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Surgical Options in Synchronous Liver Metastases from Colorectal Cancer

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ABSTRACT

Currently, the treatment of liver metastases of colorectal cancer (CRC) requires a multidisciplinary approach and should be individualized for each patient. Liver resection provides 5 years survival rates ranging between 30 and 58% in patients with liver metastases of CRC. The optimal timing of liver resection, resection of the primary tumor and neoadjuvant chemotherapy has not been fully established, yet, neither for initially resectable synchronous liver metastases, nor for those initially unresectable which could be converted to resectability. Advocates of simultaneous resection and those of staged resection (delayed liver resection or "liver first approach"), both presented theoretical arguments in favor of each of these therapeutic strategies. Progresses in liver surgery, anesthesia, intensive care and oncology caused a paradigm shift regarding the approach of synchronous colorectal liver metastases, with simultaneous resection (SR) becoming a safer procedure in the last decade. As well, the oncologic outcomes of SR are similar to those achieved by staged resection. In this review we present the literature data concerning the results achieved by each of the currently available therapeutic approaches.

Abbreviations: CLMs – colorectal liver metastases, SCLMs – synchronous colorectal liver metastases, CRC – colorectal cancer, PVL- portal vein ligation, PVE – portal vein embolization, SR – simultaneous resection, DR – delayed liver resection, SgR – staged resections, FLR – future liver remnant, CHT – chemotherapy, OS – overall survival, DFS – disease-free survival, ETS – early tumor shrinkage

Key words: colorectal liver metastases, simultaneous resection, delayed resection, "liver-first" approach, initially unresectable liver metastases

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of adult cancer, representing the 4th cause of cancer-related death (1,2). The leading cause of death in patients with CRC is metastatic disease and the liver is the most frequent location of metastases (3). Thus, approximately 50-65% of patients with CRC will develop liver metastases (CLMs), whilst about 20% are present at

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the moment of the diagnosis of the primary tumor. (4-7).

Metastases discovered during preoperative work-up of patients newly diagnosed with CRC or detected at the time of surgery addressed to the primary tumor are referred to as synchronous colorectal liver metastases (SCLMs).

However, past years statistics show a decrease in both the incidence of CRC and the rate of death from this disease (8,9). Factors that were independently correlated with the decrease in mortality from CRC were the performance of surgical resection of CLMs on a larger scale and the advent of effective oncologic medication (10-14).

Currently, in patients with CLMs, liver resection is considered the only potentially curative therapeutic method, offering significantly higher 5-years survival rates (30-58%) than other treatment modalities (ablative therapies, chemotherapy, targeted therapies, interventional oncology) (15-19).

In the latest two decades, because of the results achieved by hepatectomy, there has been a significant expansion of the frontiers of liver resection for CLMs, so currently, the definition of resectability is based on "practical" rather than "dogmatic" criteria. Thus, CLMs are considered resectable when preoperatively it is anticipated that liver metastases could be completely resected (R0), with preservation of at least two adjacent segments of the liver, whose volume (future liver remnant - FLR) can provide adequate liver function (avoiding the postoperative hepatic failure) (20,21).

However, in patients with SCLMs, the optimal timing of liver resection, resection of the primary tumor and neoadjuvant chemotherapy has not been fully established, yet, neither for initially resectable SCLMs, nor for those initially unresectable SCLMs (which could be render resectable). Also, the presence of primary tumor complications may change the treatment strategy.

Below we present a review of the literature regarding arguments and counter-arguments to each of the available therapeutic approaches, trying to synthesize the results and indications of these surgical strategies.

A. INITIALLY RESECTABLE SCLMS

Currently, there are three possible surgical approaches for these patients:

Simultaneous resection (SR) – it involves concurrent resection of the primary tumor and liver metastases.

Delayed liver resection (DR) consists in initial resection of the primary tumor followed by 4-6 cycles of neo-adjuvant chemotherapy (CHT) and thereafter, hepatic resection is performed, if CLMs do not progress (22,23).

"Liver first approach" – it is usually preceded by three months of neoadjuvant chemotherapy followed by SCLMs resection (if they do not progress), conducting subsequently the primary tumor resection. In patients requiring radiotherapy for rectal tumors, this is performed in the interval between the two operations (18).

