Govaresh 2003; **9**: 132-41

The Treatment of Liver Metastases from Colorectal Cancer: Questions More than Answers?

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ABSTRACT

About 50% of all patients affected by CRC develop liver metastases. Surgery remains the only potentially curative strategy, but is impossible in the majority of patients. For non-resectable patients, two options are available: local treatment strategies (radiofrequency ablation and cryosurgery: alone or in combination with surgery) and chemotherapy. High rates of objective response achieved with Fluoropyrimidines, Oxaliplatin (OHP) and Irinotecan (CPT-11) based chemotherapy, enable initially non-resectable patients to undergo surgery, with a 5-year survival rate comparable to that observed for primary resectable patients. Therefore, chemotherapy has not only a palliative aim, but becomes a strategy with curative purposes. Adjuvant therapies have been investigated to reduce recurrence rates, some testing hepatic arterial infusion (HAI) schedules but definitive data are not yet available. Our experience, based on results from retrospective studies, suggests a possible role of systemic adjuvant chemotherapy in reducing recurrence rates after surgery. New targeted drugs and new loco-regional therapies are expected to further improve prognosis in neoadjuvant, adjuvant and palliative settings. *Govaresh* 2004; **9**: 132-41

Keywords: Colorectal cancer, Liver metastases, 5-fluorouracil, Oxaliplatin, Irinotecan

List of abbreviations: CRC: Colorectal cancer, chrono: chronomodulation, ci: continuous infusion, 5Fu: 5-fluorouracil, FUDR: fluorodeoxyuridine, FA: folinic acid, HAI: hepatic artery infusion, LV: leucovorin, ns: not significant, nv: not evaluable, OHP: oxaliplatin, CPT-11: irinotecan, OS: overall survival, RR: response rate, PR: partial response, PD: progressive disease, EGFr: Epidermal Growth Factor receptor, VEGFr: Vascular Endothelial Growth Factor receptor

INTRODUCTION

By frequency CRC is the third leading cause of tumours in western countries after lung and breast tumours. The liver is the main target organ for CRC metastases. Around 50% of patients operated for stage III and 20% of those operated for stage II CRC are destined to develop liver metastases. Overall, including patients who are diagnosed in advanced stage, liver metastases develop in 50% of all cases. Around 20-40% of resected patients with liver metastases are still alive at 5 years[(1)]. As a consequence, the

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importance of an optimal treatment of this pathology, for which the collaboration between the oncologist, surgeon and radiologist represents the best therapeutical strategy available, becomes understandable. New drugs and agents, new surgical techniques, new local treatment strategies are available but the agreement on the best choice of treatment is still to be found. In this article we will analyse the main problems and achievements on this topic.

The natural history of liver metastases

Few studies can allow us to determine the natural history of liver metastases in the absence of treatment. The median survival period for untreated patients rarely goes beyond 9 months. Factors that influence the survival rate are: the extent of liver involvement, the presence of extra-hepatic disease, metastatic mesenteric lymph nodes, CEA level, and age[2]. Only a few retrospective studies are available on the outcome of patients with potentially resectable but untreated lesions. The OS in the operated patients is 36 months in comparison with 19 months for non-operated ones. These data support that surgery represents the only potentially curative form of treatment for these kinds of patients, representing the only hope of long-term survival. Liver transplantation has been abandoned because subsequent immunosuppression was related to relapse of cancer in all patients[4].

Criteria for surgery

The resectability of the tumour varies according to many factors:

a. Multiple bilobar, or ill-located metastases involving large hepatic vessels (portal vein, hepatic artery and vena cava/soprahepatic), portal thrombosis, extrahepatic disease
b. ASA classification and coagulability
c. Liver function (Child-Pugh > 5)
d. Co-morbidity

