

OPTIMAL TIMING FOR SURGICAL TREATMENT OF COLORECTAL LIVER METASTASES

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Metachronous CRCLM should be evaluated by multidisciplinary oncologic consilium. Diagnostic evaluation must be completed by dynamic CT or MR of the liver. In the case of a small number of metastases, operation could be performed immediately. In such cases, neoadjuvant therapy could be recommended because of decreasing recurrence rates, slight increase of the overall survival rate and to evaluate malignant potential.

Neoadjuvant therapy is mandatory in cases with >4 metastases and potentially resectable metastases, due to possibility to convert 25% of them to secondary resectable category.

In the case of incidentally discovered metastases (during the primary colorectal operation), the removal of primary tumor should not be abandoned. Biopsy of metastatic lesion is not recommended.

Complications of CRC should be treated by palliative procedures (stoma, palliative resection, interventional endoscopy or radiology) followed by consilium multidisciplinary treatment and liver surgery in the second operative act.

Asymptomatic T 1,2, N 0,1 primary tumors of the right colon could be treated by simultaneous major liver resection. Left colonic and rectal resection could be safe combined with minor liver resection (up to 2 liver segments). In the cases of T 3,4, N 1,2 CRC with synchronous liver metastases neoadjuvant therapy is mandatory, as in the cases of multiple (>4) metastases. Reverse strategy could be effective in these cases. *Acta Medica Medianae 2015;54(1): 87-96.*

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Introduction

Liver is the well-known target organ for all malignant processes. It is the first and the most common site of metastases of colorectal cancer (CRC). In 20-25% patients with CRC, liver metastases are present in the time of primary tumor diagnosis (synchronous metastases). In the same percent of the patients, metastases will develop inside two years from primary tumor resection (metachronous metastases). Primary resection of liver metastases is possible in 20-25% (1-4).

Overall survival of the untreated patients suffering of colorectal cancer liver metastases (CRCLM) is under one year. Modern chemotherapeutic protocols, (Folfox, Folfiri, monoclonal anti-EGF i anti-VEGF antibodies) increase the overall

survival up to 20 months, with 5-years survival rate of 10-15% (6).

Liver resection is the most effective treatment option with 5-years survival rate up to do 58%, the overall survival rate of 40 months and disease-free survival rate of 30 months (5-8,66).

Improved surgical and anaesthetic techniques, together with better understanding of liver anatomy and physiology, allowed more aggressive surgical treatment of CRCLM. Decreased operative risk (operative mortality under 5%, morbidity up to 20%) increases possibilities and chances to cure older persons and patients with significant comorbidities (1,6,7).

The most effective choice of treatment is radical R0 resection. Modern minimally-invasive local destructive technique (cryosurgery, RF, laser, micro-wave ablation) is less effective and reserved for patients unfit for surgery (1-3,15,17).

Current treatment of patients with CRCLM is multidisciplinary.

Diagnosis of CRCLM started with ultrasound examination (US), which is cheap, non-invasive and repetitive method with sensitivity up to 85%.

However, in the case of CRCLM under 10mm in diameter, sensitivity of US drops to 35-48%. Contrast enhanced MSCT could discover liver metastases up to 91% (70% of lesions under 10 mm) and is diagnostic tool of choice according to most guidelines (15-17). MR combined with liver specific contrast agents /like SPIO-superparamagnetic iron oxid/ is the most sensitive method (up to 99%, but 80% for tumors less than 10 mm) (21).

ASCO (American society of clinical oncology) recommends monitoring of CEA level in a 3- month period the first two years postoperatively, despite false negative results in up to 30% (15,22,23, 25).

Ultrasound, MSCT, CT arteriography or MR of the liver give to surgeon useful informations about liver anatomy, tumor diameter, tumor position and its relation to major vascular and biliary structures, factors essential for planning surgical strategy (1,3,22). Volumetric CT and functional liver tests (MEGX or Indocyanin-green test) are necessary in the case of small future residual liver remnant volumen (26). Biopsy of the CRCLM is not necessary according to the studies of Jones et al. from 1986 and 2005 because of the danger of extrahepatic dissemination (74,75).