Promoters and supporters of each of these therapeutic strategies highlighted theoretical advantages of their favorite approach, along with underlining the other options' disadvantages. The supporters of staged resections (SgR) (DR or "liver-first" approach) have postulated the safety of these approaches, highlighting the fact that, in this way, potential complications, arising from performing concurrently two medium/large scale operations, are avoided (18,24,25). In addition, it was assumed that, by performing neo-adjuvant CHT, the biological behavior of tumor could be assessed, allowing a better selection of patients, feature that might lead to higher rates of survival (26). At the same time, the promoters of SR argued that the simultaneous resections of the primary tumor and SCLMs increases the patient comfort (avoiding the second surgery under general anesthesia), reduce the length of hospital stay, improve the cost-effectiveness ratio and also eliminate the likelihood of an initially resectable SCLMs to progress to unresectability during the interval between the two surgical procedures (24,27-30).

Often, these trenchant positions, apparently irreconcilable, were partially harmonized by practical results. Currently, despite the persistent divergences on certain issues related to the short and long term outcomes, some indications referring to the surgical approach of patients with CRC metastatic to the liver have become consistently accepted. Thus, there has been reached an agreement about the fact that surgical strategy must be different depending on the presence or absence of primary tumor complications.

1. Complicated primary tumor

In case of patients having stenosis or perforation of the CRC at the moment of diagnosis, it is obvious that the primary tumor should be resected first. It has been observed that postoperative morbidity and mortality rates are significantly higher in patients undergoing emergency surgery for CRC compared to those

operated under elective circumstances (31). Performing hepatectomy in the context of intestinal obstruction or peritonitis would involve a further increase in the risk of postoperative complications, which is why SR is contraindicated in patients with SCLMs and complicated primary tumor.

In addition, in the context of intestinal obstruction or peritonitis a temporarily stoma may be required, implying a second surgical time for its closure. Therefore, performing SR in patients with complicated primary tumors and initially resectable SCLMs would not provide any significant benefit, as a second surgery is still often necessary and risks of simultaneous resection of SCLMs are not negligible. Thus, in these circumstances, patients with complicated CRC and SCLMs are recommended for DR and in the second operative step, performed electively, they will undergo both hepatectomy and restoration of digestive continuity.

2. Uncomplicated primary tumor

In the late 80's few centers that acquired experience in hepatic surgery started to perform SCLMs resection after a period of 2-4 months after primary tumor surgery (23). The publication of these seminal data brought a tremendous benefit in treatment of SCLMs, proving that their complete resection significantly improves the survival of these patients (22). Thus, SCLMs resection has been shown to be a worthwhile operation, practically changing the paradigm on the treatment of these patients.

Later, in the 90's due to advances in liver surgery and anesthesia, leading to lower rates of post-hepatectomy morbidity and mortality, simultaneous approach of SCLMs and primary tumor was tempted in some centers experienced in liver and colorectal surgery (32). However, advocates of DR have complained about potential increased rates of postoperative complications and death after SR (18,25,33,34), and pointed out that in the absence of a certain period of observation concerning the biological behaviour of SCLMs, an appropriate selection of patients for liver resection was not possible (35). Equally, proponents of SR raised concerns about the potential progression of SCLMs after resection of primary tumor and, in consequence, missing the opportunity to perform a potentially curative resection (18;36). To overcome these drawbacks, 10 years ago, Mentha et al. introduced a new surgical strategy for SCLMs, called "reverse approach" or "liver-first" approach (18). In this strategy there were combined, at least theoretically, the advantages of the other two therapeutic approaches. Thus, the patient undergoes neoadjuvant CHT, allowing time to observe the biological behavior of the metastasis, this "test of time" offering proper selection of patients. In addition, by initially resecting the liver metastases, their progression after resection of colorectal tumor was eliminated and morbidity and mortality rates were not increased by the association of two surgical procedures during a single operation. Moreover, for rectal tumors with indication of preoperative radiotherapy, this could be performed after initial resection of SCLMs (offering these patients „gold-standard" therapies for rectal cancer) (18,31,37).