During surgery evaluation, several fundamental points must be considered, covering the technical aspects and the oncological radicality as much as the patient's general conditions. Having checked for the absence of extra-hepatic disease, for the absence of comorbidity and of any other condition that may rule out surgery , we can move on to evaluate the resectability limit: if there are no oncological contraindications (technical aspects), we must keep in mind that a sufficient quantity of normal liver parenchyma must be present after the resection in order to avoid post-surgery liver failure. In the absence of liver disease, up to 75% of the liver parenchyma can be removed without inducing post-operative liver failure. It appears that pre-surgery chemotherapy does not increase the mortality or morbidity rates. Further more, we must rule out the existence of non-resectable extra-hepatic disease (a). The presence of extra-hepatic disease does not automatically rule out surgery, since in selected cases there could be factors pointing to resection of liver and lung metastases, simultaneously or during separate interventions: long term survival is reported in a significant number of patients when complete resection of extrahepatic disease is carried out, especially in case of lung metastases[5,6]. New surgical techniques, like preoperative portal vein embolization or two stage hepatectomy, enable larger resections of liver parenchyma without the risk of postoperative liver failure, and make possible the removal of bilobar multinodular disease in selected cases, with chance of long term survival [7]. It is therefore clear that how each of the aforementioned points are the result of subjective judgment and evaluations regarding both the oncological aspects and the general evaluation of the patient: the judgment on comorbidity is also subjective and the resectability criteria (technical factors) are dependant to the technical capabilities and the experience of the surgical team. Some years ago an International symposium on liver metastases was held in Bologna. Several surgeons from around the world attended this 3-day discussion. At the end of the meeting the final statement was that the indications for surgery are less restrictive, with some surgeons saying there are no limits.

In conclusion, although a series of factors and

universally recognized criteria do exist, the final evaluation is always subjective and depends on the experience and the capabilities of each individual center; therefore, we cannot establish very well defined limits.

The timing of surgery

In a patient with liver metastases that can be resected, multiple, synchronous or metachronous metastases should be differently considered. The most important factor is the resection margin, which must be greater or equal to 1 cm. Other factors are:

1. CEA preparatory levels
2. Size of the lesions/ total mass volume of tumour[8]
3. Number of lesions (< or > than 4)
4. DFS < 12 months
5. Stage of primitive tumour

An individual synchronous lesion of small size should be removed immediately, but in the case of multiple metastases, or lesions located in the deepest parts of the liver, immediate surgery might not constitute the best approach, for several reasons[9, 10].

In the case of resectable synchronous multiple lesions, delay of hepatic resection may be justified by some reasons: the incision required to remove a primitive tumour is different from that which is optimal for the removal of liver metastases, moreover haemodynamic changes that can occur as a result of vascular clamping can lead to complications at the level of digestive sutures[1]. Secondly, delayed surgery can be useful in order to observe the natural behavior of the disease. Thirdly, systemic chemotherapy performed at this stage could give us informations on the chemosensibility of the disease. Wein and coworkers published a study on 20 primary resectable patients who had a neoadjuvant chemotherapy based on a 5-Fluorouracil/Folinic Acid (5-Fu/FA)+OHP schedule[11]. The study showed response rate (RR) of 100%, with a partial response (PR) of 90% and a complete response (CR) of 10% with a potentially curative surgery in 80% of the patients. Disease free survival (DFS) at 2 years was 52% and the survival rate after the same period of time was 80%. Apart from this experience, no other data are available in the current literature.

The inoperable patient

Only10-20% of all patients are judged to be operable right after the diagnosis. In the remaining 80% of cases, the only available tool, at least initially, is chemotherapy, which leads to a median survival period of 20-22 months[12,13]. By itself, chemotherapy increases survival rates and the quality of life, but it is not curative. By introducing OHP and CPT-11 coupled with 5-Fu, systemic chemotherapy has drastically increased its efficacy (Figure 1). The high levels of objective responses, which have been observed as a result of these regimes, have made it possible to use them in a neoadjuvant aim;

