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Article Original Study

Simultaneous approach of colo-rectal and hepatic lesions in colo-rectal cancers with liver metastasis – a single oncological center overview

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Abstract: Management of synchronous colorectal cancer with liver metastases (SCLM) is still on debate, regarding timing, indications and complications of the 3 strategies: classic approach (first tumor resection), simultaneous resection and reverse approach (liver first). A retrospective single-centre evaluation of synchronous approach was accomplished, focusing on surgical technique, indications and perioperative complications. Between 2017 and 2020, 31 SCLM patients benefited from synchronously colorectal and hepatic approach: segmental colectomies/rectal resections, simultaneously with liver metastasectomies (associated with radiofrequency ablation). Post-therapeutic imaging monitoring was performed from every 3 to 6 months. There were no perioperative complications related to the combination of the two procedures, low morbidity and zero postoperative mortality. The follow-up period was from 10 to 40 months: 13 patients had no evidence of recurrence, 10 patients had hepatic metastases in regression, 4 of them had signs of peritoneal carcinomatosis and 4 patients showed progression of liver disease; all patients were on chemotherapy. During follow-up 4 patients died. Experience shows that the simultaneous approach of recto-colic and hepatic resections in colo-rectal cancers is a safe procedure, with low morbidity, the limits being dictated by the size of the liver metastases. The results at long-distance must be drawn by further consistent trials.

Keywords: Colo-rectal cancer, liver metastasis, simultaneous approach, surgical treatment, chemotherapy.

1. Introduction

The metastatic aggression of colorectal cancer is unanimously accepted, with statistical data indicating that approximately 40% - 60% of colorectal cancer patients will develop liver metastases over a lifetime and almost 15% - 25% of newly diagnosed patients have synchronous liver metastases at the time of diagnosis. Synchronous liver metastases have a more unfavorable prognosis compared to metachronous lesions, with more aggressive biological features, increased incidence of bilobary metastases and larger size [1].

Management of synchronous colorectal cancer with liver metastases (SCLM) is a current topic of debate, regarding the timing, indications and complications of the 3 strategies: the classic stage approach (primary tumor resection followed by hepatectomy after 4-6 months of chemotherapy), simultaneous resection (colorectal and hepatic resection) and reverse stage approach - liver first (initial hepatectomy followed by subsequent resection of the primary tumor), with results still controversial in the literature [2, 3, 4, 5]. The therapeutic approach of these patients is multidisciplinary, with the involvement of radiologists, surgeons and oncologists, who must evaluate the margins of liver resection, therapeutic pillars and their timing, in correlation with the genetic profile of the tumor [6, 7, 8, 9].

Therapeutic options for patients with SCLM include hepatic resections of variable amplitude (wedge resection, segmentectomy, lobectomy, multiple resections), chemotherapy according to various protocols (5-FU + Leucovorin, FOLFOX/ FOLFIRI either alone or in combination with VEGF inhibitor – Bevacizumab or EGFR inhibitor - Cetuximab or Panitumumab), as well as various local ablative hepatic therapies (Radiofrequency Ablation, Microwave Ablation, Cryoablation, Chemoembolization, Stereotactic Body Radiotherapy (SBRT), Hepatic Artery Infusion Pump). In the case of extensive hepatic metastatic disease, the association between liver resections and local ablative therapies, especially radiofrequency, is cited more and more frequently [10, 11, 12, 13].

2. Materials and Methods

We conducted a unicentric retrospective study of the synchronous colorectal and hepatic approach in SCLM, carried out in the First Surgical Department of the Bucharest Institute of Oncology, between years 2017 and 2020. In the reference period, 561 colorectal cancers received surgical treatment, of which 129 cases (22,99%) had synchronous liver metastases at onset; of these, only 31 cases (24,03%) benefited from a synchronous colorectal and hepatic approach.

The average age of the patients in the group was 52 years, with limits between 31 and 70 years, with a predominance of lesions in men, M / F ratio: 3/1; the primary lesion was localized in 19 cases at the rectal level and in 12 cases at the colonic level. The size of the metastases was between 1 and 8 cm, the number of metastases varied between 1 and 10, with a predominantly bilobar location.