In the last decade, by gathering data from several retrospective studies, it was possible to obtain information that challenged the theoretical assumptions presented above, both in terms of short-term and long-term outcomes of patients with SCLMs.

a. Short term outcomes

Initially it has been observed that after performing SR of tumors located in the right colon and minor hepatectomy, the morbidity and mortality rates were similar to those achieved by the DR (32). Subsequently, several authors have shown that if the primary tumor setting was in the left colon, short term outcomes achieved by DR were similar to those recorded by SR if SCLMs did not require major hepatectomy (32,38-40). Thus, in a multicenter study published in 2007, Reddy et al. experienced similar rates of morbidity and mortality for SR and DR, regardless of colorectal tumor location, if major hepatectomy was not performed (24,29,30,39,41). Moreover, some authors have recorded higher cumulative rates of morbidity for DR than for SR in patients with resectable CRC and SCLMs requiring a minor hepatectomy (41,42). Because the blood transfusion is a predictor of postoperative complications in patients operated for SCLMs (43-45), the lesser morbidity rate after SR than after DR could be explained by the lower blood loss during SR than the cumulative blood loss of SgR (30,46).

Thus, at present, it is almost universally accepted that in patients with uncomplicated colonic tumors and SCLMs requiring minor hepatectomy, SR is the surgical approach of choice (29-31,37,39,41,46-51).

In addition, numerous studies have shown that SR is associated with a shorter hospital stay than SgR (41, 42,47) (46,52-54). This fact is rendered in lower costs to health care system, making the SR a more cost-efficient approach to SCLMs than SgR (28). Beside this advantage, the SR improves the psychological comfort of the patients, who avoid two operations under

general anesthesia and spend fewer periods of time in hospital (55).

However, reluctant opinions persist, from several authors (21,31,48,51), regarding the safety of performing SR for SCLMs that would require major hepatectomy and in patients with primary tumors located in the lower or middle rectum.

Major hepatectomies

Consensus conferences recommendations on SCLMs were to avoid SR if major hepatectomy were needed, suggesting in these situations SgR (DR or "liver-first" approach). However, these recommendations were based on the results of retrospective studies that included patients operated more than 10 years ago. Thus, a multicenter study published in 2007 by Reddy et al. found that major morbidity and mortality rates were significantly higher after SR than after DR (36.1% vs. 15.1% and 8.3% vs. 1.4% respectively; p value <0.05) (48). Moreover, the same study revealed that the only factor that independently predicted severe morbidity after SR was resection of more than three liver segments.

However, in the last decade, several authors have recorded similar rates of morbidity and mortality following SR of primary tumor and major hepatectomy (30,39,50,56,57). Since 2007, Capussotti et al reported similar results in terms of mortality and morbidity after major hepatectomy performed either simultaneously or delayed for SCLMs (56). In this study, 31 patients underwent SR of the primary tumor and major hepatectomy, while 48 patients requiring major liver resection underwent DR. Similarly, in an article published in 2016 Muangkaew et al. compared the rates of morbidity and mortality among 55 patients who underwent major hepatectomy as part of a SR and 48 patients receiving delayed major liver resection (48). The conclusion was that both morbidity and mortality rates were not statistically significantly different between the two groups of patients. So after SR and DR, overall morbidity rates were 76.4% vs. 62.5%, respectively (p value = 0.126) and major morbidity rates were also similar (29% vs. 25%, respectively, p value = 0.513). Also, a retrospective study published in 2017 by I. Popescu et al. achieved similar rates of morbidity and mortality (p value = 1) in patients with SCLMs receiving major hepatectomy performed either successively or simultaneously (54).

So, at least for selected patients (with good performance status, without co-morbidities), treated in specialized centers in colorectal and liver surgery, the simultaneous resection of colorectal tumor and major hepatectomy for SCLMs can be performed safely. However, the trend of recent years is to perform, whenever possible, major hepatectomies in favor of limited hepatic resections (50). This trend is supported by the findings that the only factors independently associated with mortality rates after hepatectomy are the amount of blood loss and resection of more than three liver segments (58). Thus, due to the better understanding of the liver anatomy, the use of intraoperative ultrasound on a larger scale and the introducing of transparenchymatous approach to liver resections, the rate of major liver resections decreased significantly. This fact was noted in the last years in high-volume centers, which performed whenever possible ultrasound-guided parenchyma-sparing liver resections, resulting in a significant improvement of short-term results. Therefore, currently, most patients with resectable SCLMs became eligible for SR, with removal of liver metastases by ultrasound guided limited liver resections instead of major hepatectomies (55).