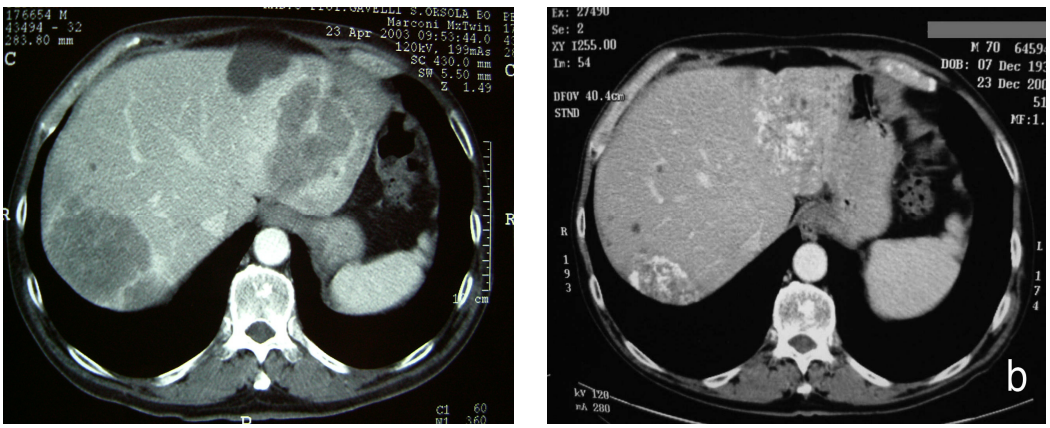

Figure 1. Evolution of liver metastases from colorectal cancer, before and after (b) six months of treatement with 5-Fu/FA and OHP

they can, in fact, reduce the size of liver metastases and render surgery a viable option for lesions that were initially labeled inoperable. Patients who are diagnosed with a life span no longer than 19-22 months become potentially operable and are thus given a chance for long-term survival. Bismuth *et al.* were the first to complete a retrospective study evaluating the impact of a neoadjuvant chemotherapy[14]. The study considered 330 patients who were initially inoperable and therefore treated with an Oxaliplatin-based chronomodulated chemotherapy. Of all patients, 56 (16%) were radically operated with a median survival rate at 5 years of 40%. Later studies showed that the rate of patients who were radically operated after chemotherapy varies between 6.7 and 32.0%. Recently, a phase II prospective study by Wein and coworkers shows that out of 53 patients treated with a weekly 5-Fu/FA-based continous infusion scheme, 11% were R0 resected[15]. Giacchetti and coworkers noted that 38% of 151 cases were operated radically after an OHP/5-Fu/FA based scheme[16]. In this instance as well, the survival rate and the DFS (at 2 years) of these patients were comparable to those of patients who underwent surgery immediately. Using a FOLFIRI scheme, Pozzo and coworkers completed a study on 40 initially inoperable patients, reporting a RR of 47% (=19 patients) with 2 CR and 11 SD. 13 patients (32.5%) underwent radical surgery after chemotherapy. The effects of this treatment on the survival rate still need to be determined[17]. Using a FOLFOXIRI scheme, Falcone and coworkers managed to radically operate 19 patients out of 74 (26%). The median survival period of all patients was of 27 months, compared to 39.6 months for those operated [18].

Equally positive are responses and resectability rates after combinations of systemic chemotherapy and intra-arterial infused chemotherapy.

A phase I study using a combination of HAI Fluorodeoxyuridine (FUDR)+CPT-11 e.v. reported response levels of 74%[19]. Another recent study by Leonard and coworkers, presented at the 2004 ASCO conference, evaluated the efficacy, in terms of RR and resection rate, of a second line combination of FUDR via HAI+CPT-11/OHP e.v. or 5-Fu/FA/OHP e.v. in patients whose first line contained CPT-11 or OHP. Out of a total of 44 patients they found a RR of 82% with a resection rate of 20% (=9 patients) (potentially 36% = 16 patients)[20]. The results highlighted in the study are particularly positive because after the failure of first line of systemic chemotherapy with CPT-11 or OHP, the RR of a second line of systemic therapy is rather scarce (whether CPT-11 or OHP is used), with variations ranging from 4% to 22% according to different studies [12,21-29] (see Table 1), and rescue surgery becomes impossible to be performed.