The criteria for including patients in the study group consisted of: ~~age under 70~~ years, good general condition, total hepatic tumor volume below 40% of liver volume, maximum 1 metastasis over 5 cm, without extra hepatic secondary lesions (the presence of intra-abdominal lymph node metastases did not constitute exclusion criterion), resectable primary recto-colic tumor, regardless of histological type (T4 tumor was not an exclusion criterion), without macroscopically visible elements of peritoneal carcinomatosis (Table 1). The possibility of a synchronous hepatocellular carcinoma was also excluded, an extremely rare, but possible situation, by specific immunological tests [8, 9].

For rectal cancer, patients received trimodality treatment, with short course protocol radiotherapy 5 x 5 Gy daily fractions, followed by surgery at 7-10 days post radiation and post-operative systemic treatment.

Colon cancer patients were operated and they received post-operative systemic treatment.

R0 resected patients received 6-month adjuvant chemotherapy, while patients with residual disease received palliative chemotherapy until disease progression.

Biological agents (Bevacizumab, Cetuximab, Panitumumab) were added according to national guidelines.

The main elements of the surgical tactic included the initial approach of liver metastases, which aimed at metastasectomies, with a safety limit of 1 cm for superficial lesions, in contact with the hepatic capsule, with dimensions less than 5 cm, or radio ablation for deep intraparenchymal lesions, with dimensions less than 5 cm. Both procedures were performed under vascular control of the hepatic pedicle and suprahepatic veins, for

metastases with localization in contact with important vascular elements. Regarding the colorectal resection, it complied with the oncological criteria of resection, including the total mesorectum excision in the case of rectal cancers, with a preference for external stoma derivations post-resection, to avoid possible anastomosis complications. Liver surgery has benefited from standard intraoperative ultrasound and advanced electro coagulation systems: LigaSure, Argon Electro coagulation, Celon system radiofrequency ablation (Table 2).

Post-therapeutic monitoring was performed by CT scan / MRI, PET-CT, CEUS at intervals of 3-6 months, simultaneously with the monitoring of tumor markers (CEA, CA19.9), with the follow-up of long-term survival, with or without signs of disease, focusing the evolution of the liver metastases and the other extra hepatic lesions, on an average period of 26 months, with interval between 10 to 40 months.

The manuscript was analyzed by the ethics committee of the Bucharest Oncological Institute, finding that it corresponds to current ethical principles, being approved with registration number 24043 from 09.11.2022.

The study did not include research carried out on laboratory animals.

The research conducted on humans was non-interventional and retrospective type, respecting the principles of the Declaration of Helsinki.

3. Results

In connection with the immediate postoperative results, it should be noted that was no increase of intraoperative incidents and accidents in the synchronous approach, compared to sequential approach. This fact also results from the established surgical protocol, with restrictive hepatic procedures, which consisted in metastasectomies and local radio ablation, on the one hand, and recto-colic resections with colostomy (temporary or permanent), without anastomosis, in cases with increased risk.

Intraoperatively, we mention 4 cases of persistent bleedings in the areas of hepatic resection, developed deep intraparenchymal, despite the vascular control of the hepatic pedicle and the suprahepatic veins, solved by coagulation with Argon, parenchymal sutures and application of haemostatic sponges.

The immediate postoperative course did not record major complications following hepatic and colorectal surgery, such as digestive or biliary fistulas, hemorrhages, occlusive syndromes or peritonitis; the only one complication was the hepatic cytolysis syndrome in 3 cases, when metastasectomies were associated with radio ablation of liver metastases. Perioperative mortality was zero.

Long-term monitoring was assessed at a mean of 26 months (range 10 to 40 months) postoperatively.

From the studied group, 13 patients presented with no signs of disease, hepatic or extra hepatic, at an interval between 11 and 32 months postoperatively. All of them received adjuvant chemotherapy. We notice in this group, that the number of metastases was maximum 3, with dimensions less than 5 cm, and metastasectomies were performed; regarding the stage of the recto-colic tumor, it was in all cases in early stages T1 / T2. About lymphatic invasion, it was present in 4 cases of this group.