Preoperative examinations are followed by careful intraoperative exploration, palpation and intraoperative liver ultrasound which can modify operative surgical tactic in 5-15% (29).

Ekberg et al. in 1986 postulated contraindications for liver resection of CRCLM: over 4 metastatic lesions, extrahepatic metastases; inability to perform tumor-free resection margin less than 1cm (29,76). Presently, contraindications are: poor general state and significant comorbidity /ASA

score over 3/; non-resectable extrahepatic metastases; inability to perform radical (RO) liver resection with satisfying future remnant liver volumen and function /invasion over 70% of the liver (6 segments), irreparable invasion of all 3 hepatic veins or both principal inflow bilio-vascular branches (4,5,8,30,31).

Numerous factors influence patient's survival and results of surgical treatment of CRCLM. The most common prognostic factors are summarized in Nordlinger and Fong scoring systems. Negative prognostic factors by Nordlinger (1992) are: >60 years, advanced primary tumor /serosa +, N+/, short disease-free interval (1 or 2 years/, elevated CEA >30mcg/l, metastasis diameter >5cm, number of metastases >4, liver resection margin >1cm.

Two-year survival rate in patients with score 0-2 are up to 79%, score 3 to 4 -60%, score 5 to 7 low -43% (35). Fong system from 1995 also takes into account an extrahepatic dissemination (36). Similar system is proposed by Lee 2008 (37). However, the analysis of Zakaria et al. showed that diagnostic value of these systems are not absolute - with prediction value from 50 do 60% (38).

CRCLM could be treated by different types of surgery, ranging from simple metastasectomy to complex and very extensive liver resections (Figure 1).

Analysis of studies on the extent and type of the liver resection showed following:

- Immediate and long-term results of anatomic and non-anatomic liver resection are similar (39,40);
- Type of the resection is dictated by the number and location of the metastases, rather than by segmental anatomy of the liver (9) ;
- Liver surgery must be spared (41);

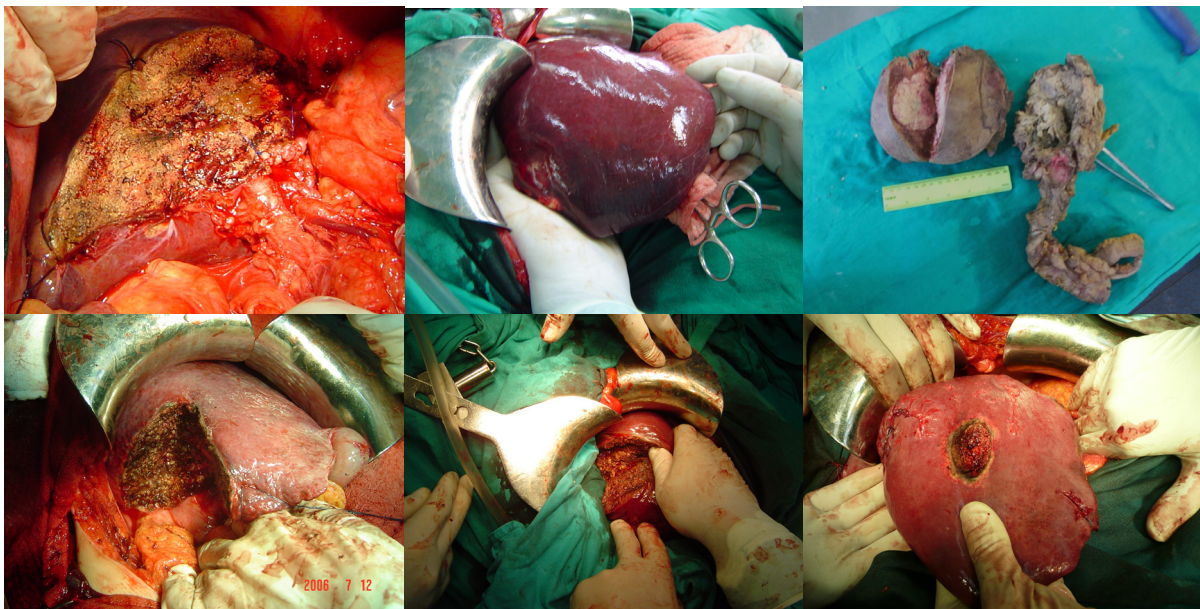


Figure 1. Different types of liver resection due to the CRCLM /author's operative material/

•R0 resection is an imperative in surgery of CRCLM (41-45);

•R1 or R2 resection increases recurrence rate two or three-folds, with the same decreasing of 5-years survival rate (42).