Tabel 1: Efficacy of a second line chemotherapy containig OHP or CPT-11 after failure of first line CPT-11 or OHP based regimens.

Author	N. of patients	Regimen	RR	PFS median	Median Survival
OHP (post CPT-11 failure)					
Janinis[21]	32	Oxali/5Fu/FA	13%	3	9
Kouroussis[22]	41	FOLFOX-2	17%	8.5	12
Ryan[23]	70	FOLFOX	11%	6.2	8.7
Rothenberg[24]	152	FOLFOX-4	9.9%	4.6	9.8
Tournigand[12]	81	FOLFOX-6	15%	4.2%	-
CPT-11 (post OHP failure)					
Andre[25]	33	FOLFIRI	6%	4.5	10.7
Ulrich-Pur[26]	38	CPT-11	21%	4.8	>9.5
Stickel[27]	26	CPT-11/5Fu/ AF	27%	5.8	10
Tai[28]	18	FOLFIRI	22.2%	-	7.5
Mabro[29]	29	FOLFIRI-2	17%	4.1	9.7
Tournigand[12]	69	FOLFIRI	4%	2.5	-

Despite the progresses of the chemotherapy only 11%-38% of patients with initially judged non-resectable lesions are suitable for surgery after a neoadjuvant first line therapy. If at this point surgery remains impossible the main goal is the delaying of the symptomatic phase of the disease and the prolonging of survival. Such kind of patients who are non-resectable (for comorbidities, intrahepatic or extrahepatic spread of the disease) are only candidate for chemotherapy or other locoregional therapies, like radiofrequency ablation (RF) or cryosurgery (CS). There is no place for debulking surgery, since survival of patients not radically resected is the same of the non-resected ones[30]. RF and CS can be also complementary to surgical treatment, when surgery alone cannot reach surgical radicality. Now RF is used more than CS for practical reasons: although both methodologies are equally effective in therms of local recurrence rates, RF can be performed by a percutaneous access because of the smaller dimensions of the electrodes compared with the probes used for CS, which is mainly performed by laparotomic access.

Few studies directly compare the efficacy of CS and RF, and are difficult to interpret. It seems that local recurrence rates are low (for both techniques) for lesions less than 3 cm in diameter, but for lesions larger than 3 cm local recurrence rates start to increase significantly for RF to over 33%. For CS the increase in local recurrence start to increase from a diameter of 5-6 cm. It is important to observe that, while RF is equally effective if performed by percutaneous or laparotomic access, for CS promising results are only described for the open approach. When both techniques are performed by a percutaneous access for lesions < 5 cm, local recurrence rates are 53% for CS versus 18% for RF. Data on DFS and overall survival after RF ablation are equally conflicting and difficult to interpret: many differences exist between the studies, in regard to the size of lesions and the way RF is applied (percutaneous, laparoscopic or laparotomic); moreover, in different studies RF is performed alone, in combination with surgery, or completed by a chemotherapy (via HAI or systemic) [31-33]. The main still unanswered question regards the radicality of these techniques, because randomized studies directly comparing surgery with RF or CS are lacking, and the impact on overall survival is not clearly defined. 2-year survival after RF varies from 50% to 75%, but once again with the limit that the studies are retrospective and difficult to compare. 1-year DFS varies from 25% to 50%[31-35]. It is important to distinguish true local relapses (which are low) from new liver metastases related to progression and multifocality of the disease in liver parenchyma. It could be suitable a systemic chemotheraphy to complete RF treatment and reduce recurrence rate related to the spread of the disease. Recently, two studies has directly compared surgery with RF: the first one is a retrospective study of 418 patients: 358 patients had surgery, RF alone or surgery plus RF (in these patients it was impossible to perform A R0 resection)[36]. Seventy patients were treated with systemic chemotherapy +/- HAI after explorative surgery. 4-year survival was 65% for surgery alone, 36% for surgery plus RF, 22% for RF alone. Overall recurrence rate was 52% for surgery alone, 64% for surgery combined with RF, 84% for RF alone. Liver recurrence rate was 11% for surgery vs 44% for RF alone. True local relapse rate was 2% with surgery alone, 5% with surgery plus RF, 9% with RF. Surgery was related with the best outcome and RF had higher recurrence rate and worse 4-year survival. The data suggests that surgery is the better. A further result of this study is that RF provides survival only slightly superior to nonsurgical treatment.