A second group consists of 14 patients, who survived with residual disease, with liver metastases in progression or regression, with peritoneal carcinomatosis or extra hepatic metastases that occurred postoperatively. These patients had more than 3 liver metastases, some of them larger than 5 cm, for which metastasectomies were associated with radio ablation, for deep intraparenchymal metastases. Regarding the primary recto-colic tumor, in 4 cases the tumors were in T1 / T2 stage and in other 10 cases in the advanced T3 / T4 stages, with lymphatic invasion present in 14 cases. In 10 cases residual disease responded to systemic treatment. In 4 cases patients developed peritoneal carcinomatosis, although liver metastases were controlled by complex treatment. Despite systemic treatment (chemotherapy + anti VEGF or anti EGFR biological agents), in 4 cases we found progression of the liver disease, with recurrences in the areas of radio ablation and new metastases in other liver segments.

The third group includes 4 cases of patients who died during the study, who showed either continued progression of liver metastases, with local recurrences in the areas of ablation of liver metastases and lymph node metastases in the liver pedicle, or developed extra hepatic metastases, with extensive peritoneal carcinomatosis, lung and bone metastases. The deaths occurred between 10 and 15 months postoperatively, during this period the patients underwent systemic treatment, the death being caused by liver failure, and cachexia with severe alterations in the metabolic homeostasis. All these cases initially presented advanced rectal colic tumors in T3 / T4 stages (Table 3).

4. Discussion

The synchronous colorectal and hepatic approach in SCLM is a unanimously accepted therapeutic option, with indication in direct relation to the complexity of hepatectomy and colo-rectal resection, extra hepatic extension of the neoplasm and, of course, the patient's comorbidities. Classical criteria for contraindication of resection of liver metastases include the presence of more than 4 metastases, the existence of extra hepatic determinations and the impossibility of a resection margin over 1 cm. At the same time, the location and size of the metastases and the post resection liver reserve are taken into account in establishing the indication for resection. Armin Thelen considers that the most important selection criteria remain the age of the patient and the extent of the associated liver resection [14].

In our study group, the indication barrier for resection / radio ablation of liver metastases (Fig. 1) was raised to a maximum of 10 liver metastases, of which a maximum of 1 more than 5 cm. We ruled out major liver resections from the beginning, opting for atypical liver resections or metastasectomies, in combination with radio ablation for voluminous and deep metastasis. We considered that any technically resectable metastasis, by "in situ" resection, under intraoperative ultrasound control, can be approached (Fig. 2) and metastases over 5 cm to benefit from radio ablation, in this first therapeutic stage. In this regard, a recent study conducted in 2021 by Dyre Kleive et al [15], states that simultaneous colorectal and hepatic resection should be avoided when major resections are required, both hepatic and colo-rectal and should be further subject of clinical trials. It is clear that a good postoperative prognostic factor in the simultaneous approach is the size of liver metastases and the extent of liver resection, confirmed in most studies [16, 17, 18, 19].

The obvious benefits of the synchronous approach were found in the group of patients in whom complete metastasectomies could be performed and the rectal tumors were in the early stages, practically an R0 resection was possible, without the risk of elements of subclinical carcinomatosis. During the 10 to 40 month monitoring period, these patients undergoing chemotherapy showed no signs of recurrence of the neoplastic disease. In an extensive 11-year study of a consistent group of 432 patients conducted by SKP John [20], long-term survival in patients with liver metastasis resections is strongly correlated with CEA values ≥ 200 ng / ml and a positive resection margin <1 mm, as a negative prognosis and is not influenced by tumor differentiation, number of metastases, biliary or vascular invasion, size, relationship to primary disease, lymph node status of the primary disease, or use of neoadjuvant chemotherapy.

As for the association between radio ablation and resection of liver metastases, during the hepatic time of the synchronous approach (Fig. 3), the aim was to reduce the metastatic mass as much as possible, through limited hepatic interventions, in this first operative time, a fact highlighted in many other studies [21, 22, 23, 24]. Under the conditions of neoplastic disease control, under adjuvant chemotherapy, with the reduction of metastatic volume, a major hepatic reintervention can be considered for the complete control of the neoplastic disease. This therapeutic attitude was proposed by T. Livraghi, under the name "Test of time Approach" [10], the radio ablation of liver metastases can achieve in some cases complete necrosis, and in other cases a partial control, with the follow-up of possible development of new intrahepatic metastases, to be included in the hepatic resection area in a second surgical time, after chemotherapy.