•Tumor-free resection margin has no influence on long-term survival rate (42,43), but some authors showed that resectional margin under 2mm is followed by increased local recurrence rate (43).

Timing of surgery for metachronous metastases

Optimal timing to operate metachronous colorectal liver metastases has not yet been defined. Before the last decades, there were two different approaches: immediate operation or operation after "test of time" (2-3 weeks to 6 months).

Most authors indicated immediate resection in order to prevent the possibility of lymphogenic and hematogenic spread (5,12,18). „Test of time" was introduced by Scheele (1995). During this period, potentially curable tumor will not become incurable because of low malignant potential. Of contrary, incurable small tumors will become visible on US and CT, with no need for resection. Author advises that tumor over 4cm in diameter needs immediate resection, but to perform „test of time" in cases of small, multiple metastases.

In the present time, decision-making for optimal timing in surgery for metachronous CRCLM became more complex after introduction of new therapeutic modalities for primary tumor treatment (stents for malignant intestinal occlusion, transarterial embolisation of bleeding tumors, preoperative chemoradiation and neoadjuvant chemotherapy with the aim of down-sizing and down-staging) (41, 47).

Modern neoadjuvant chemotherapy protocols (FOLFOX, FOLFIRI) combined with biological agents (anti-EGF i anti-vEGF monoclonal antibodies) radically changed the attitude about optimal timing in surgery of CRCLM (41,48,50).

Neoadjuvant chemotherapy of CRCLM offers numerous advantages:

- Increases resectability rate;
- It is a test of chemosensitivity;
- Eliminates micrometastases;
- Decreases explorative laparotomy rate;
- Increases conservative surgery rate;
- Decreases OP mortality;
- Increases disease free survival.

However, neoadjuvant chemotherapy has some disadvantages:

- Delay of liver operation;
- Toxic liver damage;
- Increase in complication rate;
- Complete radiological response complicates intraoperative finding of the liver metastases;
- Negative economical aspect (48);

Meta-analysis by Chu et al. shows that neoadjuvant therapy is radiologically effective in 82%. Unfortunately, it is ineffective in 18%. Partial therapeutic response is the most common (52%), radiologically stable disease is registered in 26%, while total response is rare (4%). The so-called „pathological response" after tumor cell's analysis is significantly lower than radiological response (45%), with total necrosis of malignant cells registered in only 9%. (49). Changing of CRCLM's category from unresectable to resectable (achieving of secondary resectability) is registered in 13,5% to 33% (49-52). Long-term survival of the patients in this category is almost similar to the survival in the category of initially resectable (33% 5 yrs. survival rate) (50,51).