However, in this study the comparison was made between operable and not completely operable patients, and patients candidate for RF treatment, for whom surgery was not feasible, were those at worse prognosis, whereas those treated with surgery were at better prognosis. So a well designed study should compare directly surgery and RF in primary resectable patients with

liver metastases. A non randomized study from Oshowo and coworkers, considered 45 consecutive patients with single liver metastases: 20 patients received surgery and 25 were treated with RF [37]. For the 25 patients treated with RF the resection was not feasible for technical reasons (ill-located lesions) (9 patients), co-morbidities (9 patients), extra hepatic lesions (7 patients). Median OS after surgery was 41 months, (55.4% alive at 3 years), vs 37 months (52.5% alive at 3 years after RF). This study is too small to draw any conclusion. A prospective randomized trial comparing surgery and RFA in operable patients is lacking, but we believe that it will be difficult to carry out a study like this.

After surgery

Surgery remains the standard of care, but with two fundamental limits. First, only a minority of all patients with liver metastases can be resected: in this case the resection rate can be sensibly increased by a neoadjuvant chemotherapy.

The second limit is the high recurrence rate. Recurrence rate after surgery in most studies is about 75%, and in half cases the liver is affected. Sixty six percent of all relapses is observed within the first 12 months after surgery. Now, the question is how to improve results of surgical treatment, and How to reduce recurrence rate.

Some years ago, Lorenz and coworkers published these results: they compared surgery alone with surgery plus HAI (with a 5-Fu/FA-based schedule) and didn't found any survival advantage for the treated arm, reporting also a considerable toxicity[38]. One year later a study from Memorial Sloan Kettering Cancer Center compared HAI FUDR+ systemic 5-Fu/FA with systemic 5-Fu/FA alone, showing a decrease in hepatic recurrence rate and an improved overall survival only at 2 years for the combined treatment[39]. The control arm of this study seems to be inadequate, because a direct comparison with the observation alone is laking and new standard regimens containing 5-Fu in combination with OHP and CPT-11 are more effective than 5-Fu/FA alone in advanced phase of the disease and also in adjuvant setting after resection of the primary tumour[40]. Two years ago Margaret Kemeny and coworkers published data from a study carried out on 75 patients, comparing the outcome of patients treated with HAI + systemic 5-Fu ic with the observation alone: they showed a reduced risk of recurrence but once again no advantage on survival for the treated arm[41]. No recent data concerning these studies are available. From these studies we can deduce that HAI alone does not provide any survival advantage compared with observation. HAI associated with systemic chemotherapy (5-Fu/ FA schedules) showed only a decrease in recurrence rate and consistent toxicity, with no advantage on survival. Future trials will evaluate efficacy of combinations of HAI with systemic 5-Fu, OHP and/or CPT-11 who are very promising and effective as first line treatment. Main limitations of HAI are: first, the risk of extrahepatic progression, is increased because only the liver receives a sufficient concentration of drug; that's why recent trials combine HAI with a systemic treatment. The second main limit is the risk of severe side effects: first of all hepatic toxicity: hepatitis and biliary sclerosis. These side effects were observed exclusively with FUDR and were dependent to the dose and duration of administration. The co-administration of dexamethasone can reduce the incidence of severe biliary sclerosis.

Until now only few retrospective studies investigated the role of an adjuvant systemic chemotherapy alone after resection of liver metastases, some of them showing an interesting trend of survival advantage and decreased recurrence rate for patients receiving chemotherapy[42]. An adjuvant milticenter trial is actually in progress in Europe but difficulties in the recruitment is a big obstacle for this study.