The advantages of this association resection / radio ablation are found in the group of patients who survive with signs of disease, in 10 cases out of 14 finding regression and control under chemotherapy of liver lesions, other 4 cases showing progression of liver metastatic disease, with recurrences in areas of radio ablation and new secondary lesions in other liver segments. In only one case was attempted reoperation for a right hepatectomy, after 6 sessions of chemotherapy, in a 31-year-old patient, but due to the elements of pelvic and perihepatic carcinomatosis, liver resection was contraindicated.

An extremely important element noticed in our study is related to the T stage of the colorectal tumor, noting the poor evolution at distance in T4 tumors, grafted by the development of elements of peritoneal carcinomatosis. In 4 cases out of the 8 cases of T4 stage tumors, the patients developed peritoneal carcinomatosis, under chemotherapy treatment, which finally led to the decease. In one case peritoneal carcinomatosis contraindicated the major liver resection in a second operative time, because of performance issues.

Regarding long-term survival D. Jaeck [25], in a multicenter study evaluating long-term survival over 5 years after resection of liver metastases, identifies 4 risk factors: serous tumor infiltration (T4), peri tumor lymph nodes invasion at the level of the colorectal tumor, increased CEA values and, of course, the hepatic resection margin <1cm; while other parameters, such as the location of the primary tumor, the number and size of metastases do not appear to have of statistical significance. Similar results are recorded in our study: thus, of the 13 disease-free cases, all primary tumors were in the early stages (T1 / T2) and most without lymphatic regional invasion.

Consequently, starting from this consideration, given the high potential of peritoneal carcinomatosis in colo-rectal tumors in stage T4, it may be useful to perform a peritoneal lavage with cytology, similar to the procedural algorithm in gastric cancer and with the possible application of a HIPEC protocol, after resection of possible macroscopic foci of carcinomatosis, or directly, only in conditions of positive cytology. By forcing the attitude, studies could be performed in the future to apply HIPEC directly, only in the presence of the tumor in the T4 stage. In this regard, recent studies by Geert A. Simkens et al. [26], N. B. Arrizabalaga et al. [27], D. Cortes-Guiral et al. [28] indicates that the treatment of carcinomatosis in patients with liver metastases is still controversial, without significant improvement in survival, but may be applied to carefully selected patients in clinical trials.

Concerning the complications resulting from the association of hepatic surgical time with colorectal surgical time, there were no significant complications in this limited group that would result in reinterventions or death, and we recorded only minimal post-operative grade 1-2 complications according to Clavien-Dindo Classification, which makes us to appreciate the value of this type of approach in cases with strict indications, with trained operating teams, idea present also in ample studies published in the last years, by Diamantis I Tsilimigras [29] and Ulrich Nitsche [30].

The simultaneous approach, colorectal and respectively hepatic is preferable, as far as 2016 the published studies are showing, provided that the surgical intervention is performed by surgeons specialized in colorectal surgery, respectively in hepatobiliary surgery [31]. The team that treats such a patient must be completed with a medical oncologist, a pathologist and a specialist in interventional radiology, in order to be able to offer to the patients the entire range of oncological or ablative procedures, in addition to liver surgical resections [31, 32]. It becomes obvious that these patients must be treated in specialized oncological centers, whether we are talking about a center with multiple therapeutic abilities, or whether a network is established, in which patients are referred, depending on their needs, to the medical unit that can provide the optimal treatment, at the time when it is indicated. Considering that the incidence of colorectal cancer tends to increase as the economic level of country increases [33, 34], the importance of such specialized centers for the complex treatment of colorectal cancer is emphasized once more.

For the management of liver lesions, the results obtained after extended or two-stage hepatectomies are comparable, from the oncological point of view, with minimally inva-

sive resections; liver tumor ablation methods can be used both independently and associated with limited liver resections [35, 36], as it results also from our study. Systemic oncological therapy is useful both to obtain conversion to operability of liver lesions, as well as to ensure an efficient control over the oncological disease during various staged procedures [35, 36, 37]. The most important criterion that influences the survival of patients is related to the complete resection of liver metastases, when it is possible. It has been shown that a negative resection margin of at least 1 millimeter around a liver metastasis would be optimal, otherwise FOLFOX or FOLFIRI chemotherapy is mandatory [38, 39].