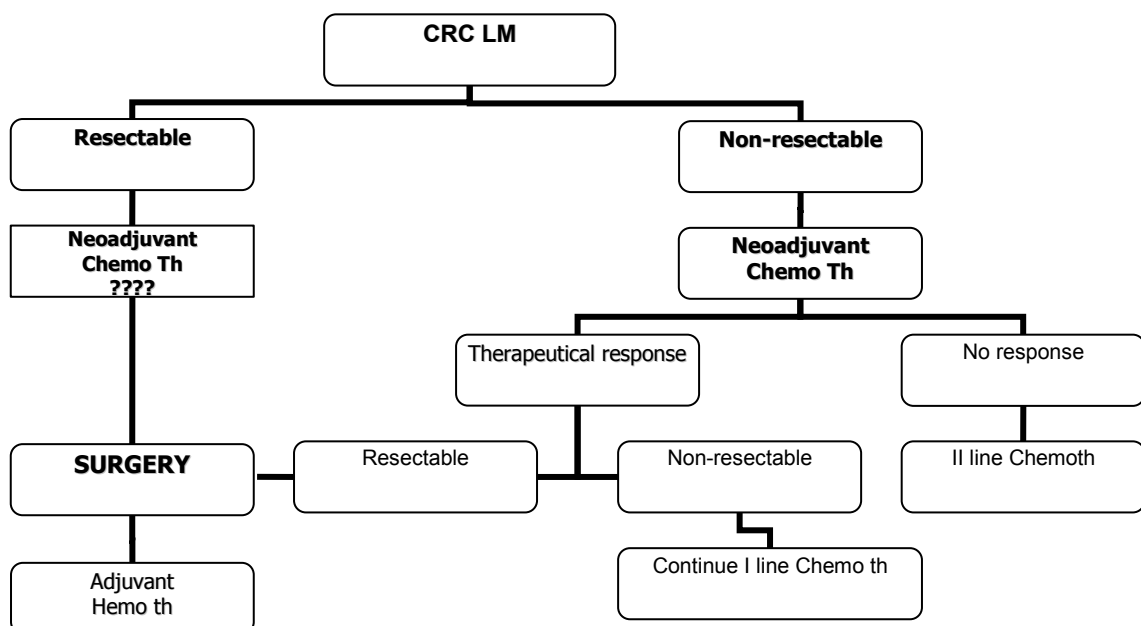


Figure 2. Algorithm for treatment of the CRCLM (48)

In primary resectable CRCLM, reasons for using neoadjuvant chemotherapy are: to test chemosensitivity; to eliminate micrometastases; to increase rate of conservative surgery (41).

The most important study focused on approximation of neoadjuvant chemotherapy in ORTC 40983 trial by Nordlinger et al. (2008, 2012) which showed slight but not significantly better results the group of patients treated with neoadjuvant therapy. The overall survival 61,3 months vs 54,3 months, 5-years survival rate 51,2% vs 47,8%, recurrent rate dropped by 25%) (50). Based on numerous studies, Benoist et al. made the world-wide accepted algorithm for treatment strategy of metachronous CRCLM (48) (Figure 2).

Timing of surgery for synchronous metastases

In 20-25% patients with CRC, liver metastases are present in time of diagnosis of primary tumor (synchronous metastases) (4,7,15-17). Synchronous metastases are the sign of aggressive disease and they are strong negative predictive factors (35,36). However, some new studies have not shown statistical difference in a 5-year overall survival rate (47% vs. 39%) or disease free interval rate (33% vs. 13%) in the groups of patients with synchronous and metachronous CRCLM, respectively (67, 68).

Despite different statistical data, it is the fact that treatment of CRCLM demands the knowledge of different therapeutical possibilities, with considerable individual approach to the patient (41).

Optimal timing to operate synchronous metastases has not been defined yet. Strategically, synchronous metastases could be solved in three ways:

- Classic, with two separate operations - colorectal resection first, followed or not by neoadjuvant chemotherapy, and liver resection in the second operation;

- Simultaneous operation of the colon and liver;

- Reverse strategy, with neoadjuvant therapy, followed by liver resection in the first and colon resection in the second operation.

Classical strategy starts from logical attitude that combining two extensive operations (like liver and colonic resection) is a risky procedure. This was confirmed by numerous retrospective studies, decades ago (44-47). Recent multicentric study of Reddy et al. (2007) showed also a significant increase in mortality and morbidity rate in the cases of combined colonic resection and major (more than 3 segments) liver resection (29).

One of the most strongest arguments against is the fact that a large number of metastases is discovered intraoperatively (during primary operation), in which cases there is no complete evidence about complete oncological and functional state of the liver and possibly disseminated metastases. In such cases, CRCLM are called „incidental metastases“. Despite recent powerful preoperative

diagnostics, CRCLM remains undiscovered in 3 - 16% (64).

In general surgery department, the most important is to remove CRC primarily. Intraoperative ultrasound and metastasectomy of the small peripheral lesions could be performed.

In specialized institution, with competent liver and colorectal surgeon, liberal procedures in one act (simultaneous liver and colon resection) could be performed safely. However, in the case of „incidental metastases“, it is very difficult to evaluate biological potential by „chemosensitivity test“, which can result with poor long-term outcome. Because of these facts, synchronous colonic and liver operation of „incidental metastases“ is not recommended even in the specialized institution (40,50-53).