Another criticism addressed to the simultaneous approach in patients requiring major hepatectomies or parenchyma sparing liver resections for metastases located in the right hemiliver is related to the incision that should be performed to resect both primary tumor and SCLMs. Usually, this type of hepatectomy requires the surgeon to perform a right subcostal incision. Although this approach provides sufficient space for a safe liver resection, it does not usually offer an optimal approach for colorectal resection, especially for tumors located in the left colon or rectum. Therefore, in such cases the right subcostal incision is associated with a median incision. This complex incision sectioning the white line, the recti abdominis muscles and the wide muscles of the anterior abdominal wall, expose the patient to increased risk of parietal complications (mainly incisional hernia). To overcome this disadvantage, the advent of minimally invasive surgery has a tremendous importance. Thus, the colon cancer could be resected by laparoscopic approach and the hepatectomy may be performed via a right subcostal incision. Moreover, this incision could also be used for the extraction of the colectomy specimen (50). In centers with increased experience in laparoscopic surgery, selected patients with SCLMs can undergo laparoscopic resection of both primary tumor and metastases (59-63). Due to the recent concerns regarding the laparoscopic resection of rectal cancers, in such patients, the resection of the rectal tumor could be performed by robotic approach and the hepatectomy for SCLMs by right subcostal incision (50).

Rectal tumors

Most centers considered that the association of

pelvic surgery with liver resection exposes the patient to an increased risk of postoperative complications and death, which is why they recommended performing the rectal resection and hepatectomy in a staged manner (25;42;64). These assertions are based on small groups of patient usually operated before using on a larger scale the "sphincter-saving" procedures (25,42). Thus, the evidence level, of recent consensus confereneces (37,51), is II to III with grade C recommendations (42). More recent retrospective studies, challenged this recommendations. A study published in 2015 by the MSKCC group included 145 patients with rectal cancer that underwent SR and 53 patients with synchronous liver metastases of rectal origin undergoing SgR (55). The rate of major complications (grade III or IV according to Dindo-Clavien) was 15% in the SR group and 19% in the SgR group (p value = 0.51). Also, there were no deaths registered in either of the two groups. In addition, the rate of incomplete resection (R1, R2) was similar between the two groups of patients (p value = 0.31). Similar results have been reported by I. Popescu et al. which reported an overall rate of complications of 45% in 80 patients with rectal cancer that underwent SR and 30.7% in 13 patients that underwent SgR for rectal cancers with SCLMs (p value = 0.3825) (54). In this study, mortality rates were also similar (1.25% vs. 0% in the SR group SgR group; p value = 1). Furthermore, in a study published in 2015 that included 50 patients with rectal cancer and SCLMs, morbidity and mortality rates were similar regardless of whether metastasis resection was performed simultaneously or staged (65). Since in these studies more than 80% of patients receiving SR benefited from "sphincter-saving" procedures, these results demonstrate the fact that in order to achieve such short-term results it is necessary for these interventions to be performed in centers with experience not only in liver surgery, but also in colorectal surgery. Therefore, these studies show not only the safety of a simultaneous approach, but also that such safety relies on patient selection by experienced surgeons (55). However, rectal tumors requiring abdomino-perineal resection were more likely to be chosen for a staged approach, while the patients with rectal cancer and SCLMs requiring major liver resection were more likely to be chosen for a staged approach (55).

Thus, SR of rectal tumors (especially by “sphincter-saving procedures”) and SCLMs (by minor hepatectomies) could be safely performed in high-volume centers experienced in colorectal and liver surgery.

b. Long term outcomes

Although the safety of SR was accepted by most authors, at least in patients with colon cancer and SCLMs manageable by a minor hepatectomy, the supporters of DR are still reluctant to accept that SR could achieve similar survival rates as DR (66-68).