It is fully accepted that liver metastasis is the most common way of dissemination in colorectal cancer, approximately half of the patients developing liver metastases and that the survival time of patients is correlated with a good control of liver metastases [40, 41, 42]. Surgical procedures, ablative techniques and systemic therapy have each proven their therapeutic potential and, under the conditions of a good control of liver lesions, metastases with other locations become a subject of interest to prolong the survival of patients [41, 42]. Recent research shows that, for the control of liver metastases, metastasectomies would be the most effective therapeutic procedure, obtaining a cure in approximately 20% of cases and a 5-year survival rate of over 50% [42].

This objective regarding the control of liver metastases is not easy to achieve, if we consider that 80% to 90% of patients with colorectal liver metastases are ineligible for primary resection [43]. For these patients, a correct evaluation in the tumor board and the choice of the optimal sequence of multidisciplinary treatment, combining systemic therapy and ablative techniques, with a double aim: either obtaining the conversion to surgical respectability, or at least controlling the progression and spread of the cancer [43] is necessary. Another solution considered recently, for patients with colorectal cancer and unresectable liver metastases, is regional systemic therapy, delivering chemotherapy via the hepatic artery. Irinotecan transarterial chemoembolization and transarterial radioembolization have provided interesting results, but additional studies are needed to confirm them [44].

All therapeutic procedures addressed to colorectal cancer with liver metastases have both results and specific risk profiles, but they provide a basis from which individual treatment strategies for patients with colorectal liver metastases can be selected and combined. Multidisciplinary treatment and the current transition to personalized therapy bring major improvements and push the limits of curative treatment in metastatic forms of colorectal cancer. Surgical procedures aimed at complete tumor clearance represent the central instrument to achieve long-term survival [45].

5. Conclusions

The experience from our series of cases shows that the simultaneous approach to recto-colic and hepatic resections in SCLM, in association with radio ablation of liver metastases, as a preliminary time is a safe procedure, grafted with low morbidity, the limits being dictated by the size of the liver secondary lesions, the stage of the recto-colic tumor, with possible elements of the associated subclinical carcinomatosis. The long-term results have to be drawn by further consistent trials.

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Table 1. Characteristics of the study group

The study group - 31 cases of SCLM - Characteristics of primary colo-rectal tumor and liver metastases	
Liver metastases - Number of cases	
Size : 1-3 cm ; 3-5 cm ; 5-8 cm	10 ; 15 ; 6
Number : 1 ; 2-5 ; 6-10	4 ; 19 ; 8
Localization : Unilobar ; bilobary	10 ; 21
Primary colo-rectal tumor – Number of cases	
Colo-rectal tumor stage: T1 / T2 ; T3 / T4	4/13 ; 6/8
Lymphatic invasion : Present ; Absent	23 ; 8

Table 2. Surgical procedures in the study group

Synchronous surgical approach SCLM – 31 cases			
Lesion type	Number of cases	Type of colo-rectal procedure	Type of hepatic procedure
Right colon 5 /6 / 8/ 10 liver metastases bilobary	4 cases	4 Right Hemicolectomies	2 Metastasectomies + vascular control of the hepatic pedicle and suprahepatic veins 2 Metastasectomies + Radiofrequency ablation + vascular control of the hepatic pedicle and suprahepatic veins
Left colon 1 / 1/2/ 3 / 3/3 /5/ 6 liver metastases unilobar/bilobary	8 cases	6 Left Hemicolectomies 2 Left Hemicolectomy with colostomy + Lymphadenectomy inter-aortic-cave	6 Metastasectomies 2 Metastasectomies + Radiofrequency ablation
Upper rectum 2 / 3/ 5/6 liver metastases unilobar/bilobary	4 cases	4 Anterior recto-sigmoidian resections with colostomy	2 Metastasectomies 2 Metastasectomies + Radiofrequency ablation + vascular control of the hepatic pedicle and suprahepatic veins
Middle rectum 1 / 1 / 3 / 3 / 3/ 4 / 5 / 6 /6 liver metastases unilobar/bilobary	9 cases	2 Low anterior resection with TME + colostomy + Lymphadenectomy inter-aortic-cave 7 Low anterior resections with TME + colostomy	4 Metastasectomies 5 Metastasectomies + Radiofrequency ablation
Lower rectum 2 / 3/ 3 / 4 / 4 / 6 liver metastases unilobar/bilobary	6 cases	6 Abdomino - perineal resections	4 Metastasectomies 2 Metastasectomies + Radiofrequency ablation + vascular control of the hepatic pedicle and suprahepatic veins

