

STRATEGIES TO INCREASE RESECTED LIVER METASTASES IN PATIENTS WITH COLORECTAL TUMORS

Estratégias para aumentar a ressecabilidade em pacientes com metástases hepáticas de tumores colorretais

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HEADINGS - Partial hepatectomy. Hepatic metastases. Colorectal cancer. Radiofrequency. Embolization.

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DESCRITORES - Hepatectomias parciais. Metástases. Neoplasia colorretal. Radiofrequência. Embolização.

ABSTRACT – Introduction: Nowadays, liver resections can be performed with acceptable morbi-mortality rates. In specialized centers, mortality as low as 1% can be achieved, even with the advent of new hepatotoxic chemotherapy regimens. In order to reduce morbidity and mortality, newer strategies can be undertaken, such as portal vein embolization, radiofrequency ablation techniques, re-hepatectomies, major vascular resections and two stages hepatectomies. **Method** - Literature review was conducted on sites search PubMed, BIREME, SciELO, with the headings "partial hepatectomy, hepatic metastases, colorectal cancer, radiofrequency and embolization". Were selected mainly studies with the application of techniques and surgical procedures in the treatment of liver metastasis. **Conclusion** - Survival rates as good as 50% in 5y can be achieved in selected cases when a multidisciplinary team is involved. Better surgical techniques, with parenchymal sparing strategies and the advent of neoadjuvant chemotherapy can turn unresectable liver lesions to resectable and increase survival rates.

RESUMO – Introdução - Atualmente, as ressecções hepáticas podem ser realizadas com taxas aceitáveis de morbimortalidade. Em centros especializados, mortalidade ao redor de 1% pode ser alcançada, mesmo em fígados previamente submetidos à quimioterapia por longo prazo. Com o objetivo de reduzir essas taxas, novas estratégias têm sido empregadas, como a embolização portal, ablação por radiofrequência, re-hepatectomias ressecções vasculares com reconstrução e hepatectomias em dois tempos. **Método** - Foi realizada revisão de literatura nos sites de pesquisa PubMed, Bireme e Scielo, com os descritores "hepatectomias parciais, metástases, neoplasia colorretal, radiofrequência e embolização". Selecionaram-se, principalmente, os estudos de aplicação de técnicas e procedimentos cirúrgicos no tratamento das metástases hepáticas. **Conclusão** - Sobrevida ao redor de 50% em cinco anos podem ser conseguidas em casos selecionados quando equipe multidisciplinar está envolvida no tratamento. Com a melhora na técnica operatória, poupando-se parênquima hepático, e com o advento de novos agentes quimioterápicos, lesões metastáticas hepáticas irressecáveis podem se tornar ressecáveis e a sobrevida a longo prazo pode ser alcançada.

INTRODUCTION

A few years ago, only 15 to 20% of patients with liver metastases of colorectal cancer were considered candidates for surgical treatment with curative intent. With the strategies discussed here involving the performance of a multidisciplinary team including a surgeon, oncologist, radiologist and interventional radiologist, currently the resection of hepatic metastases from colorectal tumors can be accomplished in 30% to 40% of patients.

Is considered resectable the liver metastases that are capable of being removed with free margin and when around 25% to 30% of functional liver mass is preserved.

In 2006, the Consensus of Resectability IHBPA defined as: 1) ability to preserve two contiguous liver segments with adequate preservation of the influx, efflux and biliary drainage of the remnant liver parenchyma and

2) remnant liver greater than 20% without disease (liver disease) . It is recommended safety margins greater than 1 cm but these are not mandatory and the presence of resectable extrahepatic disease is not a contraindication to liver resection^{1,9,11}.

In everyday practice, we can divide the patients suffering from the disease in easily resectable, marginally resectable and unresectable. Obviously special attention must be focused on the last two groups, since the technical feasibility of hepatectomy becomes defiant and preoperative clinical approach demand integration among different professionals (radiologists, surgeons and oncologists). The main causes of non-resectability are the presence of multiple nodules in both hepatic lobes, involvement of the hepatic pedicle and the hepatic veins and the presence of extrahepatic disease.

In the present article will be reviewed the main strategies used in marginally resectable patients that aim to make them resectable. Among these different tactics, exist the portal embolization, radiofrequency, liver resection in two stages, the re-hepatectomy and extreme liver resections.

There is no doubt that chemotherapy is part of strategies to increase resectability, decreasing the size of the nodules and also helping to increase survival in patients undergoing resection of metastases. Neoadjuvant chemotherapy has been used routinely in patients with liver metastases of colorectal tumors with the aim of eradicating not visible disease, to test the biological sensitivity of the tumor and chemotherapy to become resectable in patients considered unresectable¹⁵.

Selective portal embolization

Aims to lead to hypertrophy of the remnant liver to prevent postoperative liver failure. This is more common in patients who were previously treated with chemotherapy which can cause hepatotoxicity (liver where the regenerative capacity is impaired) and require resection involving more than 60% to 70% of the hepatic parenchyma. The hepatocellular damage caused by chemotherapy depends on the agent used. It is known that irinotecan leads to steatohepatitis and this condition increases the mortality of liver resections, whereas oxaliplatin leads to sinusoidal dilatation, increasing the risk of intraoperative bleeding, but with no impact on mortality^{20,23}.