In 2004, the Paul Brousse group reported that in patients whose LM progress under neo-adjuvant chemotherapy, the 5-year overall survival (OS) rates achieved by liver resection (8%) are significantly lower than those achieved in patients responsive to CHT (30%) or presenting stable disease (37%) (69). Thus, it was hypothesized that SgR allow a better selection of the patients with SCLMs, because, during the observation interval before hepatectomy, could be assessed the biologic behavior of LM to neo-adjuvant CHT.

However, the above-mentioned study, presents few limitations: there were analyzed only 131 patients, each of them presenting at least 4 LM. Moreover, the patients were enrolled between 1997 and 2000, in period when modern oncologic therapies (such as intra-arterial chemotherapy, targeted therapies, etc) were not available. Thus, it is hazardous to extrapolate the results of this study to all the patients with SCLMs, especially in the era of modern oncologic treatments. Therefore, a study published in 2012, on 2143 patients, revealed that in patients with progressive disease under neo-adjuvant CHT, the independent prognostic factors associated with poor survival after liver resection were more than 3 LM, metastases larger than 5 cm and CEA level > 200 ng/ml. In patients who did not present any of the above mentioned poor prognostic factors, although the disease progresses under neo-adjuvant CHT, the 5-year OS rate was 53.3%. Moreover, this study revealed that the risk of progression was increased after 5-FU or irinotecan (22.7 % vs. 6.8 % after other regimens, $p < 0.0001$; 14.9 % vs. 7.2 %, $p < 0.0001$), while it was reduced after oxaliplatin (5.6 % vs. 12.0 %, $p < 0.0001$) and still diminished among patients receiving targeted therapies (2.6 %) (70). Similarly, other authors revealed that modern chemotherapy regimens enable progression-free survival (PFS) rates longer than 6 months in patients with metastatic CRC and the likelyhood to assess the biologic behavior of SCLMs during an observation interval of 2-4 months is exceptional.

Moreover, in patients with small liver metastases, preoperative chemotherapy could lead to radiologic disappearance of some of these lesions (71,72).

Unfortunately, even when these vanishing metastases are not found at laparotomy, viable tumor cells are still present, in more than 80% of cases (73,74-76). Frequently, a complete resection of the initial sites of these metastases could not be achieved at laparotomy, these patients missing the chance of a potentially curative resection.

The aforementioned observations questioned the usefulness of neo-adjuvant chemotherapy in selecting patients with SCLMs for liver resection. By these reasons some authors consider that the traditional treatment paradigm centering on the utility of pre-hepatectomy chemotherapy for resectable SCLMs should be reconsidered (29).

As well, most studies presented until now revealed that SgR failed to achieve significantly higher OS rates than SR (32,38,39,47,77,78). Therefore, in present, there are consistent doubts about the ability of neoadjuvant CHT to improve OS rates in patients with SCLMs. Until now, no one study revealed that in patients with SCLMs, neoadjuvant CHT improved OS. There are only two retrospective studies which suggested that neoadjuvant CHT improved OS in patients with CLMs; both studies enrolled patients with synchronous and metachronous metastases. In 2003, Tanaka et al reported the results achieved by liver resection in 71 patients with five or more bilobar liver metastases (79). Out of these, 48 patients received neoadjuvant CHT and 23 underwent up-front surgery. The 3- and 5-year OS rates of patients treated with neoadjuvant CHT were significantly higher than those achieved by patients with up-front surgery (67% and 38.9% vs. 51.8% and 20.7%, respectively; p value = 0.039). In 2015, Ayez et al. investigated the impact of neoadjuvant CHT on OS in 363 patients with resectable CLMs. They stratified the patients by the clinical risk score (CRS) according to Fong et al (80), revealing that in the low CRS (0-2) group there was no significant difference in median OS between patients with and without CHT (65 months vs. 54 months, p value = 0.31). In the high CRS (3-5) group, there was a significant difference in OS between patients with and without CHT (46 months vs. 33 month, p value = 0.004). The authors concluded that patients with a high CRS benefit from neo-adjuvant CHT, while in patients with a low risk profile, neo-adjuvant CHT might not be beneficial (81).

