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Up front hepatectomy for metastatic rectal carcinoma – reversed, liver first approach. Early experience with 15 patients.

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Timing and sequence of therapeutic interventions in patients with colorectal cancer (CRC) and synchronous liver metastases is a matter of ongoing discussion. The aim of this report is to show the feasibility and safety of a reversed strategy in patients with up front resectable synchronous liver metastases.

Consecutive series of 15 patients with locally advanced rectal carcinoma and liver synchronous metastases where up front liver resection was carried out as an initial intervention is presented. Local treatment of both, metastatic disease and primary tumor, was preferred. Liver resection was followed by neoadjuvant (preoperative) concomitant radiochemotherapy (RCT) for local pelvic disease control and subsequent resection of rectum. Systemic adjuvant chemotherapy was placed at the end of the entire treatment cycle.

All 15 patients after up front hepatectomy were able to proceed with their treatment plan. 14 patients completed their RCT for primary tumor and subsequent rectal resection was successfully caried out in 12 of them. 3 patients showed complete clinical response on cross sectional imaging and a careful „wait-and-see" policy was adopted for them. In two patients metastatic disease progression was noticed during the treatment cycle.

Liver first approach in patients with up front resectable colorectal liver metastases (CRLM) is safe and feasible. Local neoadjuvant treatment after CRLM resection may result in preoperative downsizing or even complete clinical response of the primary tumor. Reversed strategy may to a degree eliminate negative oncologic impact of surgical complications after rectal surgery as CRLM has been already addressed.

Key words: hepatectomy, liver first approach, reversed strategy, synchronous liver metastases

Completing the whole therapeutic plan in patients with stage IV. rectal cancer is of utmost importance in order to achieve long term survival. The liver first approach avoids possible liver metastases progression into an inoperable state while operating on primary [1-3]. Moreover, anastomotic complication after rectal resection in classical, „rectum first" approach may lead to a delay of systemic treatment, again with a possible conversion of initially resectable liver disease into an advanced inoperable state [2,4]. A generally lower hepatectomy complication rate [5-10] compared to complication rate after rectal resection, seems to apply to the liver first approach as well (27.3 % vs 44.4 % reported by de Jong et al. in the liver first approach) [4]. The reversed strategy therefore, seems to give a better opportunity for the patient to get addressed both, liver disease and primary [11]. The proportion of patients who complete their full treatment protocol after liver first approach is reported about 73-81 % by several authors [4,6,12,13]. In 2012 analysis based on LiverMetSurvey by Andres et al., up to 80 % of patients resected liver first successfully underwent the complete treatment plan, compared to less than 30 % of those undergoing the classical rectum first approach [14].

Preoperative, neoadjuvant concomitant radiochemotherapy (RCT) results in better local control in patients with advanced rectal cancer [15,16,17]. In patients presenting with metastatic disease, initial systemic chemotherapy is preferred [11,18]. Radiotherapy in this setting is usually administered in adjuvant fashion after rectal resection to ensure local control. Patients

experiencing serious anastomotic complications after rectal resection are often left without radiotherapy at all. Reversed approach in this particular group of patients addresses liver disease early and enables them to benefit from neodjuvant RCT for rectal tumor. Systemic chemotherapy may then follow surgery in an adjuvant fashion. Risk of local complications from a tumor left in situ while resecting liver disease and receiving RCT is relatively low [1,19,22,23] and can be avoided by constructing loop ileostomy during the hepatic procedure if the patient is already symptomatic.

Patients and methods

During the period of 2011-2012, 75 hepatectomies were performed at our institution. In 56 cases, surgery was indicated for CRLM, 35 from these for synchronous lesions. Based on a multidisciplinary cancer team conference, there were 15 consecutive patients with locally advanced rectal carcinoma (T3b and more, or N+) presenting with synchronous up front resectable, liver only metastastases. The staging assessment of the primary tumor was based on colonoscopy, histology, computed tomography (CT), magnetic resonance imaging (MRI) and transrectal ultrasonography. CRLM were assessed as clearly resectable by liver surgeon. The staging was based on standard 3 phase CT scanning, or MRI. Positron emission tomography (PET) was not considered mandatory. After the panel discussion, every patient was given an informed consent and agreed to the proposed treatment strategy. This group was retrospectively compared to a corresponding cohort of patients treated in a period of 2009-2010 when classical, rectum first approach was used.

Results

1-7 CRLM lesions per patient were resected during up front hepatectomy taking into account a general tendency towards liver sparing surgery. Despite prevailing non anatomic, limited resections, 6 major procedures (right, left hemihepatectomy with or without concomitant contralateral metastasectomy) had to be performed. Altogether, 6 major hepatic resections, 2 bisegmentectomies and 23 complete metastasectomies were performed for 46 lesions in 15 patients (Table 1). The loop ileostomy in 6 patients and terminal sigmoideostomy in one case were constructed at the time of hepatectomy for symptomatic rectal tumor obstruction. The aim was to relieve present obstruction symptoms which would be further worsened by upcoming RCT and to protect subsequent low colorectal anastomosis after the planned rectal resection.