Our experience concerns a retrospective study on 84 consecutive patients with liver metastases at first recurrence: after R0 resection, 27 received an adjuvant 5-Fu/FA +/- OHP or CPT-11 based chemotherapy, 57 did not. Characteristics of patients and number or size of lesions did not

differ between the two groups. All patients were at first metastatic recurrence and underwent a R0 resection. The DFS at 40 months is higher in treated than in untreated patients, with a median value of 13.3 vs 9.3 months, but with no significant difference (p=0.081), probably because of the small number of patients included (see Figure 2) [43].

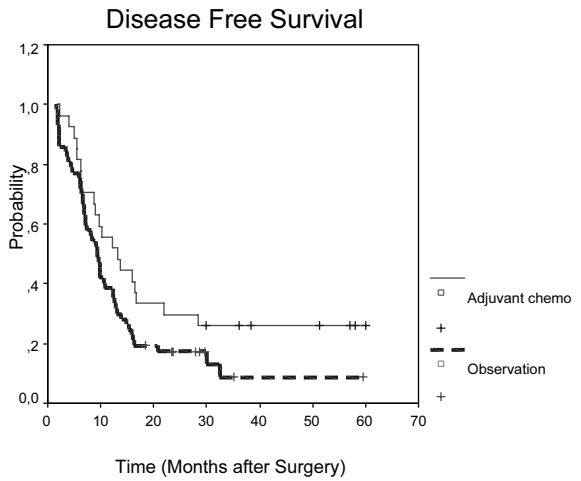

Figure 2: Disease free survival of 84 patients with liver metastases at first recurrence who were R0 resected in our centre. 27 patients had an adjuvant postoperative chemotherapy, 57 did not, with a median DFS of 13.3 months vs 9.3 months respectively

These results and those of other retrospective studies suggest that systemic adjuvant chemotherapy after resection of metastases of colorectal cancer could have a role in improving prognosis of these patients, and could be suitable for patients at high risk of recurrence. But large prospective trials are needed to clarify this controversial point. Finally, we know that up to 70% of all patients undergoing resection will develop recurrence, one third of which confined to the liver[44]. In such patients it seems to be a good strategy to perform a second and even a third hepatectomy whenever possible, since most series report comparable survival benefit for second and third hepatectomy to that of first hepatectomy, with the same morbidity and mortality rates [45, 46].

CONCLUSIONS

In conclusion, several doubts are still persisting about the better choice in the treatment of liver metastases from colorectal cancer. Surgery is the first option. When surgery is not possible, local or systemic chemotherapy are the therapeutic alternatives. HAI requires experience and awareness of the associated side effects. This is a very expensive procedure without substantial gain of survival in comparison with intravenous therapies. On the contrary, systemic treatment with new regimens containing 5Fu/FA and OHP or CPT-11 demonstrated efficacy in both survival and local control of the metastasis. The systemic treatments are actually proposed in the neo-adjuvant setting for non-operable patients.

This is what we know until now. But the paramount is rapidly changing. New drugs are proposed for local intravenuos or HAI treatments, new local strategies such as surgical approaches or radiofrequency ablation alone or together are tested in phase II trials, new agents are demonstrating efficacy in the treatment of advanced disease. In particular, about these new biological therapies a debate in the scientific community is open. The antibody anti-EGFr and the antibody anti-VEGFr are approved for the clinical use after the results of phase II and III trials; however, they are very expensive and, most importantly, definitive criteria of patients selection for therapy have not yet been established. The new options are a lot. Probably there are more therapeutic choices than patients to be treated in clinical trials.

To avoid confusion in the clinical practice we should follow established criteria, keeping in mind that the availability and the experience of the local surgical team is mainly important (Figure 3).

Three years ago we published a review paper. The question was “Treatment of liver metastases from colorectal cancer: what is the best approach today?”[47]. In these years some progresses have been made but the question has not yet a definitive answer.