The results of the only one randomized trial who tried to assess the effectiveness of chemotherapy in patients with resectable CLMs were presented in 2008 and 2013 by Nordlinger at al. (82,83). In this study 364 patients were randomly assigned in two arms: in CHT group the patients received 6 cycles of FOLFOX4 before surgery and 6 cycles of FOLFOX4 after hepatectomy; in hepatectomy group the patients underwent only liver resection, without preoperative or postoperative CHT. The authors found no difference in OS with the addition of perioperative chemotherapy compared with surgery alone. An intention-to-treat analysis revealed that the addition of perioperative CHT, did not significantly increase the rate of DFS at 3 years (p value = 0.058). Only in patients who underwent liver resection, the DFS was significantly higher in CHT group than in surgery alone group (42.4% vs. 33.2%, p value = 0.025). Moreover, in the surgery alone arm, the patients did not receive CHT even postoperatively. This could bias the survival rates, because most studies revealed that postoperative chemotherapy improves both OS and DFS rates of patients who's CLMs were resected (21). Due to these limitations, the results of this study cannot strongly support the benefits achieved by neoadjuvant CHT in patients with resectable SCLMs and the advantages of preoperative CHT should not be over-estimated.

However, in patients with high CRS, when neo-adjuvant CHT is considered (based on a multidisciplinary team decision), it could be started preoperatively and SR might be subsequently performed. Thus, the need for neoadjuvant CHT might not represent an argument for DR, even more as primary tumor resection may stimulate the progression of SCLMs and in case of post-operative complications may delay the initiation of CHT (84).

A peculiar situation is those of patients with locally advanced rectal cancer and SCLMs. Usually these patients needs radio-chemotherapy before rectal resection to decrease the local recurrence rates (85). Because this therapy delays resection with almost 3 months, there is a high risk of liver metastases progression during this time interval, especially when border-line resectable SCLMs are present. To avoid the progression to unresectability of their SCLMs, these patients seem to be the most appropriate candidates for a "liver-first" approach (18,48,85-87). Using this approach, the chance for potentially curative surgery is not compromised because of progression to un-resectability of SCLMs and the "gold-standard" therapy for rectal cancer is employed.

B. INITIALLY UNRESECTABLE SCLMS

As mentioned before, hepatic resection offers the highest rates of survival to patients with liver metas-tases from colorectal cancer (13). Unfortunately, at the moment of their diagnosis, almost 75% of the patients

with SCLMs present unresectable SCLMs (88). The only possibility to significantly improve the survival of these patients is the employment of several strategies able to achieve complete clearance of the liver, eventually (84,89-91).

In these patients, liver resection could not be initially performed because the estimated volume of the remnant liver (FLR) after complete resection of SCLMs would be too small to avoid postoperative liver failure. Under these circumstances, the resectability could be achieved if the FLR volume is expanded.

Roughly, there are two modalities to acquire a higher volume of the FLR – either by inducing the hypertrophy of the remnant liver (based on the regenerative capacity of the liver parenchyma) or by decreasing the volume of liver metastases (after an efficient oncologic treatment).

Because the ablative techniques are able to produce complete destruction of CLMs smaller than 3 cm, another potential modality to achieve complete clearance of the liver consists in resection of the bulk metastatic burden and in situ ablation of the small lesions located in the FLR (Combines ablation and resection – CARe).

In 2014 ESMO classified the initially unresectable CLMs in the following groups:

Group 1: Potentially resectable metastatic disease with curative intention

Group 2: Disseminated disease, technically 'never'/ unlikely resectable

Group 3: Never-resectable metastatic disease.

The above mentioned modalities to render resectable the initially unresectable CLMs, can be applied mostly in group 1 patients.

In this review, we shall focus on the modalities to employ these strategies in group 1 patients with initially unresectable SCLMs.

1. Complicated primary tumor

When the primary tumor is complicated by perforation or intestinal obstruction, colorectal resection is mandatory if the possibility of conversion to resectability of the SCLMs is anticipated. In patients with Group 3 SCLMs and intestinal obstruction, resection of the primary tumor is no longer mandatory and performing a digestive bypass is accepted.