Table 3. Clinical evolution of patients

Long-term monitoring in study group SCLM – 31 cases		
<i>Clinical evolution of patients</i>	Survive with no signs of disease – 13 cases (41.93%)	
	Survive with signs of disease 14 cases (45.16%)	Hepatic metastases in regression - 6 cases (19.35%)
		Hepatic metastases in progression - 4 cases (12.9%)
		Hepatic metastases in regression + peritoneal carcinomatosis – 4 cases (12.9%)
	Deceased - 4 cases (12.9%)	Local recurrences in the areas of ablation of liver metastases and lymph node metastases in the liver pedicle – 2 cases
		Extensive peritoneal carcinomatosis, lung and bone metastases – 2 cases
Long-term monitoring	mean of 26 months (range 10 to 40 months)	
Survival rate	87.09%	

Fig 1. Radioablation of liver metastases, under intraoperatively ultrasound guidance, via open surgery

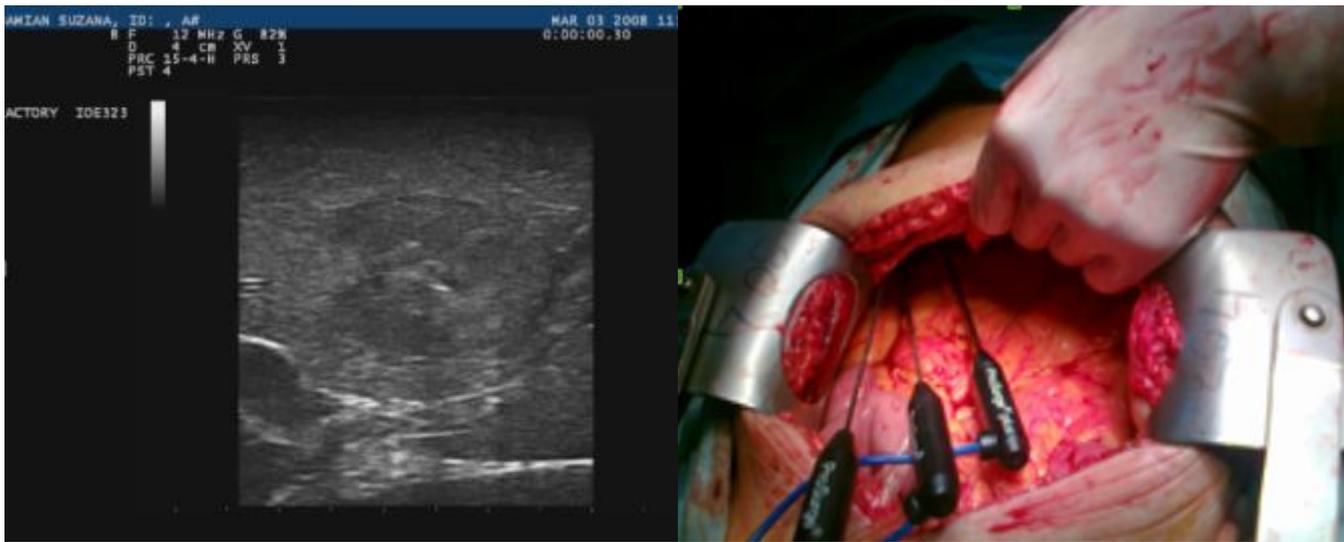


Fig. 2 Pre- and post-radioablation CT appearance of liver metastases (postoperatively, 1 month post-procedure)
Destroyed tumours by RFA (radiofrequency ablation) appear as hypodense areas, without changes after contrast injection; a peritumoral halo may appear, generated by hyperemia and the inflammatory reaction