No patient experienced primary tumor related complications (obstruction, bleeding) during hepatectomy and neoadjuvant treatment period. None of the patients within the group died and no postoperative liver failure, bleeding or biliary leak was noticed. No patient required hepatectomy related reoperation. One liver resection surface infection was noticed and this was evaluated as an ascendent nosocomial infection through an intraoperatively placed drain. This patient had prolonged hospital stay and percutaneous intervention was needed to drain residual perihepatic collection. The same patient experienced subsequent complications after both rectal resection and resection of protective loop ileostomy. In the end, an immune system disorder was revealed and immunomodulation treatment was installed accordingly. In another patient a twist of loop ileostomy occurred, requiring a simple orthotopic reinsertion during the same hospitalization. This did not result in any delay in his treatment protocol. We assigned this complication to surgeon‘s technical failure.

After liver first resection all but one patient completed their neoadjuvant treatment for better local control of the primary tumor. Patient number 9 (Table 1) had been treated for Hodgkin disease in the past, in which he received radiotherapy (40 Gy). This was the reason why he was not eligible for concomitant RCT after liver first hepatectomy. Because of this modified treatment plan patient number 9 was excluded from further consideration. Neoadjuvant RCT resulted in downsizing of the primary tumor (RECIST criteria used) or in downstaging of the N or T status in 10 patients (Table 1). In 2 patients stable disease after RCT was suggested on CT/MRI and was subsequently confirmed on their histopathology. The other 2 patients were evaluated as having complete clinical response based on MRI finding. In these patients a cautious „wait-and-see“ policy was adopted with repeated sigmoideoscopy and multiple biopsies every 3 months.

In the classical, „rectum first approach period“ (2009-2010) there were 16 patients with clearly resectable synchronous CRLM and locally advanced rectal cancer identified retrospectively. After rectal resection only 12 of them went on with their treatment plan and had hepatectomy for CRLM. 4 patients (25 %) had no hepatectomy because either the disease progression or complication after rectal surgery. This is in contrast to „liver first approach period“ (2011-2012) where all 15 liver first resected patients either underwent rectal resection, or had complete clinical response after RCT. 13 liver first resected patients have their „surgical cycle“ completed so far (hepatectomy followed by RCT and subsequent resection of rectum). 2 patients do not have their rectal tumor resected yet, both are experiencing complete clinical response with close follow up. Disease progression during the treatment cycle occurred in two patients. In one patient second line systemic chemotherapy resulted in complete clinical response both within the liver and the pelvis, another patient was given chemotherapy with palliative intent .

An average interval between hepatectomy and neoadjuvant treatment was 28,79 (14- 55) days and average „delay“ of rectal resection after liver first plus neoadjuvant RCT was 128,77 (91-260) days. Adjuvant chemotherapy (6 months after colorectal surgery) with disease restaging is not finished yet and further evaluation is ahead.

Table 1. Patient characteristics with regard to type of surgical intervention, effect of preoperative RCT and intervals between hepatectomy and neoadjuvant RCT, hepatectomy and resection of the primary and hepatectomy and adjuvant chemotherapy.

	Type of hepatectomy	Resection of rectum	RCT effect on primary	Hepatectomy-RCT (days)	Hepatectomy-colectomy (days)	Hepatectomy- adjuvant chemotherapy (days)
1.	2x CM	LAR	PR/N downstage/histopathol. +	14	100	141
2.	biseg S2+3, 2 x CM, PIS	LAR	PR/N downstage/histopathol. +	29	118	refused by patient
3.	biseg S2+3, 3 x CM, CHE, PIS	LAR	PR/N downstage/histopathol. -	19	91	152
4.	CM, CHE, PIS*^{lpsk}	LAR	PR/N downstage/histopathol. +	24	113	141
5.	LHH S1-4, PIS	LAR	PR/N downstage/histopathol.+	28	115	163
6.	2 x CM, PIS	LAR	PR/N downstage/histopathol. +	21	106	155
7.	2 x CM, sigmoideostomy	wait and see	CR	55	-	-
8.	RHH S5-8	APR	PR/N downstage/histopathol.+	30	119	143
9.	RHH S5-8	wait and see failure – LAR	CR + progression	-	260	289
10.	RHH S5-8, CM	LAR	PR/CR/T , N downstage/histopathol. T+, N+	29	155	198
11.	2 x CM, CHCE, PIS	LAR	PR/T, N downstage/histopathol. T-, N+	47	131	168
12.	LHH S2-4, 3 x CM	wait and see	CR	35	-	-
13.	3 x CM	APR + IORT	PR/T , N downstage/histopathol. +	16	108	147
14.	RHH S5-8	LAR	PR/T, N downstage/histopathol. T+, N-	27	126	161
15.	2 x CM, CHCE*^{lpsk}	TPE	SD	29	132	167