Table 1. Morbidity and mortality rate after simultaneous operations of CRCLM

Author	Year	Number	Resection type	Morbidity (%)	Mortality (%)
Vogt	1991	36	19 simultaneous	5.2	0
			17 in two acts	17.6	
Sheele	1991	98	60 simultaneous	No data	2
			38 in two acts		
Jaeck	1996	41	20 simultaneous	20	0
			21 in two acts	10	
Nordlinger	1996	1008	115 simultaneous	No data	7
			893 in two acts		12
Bolton	2000	165	50 simultaneous	No data	12
			115 in two acts		4
Lias	2001	112	26 simultaneous	27	0
			86 in two acts	35	2.3
Martin, Blumgart	2004	240	134 simultaneous	49	3
			106 in two acts	67	3
Theler	2007	219	40 simultaneous	18	10
			179 in two acts	25	1.1
Stojanović	2008	100	38 simultaneous	15,78	0
			62 in two acts	17,74	0

Classic approach has the following disadvantages:

- Two hospitalisations, two operations, two anaesthesias;
- Cumulative prolonged OP time, blood loss, complication rate, hospitalisation;
- Delay of the second OP (up to 3 months);
- Negative psychological moment;
- Risk of the liver metastasis progression;

•Negative systemic effects of the chemotherapy (4,64).

Simultaneous colorectal and liver resection performed by experienced colorectal and liver surgical teams, in the selected cases, are safe and effective operations (4,7,54-64).

Avoiding second operation, decrease in cumulative operation time, blood loss, complication rate and length of hospitalisation are logical, oncologically based procedures with strong positive psychological effect (4,64). According to the extent of colorectal and liver resection, current recommendations are:

•Any kind of liver resection can be performed together with right hemicolectomy;

•Any kind of colon resection can be performed together with resection up to 2 liver segments;

•Simultaneous resection of the left colon and right hepatectomy could be performed in young and fit patients;

•In the case of bilobar metastases, during the operation of colorectal primary, minor liver resection, together with portal branch ligation or first act of ALPPS procedure could be performed (15-17,26,64). (Table 1)

One of the main disadvantages of a simultaneous procedure is a possible risk of the septic complications. Combination of „contaminated and clean“ surgery and disturbed anastomotic healing, because of use of Pringle manoeuvre, could be avoided by careful patient's selection, adequate colon preparation and meticulous, bloodless and precise liver and colorectal surgery (55-57,64).

Initial study addressed the long-term results of simultaneous operations, and showed their negative impact on a 5-years survival (59). However, recent studies have confirmed a 5-year survival rate similar to the rate after classic approach, ranging from 22 to 55% (60-63,66) (Figure 3).

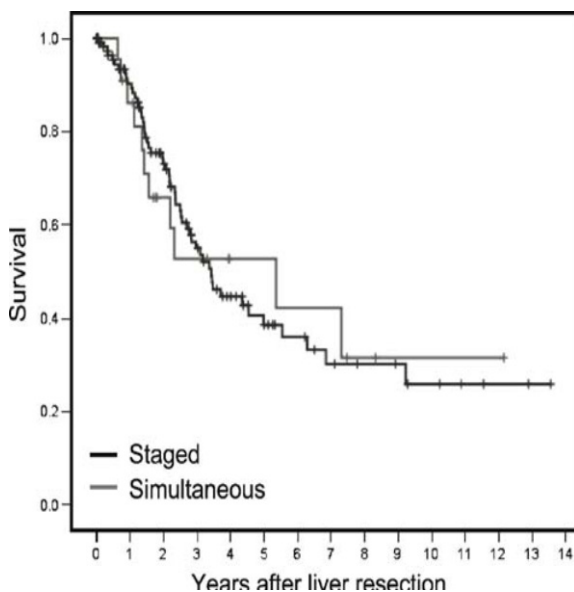


Figure 3. Long-term results of staged and simultaneous operations of CRCLM (60)