Fig. 2 a: preoperatively

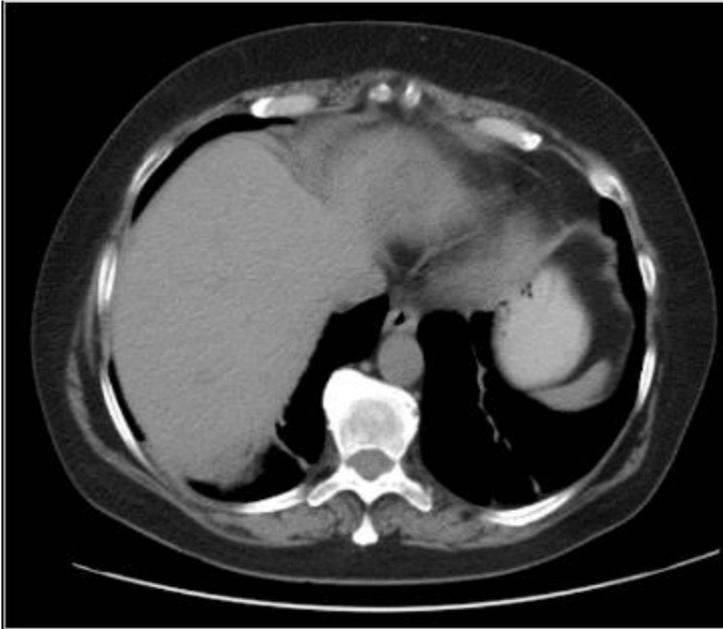


Fig. 2 b: postoperatively



Fig. 3 Patient with right colon cancer and multiple liver metastases, who underwent right hemicolectomy, concomitant with multiple liver metastasectomies and radiofrequency ablation of unresectable lesions

Fig. 3 a: preoperatively

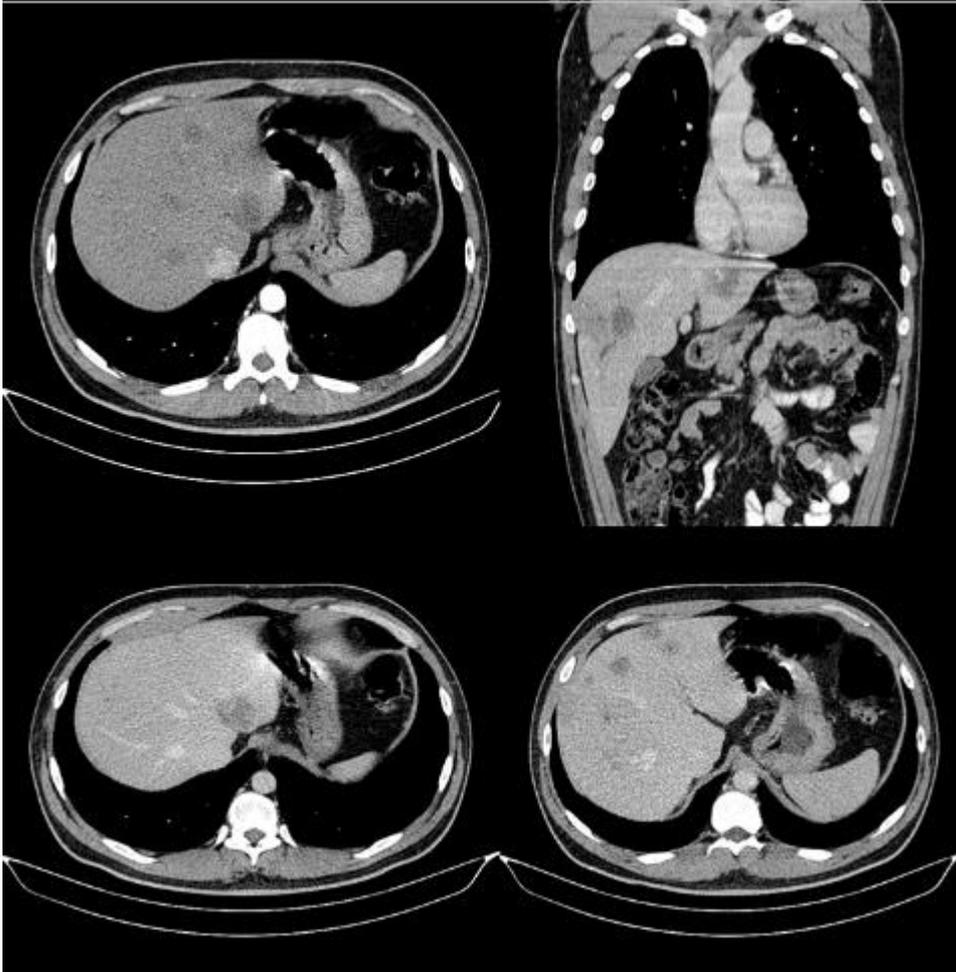


Fig. 3 b: postoperatively