2. Uncomplicated primary tumor

In this situation for group 1 ESMO patients one of the following strategies can be used to achieve complete clearance of the liver:

a. Liver resection after portal vein occlusion (ligation/embolisation)

This approach is recommended to patients having SCLMs confined to the right hemiliver and segment 4 and without metastases in remnant liver, whose estimated FLR is less than 25 - 30%. In such patients, initial resection of the primary tumor should be associated with right portal vein ligation. Following right portal vein ligation (PVL), cytokines, growth factors and hormones are released. All these factors will induce hypertrophy of the contra-lateral hemiliver, making possible a safe subsequent resection of SCLMs.

The hypertrophy of the right hemiliver should be assessed after 4-8 weeks following PVL. If a sufficient liver hypertrophy is accomplished (FLR volume > 30% of total liver volume), liver resection should be performed as soon as possible.

Using this strategy, resectability rates ranging between 55% and 65% were achieved and 5-year overall survival rates after complete resection of SCLMs was up to 40% (50,92,92-94).

Potential disadvantages of this method are the insufficient hypertrophy of the remnant liver that will not allow a curative-intent hepatectomy and the long interval needed for this process (the remaining liver hypertrophy will be achieved in 4-8 weeks after PVL), period that can favor new metastastes occurrence (90).

The main limitation of this strategy is the impossibility to use it in patients with SCLMs in the FLR.

b. "Two-stage" liver resection

This approach is recommended in patients with main metastatic burden located in the right hemiliver and few SCLMs in the FLR.

The operation consists in simultaneous resection of the primary tumor and of the SCLMs located in the FLR (sparing as much as possible of the FLR) during the first stage. Frequently, during the first stage, right PVL is recommended to achieve an adequate hypertrophy of the FLR. Similar to the previous approach, the second stage should be performed 4-8 weeks later, if the FLR volume represents more than 30% of the total liver volume (TLV).

Resectability rate achieved by this strategy is almost 75%, but morbidity and mortality rates are higher than those achieved when performing hepatic surgery in patients with initially resectable SCLMs (91,95). The 3-year OS rates exceed 35% in most studies, making this strategy a worthwhile approach to colorectal cancer with bilobar SCLMs (96-100).

Same as hepatic resection after PVL/PVE, the major

drawbacks of this approach are the possible insufficient hypertrophy of FLR and the long interval required for obtaining adequate liver hypertrophy.

c. Associating Liver Partition and Portal vein ligation for Staged hepatectomy - ALPPS

This approach has been employed to overcome the disadvantages of the two previous strategies (101). This operation was performed until now almost exclusive in patients whose primary tumor has already been resected. It consists in initial resection of CLMs from the FLR, associated with PVL and in-situ splitting of the liver (102-106). It was observed that such a strategy was able to achieve a more rapid and robust hypertrophy of the FLR (107). Thus, the volume of the FLR increased to more than 30% of TLV in more than 90% of patients and this hypertrophy was achieved after 7-10 days following the first stage (101,107,108). These results led to an impressive higher resectability rate, exceeding 90% (89).

Unfortunately, the rates of major mortality were almost 40% in most studies, and the postoperative mortality rates ranged between 8 and 12% (109-112). Due to these poor short-term outcomes, the association of the primary tumor resection during the first stage of the ALPPS seems to be hazardous. Moreover, experienced liver surgeons wondered if the basic therapeutic rules should be sacrificed in the name of innovation (113,114).

By these reasons, the place of this strategy in the therapeutic arsenal addressed to patients with initially unresectable bilobar SCLMs is not well-established, yet. However, it seems to be more cautious in such patients to perform a "two-stage" liver resection and only if the hypertrophy of the FLR is not sufficient, will be reccomended to perform in-situ splitting of the liver and subsequent liver resection (115).

d. Liver resection after down-sizing chemotherapy

This approach is used in case of large SCLMs and of whose resection would not allow a sufficient FLR. Recommended treatment regimen includes 3 chemotherapic drugs – 5-fluorouracil (5-FU), Oxaliplatin and Irinotecan – FOLFOXIRI, in combination with monoclonal antibodies (21).

In case of wild type RAS (WT RAS) CLMs there are recommendations to use anti-EFGR monoclonal antibodies (Cetuximab or Panitumumab), while for RAS mutant CLMs are preffered anti-VEGF monoclonal antibodies (Bevacizumab).

These therapeutic regimens should be continued until the CLMs become resectable, for a prolonged use of CHT can lead to the disappearance of CLMs and to a higher rate of surgical complications (73,74,116,117).