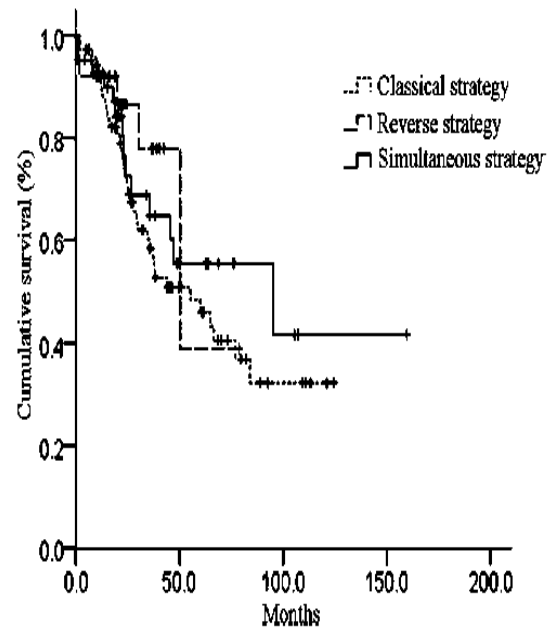


Figure 4. Long-term results of different strategy treatments of synchronous CRCLM (66)

Reverse strategy consisting of primary use of neoadjuvant chemotherapy addressed predominantly liver metastases, but it is efficient also against primary tumor. In the case of positive therapeutic response, liver resection is performed. Definite treatment of primary tumor is postponed 3 to 8 weeks after liver resection or after ending the local radiotherapy (if it is indicated). This approach was proposed by Mentha (2006), with 4-years survival rate of 56%, and overall survival of 46 months (65).

There are a few explanations for this „reverse approach,“: potent neoadjuvant chemotherapy rapidly treats liver disease, being responsible for lethal outcome in most of the cases. On the other hand, it serves as a „chemosensitivity test“ to distinct groups of the patients who might be candidates for the operation from „non-responders“ (52,53).

Brouquet et al. compared three strategies in the treatment of patients with CRCLM. They showed the best five-years survival rate with the use of simultaneous strategy (55%), versus classical 48% and reverse strategy (39%)(Figure 4) (66).

Surgical tactics of treatment of synchronous CRCLM depend on:

- Symptomatology of the primary tumor;
- Locoregional status of the primary tumor;
- Resectability of the liver metastases;
- Surgical teams experience.

In the case of the complicated CRC, there is no reason to perform simultaneous colorectal and liver resection. Primary tumor complicated with occlusion, perforation or bleeding with resectable synchronous CRCLM could be treated with classical strategy, or temporary palliative non-surgical procedure (internal stent, chemoembolisation) fol-

lowed by simultaneous or reverse oncosurgical strategy (9, 69,70).

Locally advanced asymptomatic primary colorectal tumor (T4) with resectable synchronous CRCLM is strong negative predictive factor (35). Results of simultaneous operations are disappointing with a three-years survival rate of 17,7 %, versus 60% in the group of the patients treated in 2 acts (56,9,76).

Locoregional lymphadenopathy of primary tumor is also a negative prognostic factor. Fujita et al. showed that the presence of 6 or more metastatic lymph nodes is associated with a five-years survival rate lower than 10%. Because of that, simultaneous liver resections in these cases could not be curative and are contraindicated (56).

Resectability and the number of metastases in case of synchronous CRCLM are the factors which depend on numerous parameters. The most important factors are extent and type of future liver and colonic resection and experience of surgical teams. Patients with less than four metastases could be operated immediately, without preoperative chemotherapy (8,9,59,69).

One of the most important factors in surgery are surgical knowledge and experience of the operating surgeon, complete surgical team and institution. Overall and annual number of operations on institutional and personal level have strong influence on the results of any kind of surgery. Personal experience of surgeon in a delicate surgical field, as liver and colorectal surgery has impact of 55% on institutional experience (78).

Progressive cummulation of knowledge and experience, followed by centralization of the patients in specialized centers, resulted in the 2-fold increasing of resectability rate of the patients with CRCLM (from 20 to 40%) and similar rate of

long-term survival (8,48,50). Educated multidisciplinary teams dedicated to this pathology should be established in tertiary referral centers which cover population up to 2 milion inhabitants (15,79,82).

Conclusion

Metachronous CRCLM should be evaluated by multidisciplinary oncologic consilium. Diagnostic evaluation must be completed by dinamic CT or MR of the liver. In the case of a small number of metastases operation could be performed immediately. In such cases, neoadjuvant therapy could be recommended because of decreasing recurrence rates, slight increasing of the overall survival rate, and also to evaluate malignant potential.