Legend : patients are sorted in chronological order; type of hepatectomy : CM – complete metastasectomy, LHH – left hemihepatectomy, RHH – right hemihepatectomy, biseg – bisegmentectomy, CHE – cholecystectomy, *^{lpsk} – laparoscopic resection; resection of rectum : LAR – low anterior resection, PIS – protective loop ileostomy, TPE – total pelvic exenteration, IORT – intraoperative radiotherapy, APR – abdominoperineal resection; RCT effect on primary : CR – complete clinical response, PR – partial response, SD – stable disease, (CR, PR, SD assesment on restaging imaging after neoadjuvant treatment according to RECIST criteria), TNM downstaging based on cross sectional imaging after neoadjuvant treatment, histopathol. + suggested downstaging confirmed on final histopathology, histopathol. – suggested downstaging not confirmed on final histopathology for T or N status respectively

Discussion

In the past, a presence of colorectal cancer metastases within the liver was considered contraindication to curative intent surgery as disease dissemination was universally expected. Nowadays liver only, or liver limited metastatic disease is accepted to be localized, provided that overall dissemination of the disease cannot be proved. The fact, that the liver is the only site of CRLM in 30% of patients is widely acknowledged [22,23]. At present it seems, that we can in some cases even say, that patient has limited extrahepatic disease and this applies to peritoneum as well. Altough patients with extrahepatic metastatic involvement have a much worse prognosis, surgery is worthwhile in carefully selected cases and the line between local and systemic disease is becoming less clear [24-26]. In this study, based on this trend, a patient with synchronous liver only CRLM was considered to have a localized disease in two compartments. In our therapeutic protocol, emphasis was put on local treatment of liver metastases and local pelvic control by RCT followed by rectal resection. Prehepatectomy chemotherapy was not used and systemic adjuvant therapy was launched after complete surgical resection of the disease. Giving up prehepatectomy chemotherapy delays early treatment of micrometastatic disease, but the benefit of prehepatectomy chemotherapy in resectable CRLM is currently questioned. Even though it appears, that a short course of preoperative chemotherapy is common practice in a majority of centres [6,27-29], some authors assume that the role of prehepatectomy chemotherapy should be reconsidered [8,30-36]. In a systematic review of Lehmann et al. [34] routine use of preoperative chemotherapy in resectable CRLM could not be recommended. To resect CRLM up front is an intriguing option for many surgeons. An intact liver without chemotherapy- induced liver injury means more predictable future for liver remnant (FLR) function, lower complication rate and no missing lesions issue [37-42]. On the other hand, the most important benefit of neoadjuvant preoperative chemotherapy is probably to identify and select patients with favourable tumor biology [43]. When resecting liver first without preoperative chemotherapy, patients run the risk of subsequent tumor non response and rapid disease progression. Non response to systemic therapy is currently attributed to particularly aggressive tumor biology. Consensus on management of such aggressive tumors is not settled yet, because non response or disease progression while on certain chemotherapy regimen does not necessarilly mean non response at all. Interestingly, proceeding to liver resection, if possible, is also considered a valuable option even in this subgroup of patients [31,32,34]. Preoperative use of chemotherapy offers an early treatment of micrometastatic disease and a possibility of tumor shrinkage enabling for liver sparing surgery in some cases. However, missing lesions issue and liver toxicity are the most important drawbacks of this strategy [27,41,44,45-48]. Pros and cons of preoperative chemotherapy make it hard to identify

which therapeutic sequence is the best in synchronous metastatic CRC patients [2,30,49]. Disregarding the initial strategy, achieving radical tumor clearance must be the goal, as this is the only chance for survival.

There are several reports on nonoperative, „wait-and-see" strategy for patients with complete clinical response of primary rectal tumor after neoadjuvant RCT. It seems, that about 80 % of carefully selected patients with complete clinical response can be safely spared rectal resection and reach long term survival with rectum left in situ [50,51,52]. Intensive follow-up is mandatory. In our series, there were 3 patients with complete clinical response after neoadjuvant treatment based on MRI, repeated sigmoideoscopy and multiple biopsies every 3 months. „Wait-and-see" policy failed however in one patient (patient number 9 (Table 1)). Eventually, this patient had his rectal resection 260 days after hepatectomy with a final pathological staging equivalent to inicial pretreatment evaluation. The other two patients remain without any evidence of primary tumor recurrence.

According to a recent systemic review in as many as 19 % of patients disease progression may occur during the liver first protocol period [53]. In our series, two patients experienced metastatic disease progression during a treatment cycle. 5 year overall survival from 31 % to 41 % with recurrence rate from 22 % to 70 % can be expected for reversed strategy according to lately published report [54]. For patients from this series the short follow-up period currently does not allow for recurrence or overall survival data evaluation.

Conclusion

Liver first strategy compared with classical, rectum first approach, enables to accomplish the whole treatment plan to a higher proportion of patients presenting with metastatic rectal carcinoma. Addressing liver disease early avoids liver progression into an inoperable state while resecting primary. Moreover, the reversed strategy partially eliminates negative oncologic impact of surgical complications after rectal surgery, as CRLM have been already addressed. After up front resection of CRLM, patients with locally advanced rectal carcinoma can benefit from concomitant RCT leading to better local pelvic disease control, possible preoperative downsizing, or even complete clinical response of primary tumor. The benefits of liver first approach are, however dependent on low hepatectomy complication rate, which has to be kept to minimum in order to prevent a delay in planned treatment protocol.

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