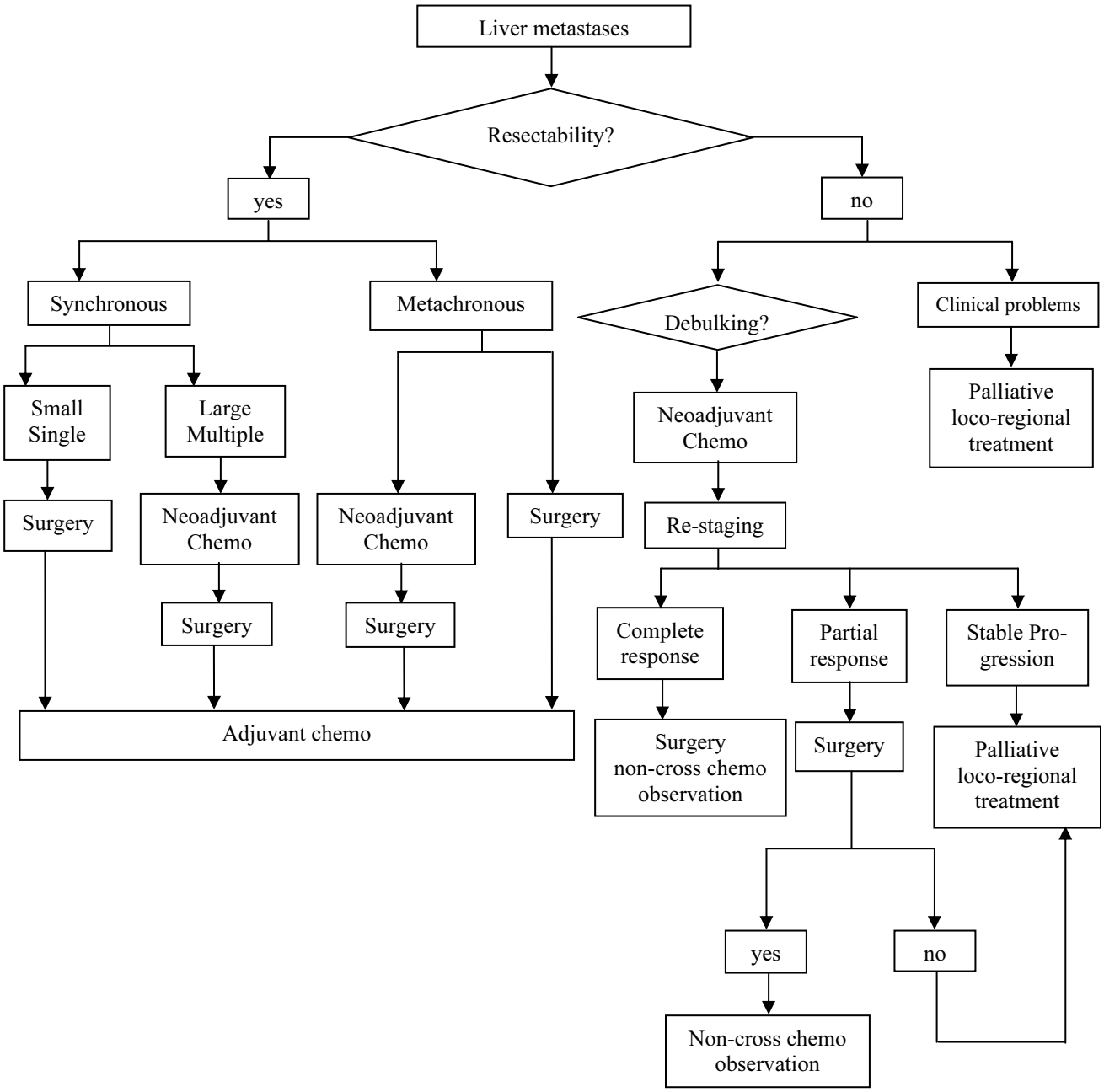

Figure 3: A decisional flow-chart for the treatment of liver metastases from colorectal cancer

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