Neoadjuvant therapy is mandatory in cases with more than four metastases and potentially resectable metastases, due to possibility to convert 25% of them to secondary resectable category.

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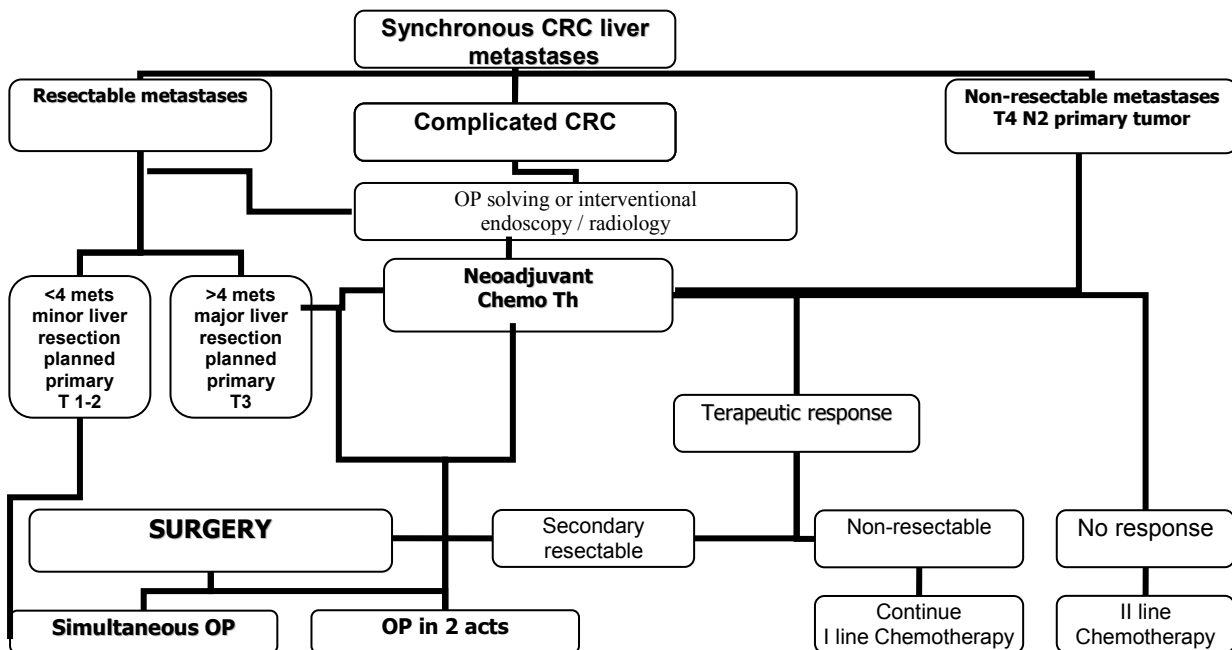


Figure 5. Original author's algorithm for treatment of the synchronous CRCLM

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OTIMALNI TAJMING HIRURŠKOG LEČENJA METASTAZA KOLOREKTALNOG KARCINOMA U JETRI

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Hemoroidi su veoma često i obično hronično anorektalno oboljenje definisano simptomatskim uvećanjem i ispadanjem normalnih analnih jastučića. Hemoroidalna bolest je stara koliko i ljudska rasa.

Od antičkih vremena do danas korišćeni su mnogi načini lečenja, nehirurški i hirurški, u pokušaju da se otklone simptomi i uskladi zadovoljstvo bolesnika sa prihvatljivim komplikacijama, sa boljim ili lošijim rezultatima. Rasprava o tome koja je najbolja metoda lečenja traje do danas.

Ovaj članak predstavlja različite mogućnosti lečenja hemoroida tokom vremena, sa posebnim osvrtom na efikasnost pojedinih metoda i komplikacije koje ih prate, kao i savremene preporuke o lečenju hemoroidalne bolesti. *Acta Medica Medianae* 2015; 54(1):87-96.

Ključne reči: hemoroidi, ambulantno lečenje, hirurške intervencije