

The risk factors of post-operative complications are summarised in table 3. A BMI higher than 25 Kg/m², presence or absence of pre-operative chemotherapy, chemotherapy based on oxaliplatine or irinotecan, pre-operative targeted therapy, initial resectability, surgery extension and CARes were not related to more post-operative complications

In univariate analysis, presence of NRH, SOS or CASH lesions was not correlated with an augmentation of post-operative complications.

Liver failure

Four patients died with a hepatic liver failure but for 3 of them, PHLF was a symptom of other complications: digestive anastomotic leakage, septic complication, haemorrhage. Only the fourth patient died from a primitive PHLF with a cytolysis, after just an IOA, without hepatic resection.

DISCUSSION

Our series is retrospective and non-comparative but to our knowledge, it is the first that reports a homogenous experience established 12 years ago on the concept that normal parenchyma was not a target and had: 1) to be spared as much as possible; 2) to be protected as much as possible from cytokine stress.

Indeed, only few teams have been practicing PSS in the past ten years with a strict application of the concept. Therefore, attempts of comparison of so-called PSS group (usually minor resections) with retrospective comparator stemming from different statistical artificacts maybe defective.

Our data confirms that chemo-therapy is an essential component of this multidisciplinary strategy with an acceptable level of harm.

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