Therefore, patients should be evaluated by imagistic studies (CT or RMN) every two months after starting CHT. According to the CLMs response there are multiple possibilities of evolution.

In case of partial response of CLMs that have become resectable after CHT the recommendation is to proceed to the hepatectomy without continuing the preoperative CHT. For partial response of not yet resectable CLMs it is advisable to continue same chemotherapeutic regimen with reassessment for resectability in two months. For stationary disease the CHT regimen can be changed in order to obtain conversion to resectability using second line regimens. However, the CHT regimen will be changed in case of disease progression.

Early tumor shrinkage (ETS) is defined by downsizing with more than 20% of the CLMs diameter at 8 weeks after initiating CHT. Achieving ETS leads to higher rate of treatment response, increased rates of resectability for initially unresectable CLMs, increased overall survival and longer progression-free survival rates in patients with KRAS WT CLMs (regardless the resectability) (118). Most studies showed that ETS is statistically significant more frequent when a combination of CHT with anti-EFGR antibodies is used (118-120).

The rate of conversion to resectability achieved by CHT regimens is about 15-20% (50,121,122). The 5-year OS rates of patients resected following "down-sizing" chemotherapy range between 25% and 33% (significantly higher than those achieved in patients undergoing palliative CHT – 6% at 5-years), justifying the effort needed to conduct this therapeutic strategy (123).

In patients with initially unresectable SCLMs, if the primary tumor is not complicated, the above mentioned oncologic regimens could be started before the resection of the primary tumor. If the SCLMs will become resectable, their resection should be performed as soon as they are rendered resectable, and the primary tumor resection should be delayed for a second stage. Thus, a "liver-first" approach seems to be the most appropriate approach, because usually the resection of such SCLMs implies a major hepatectomy or a difficult liver resection and the association of the primary tumor resection in the same operation could increase the morbidity and mortality rates in patients with such an advanced disease. If the primary tumor was resected before starting CHT, obviously, liver resection is performed after achieving adequate "down-sizing" of SCLMs under CHT.

e. Combined ablation and liver resection (CARe)

This approach is effective for patients with multiple, bilobar CLMs, in which after resection of the main tumoral mass still remain some lesions less than 3 cm adjacent to major vascular structures or in the FLR (124-128). Ablative therapies that can be used are radio-frequency ablation (RFA), microwaves ablation and cryosurgery. Among these, RFA is the most used, most of the studies showing a recurrence rate similar to hepatic resection when used for less than 3 cm CLMs (129). The advantages of combined liver resection and ablation are the avoidance of major hepatic resections, preserving an important non-tumoral hepatic parenchyma (130,131). A pitfall in using this approach concerns the fact that patients with CLMs larger than 3 cm or without complete ablation of CLMs cannot obtain similar long-term outcome. The overall survival of patients benefiting from this method is undoubtely higher than that of palliative treated patients (125).

Also, considering that the results are similar to those achieved by "two-stage" liver resection (regarding morbidity, mortality and survival rates) (132), this strategy has come to be accepted by more and more surgeons.

In patients with SCLMs, this approach could be performed either simultaneous with the primary tumor resection, or in a delayed manner, taking into account the location of the primary and the difficulty of the liver resection.

CONCLUSION

In summary, patients with SCLMs and complicated primary tumor, should be treated by DR. Most patients with uncomplicated colorectal tumors and initially resectable SCLMs are eligible for SR. In such patients, the morbidity, mortality and survival rates achieved by SR are similar to those achieved by SgR. A careful selection of patients in high volume centers experienced in liver and colorectal surgery allows performing simultaneous both the rectal tumor resection and the liver surgery, even in the case of required major hepatectomy. Replacing major liver resections by parenchyma sparing hepatectomies may increase the number of patients with SCLMs suitable for SR. In patients with left-sided colorectal tumors and SCLMs scheduled for SR, the minimal invasive surgery might be beneficial. SR offers a better psychological comfort to the patients, who undergo one operation and experience a shorter hospitalization. SR is a more cost-efficient procedure than SgR. Up to 40% of patients with initially unresectable SCLMs could be rendered to resectability by an aggressive onco-surgical management, improving their long-term outcomes.

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