Typically, in healthy livers, resection of 70% to 80% of the liver do not progress to liver failure. However, in the presence of prior liver injury (chemotherapy, steatosis or cirrhosis) resection of more than 60% of the liver can lead to a condition of postoperative liver failure. Therefore, when treating liver undergoing chemotherapy, for more than 3 to 4 months, remaining liver (measured by liver volumetry using computed tomography) less than

40% it is recommended portal embolization. This should also be recommended in patients with metabolic diseases (obesity) where hepatic steatosis is frequent.

Hepatic measuring does not mean measurement of liver function; however the studies take into account in the West are focused more in mass size than functional aspects. In the East, the function measurement can be accomplished by determining the clearance of indocyanine green (drug completely metabolized in the liver). In the West, studies take into account the existence of tissue damage (revealed by biopsy, imaging, or by changes in the use of hepatotoxic drugs). Liver volume is measured by the total surface of corporal area - ASC (total liver volume = $-794.41 + 1268.28 \times \text{BSA}$). The remnant liver volume - VFR - can be measured using the formula = $\text{VFR measured} / \text{VFR}$. VFR is greater than 30% in patients undergoing multiple cycles of chemotherapy with the aim of reducing the incidence of postoperative liver failure¹⁴.

Although some authors argue that the ligation of the portal vein (branch of the side to be resected, usually the right) is as effective as embolization done by interventional radiology (through the use of springs, microparticles, cyanoacrylate), most of the services of liver surgery prefer transparietal puncture embolization^{6,24}.

After four to six weeks of embolization or ligation of the portal vein occurs hemi-compensatory hypertrophy of the remnant liver and resection can be done successfully (the largest increase in liver volume occurs at the end of the third week, where it can be seen 75% growth). During this period, chemotherapy can be performed without damage to regeneration and ablation techniques[9]. Patients who experience tumor growth or appearance of new lesions or poor hepatic hyperplasia are usually not considered candidates to resection⁷ (Figure 1).

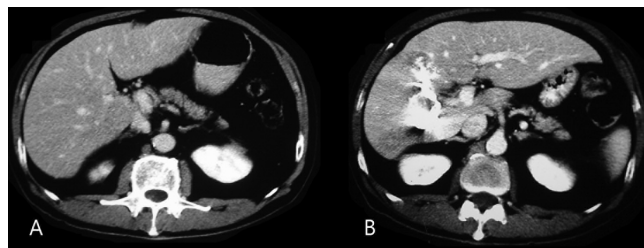


FIGURE 1 - Aspect of the liver CT before right portal embolization (A) and six weeks after portal embolization (B), where it can be observed growth of the left hemi-liver (segments II, III and IV)

Methods of tumor ablation

Among these, there is the radiofrequency (RF) as the most widely used method¹⁶. Although not considered curative method its use in colorectal

metastases has been increasing referred for both situations: disease control and helping the curative treatment (resection). Lesions up to 3 cm can be treated by RF, both percutaneously or surgically (laparoscopy or laparotomy). Usually patients are treated with RF when damage does not spread outside the liver or when there it is possibility to control (or can control) the extrahepatic disease^{2,17}. Most centers consider the patient treatable with up to four liver lesions. Lesions located on the periphery of the liver may eventually be treated by RF, although the chance of complications such as rupture, biliary fistula and bleeding are higher. However, if these lesions are in contact with abdominal hollow viscera, the risk of perforation contraindicate the procedure. The treatment of tumors adjacent to the gallbladder and the hepatic hilum may lead to thermal injury and risk of biliary fistula or biliary stricture.

The best indications are absence of clinical conditions for liver resection and in those with bilateral disease where there is need to perform a partial hepatectomy in one lobe and ablation of nodules in the remnant liver. Lesions in contact with or very near vascular vessels can be treated with some degree of effectiveness when employing certain maneuvers, such as hilar vascular occlusion, reducing the inflow of blood and thus reducing heat loss²⁵(Figure 2).

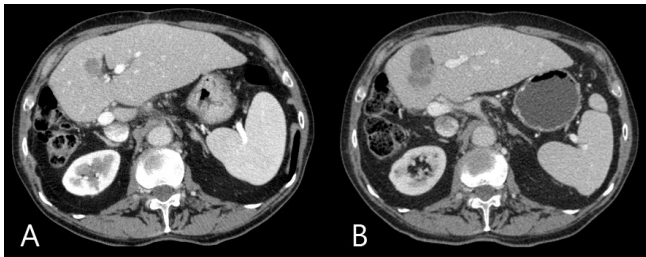


FIGURE 2 - Recurrence after right hepatectomy (A) prior to radiofrequency and after conducting it, with recurrence of the injury, six months after (B). This lesion was subsequently resected (re-hepatectomy)

Two-stage hepatectomy

It should be considered in the presence of bilateral liver disease, where resection of more than 70% of the liver should be performed in two-stage hepatectomy. In this situation, resection of the nodules on one side of the liver should be done in the first place followed or not by portal ligation/embolization (in the same surgery or postoperatively). In a second stage, resection of the previously embolized hemi-liver can be done safely. The purpose of this second strategy is to make safe and potentially curative operation, leaving sufficient functional parenchyma avoiding liver failure^{3,22}. In the interval between two operations

(or soon after portal embolization) chemotherapy can be administered two to three weeks after the procedure, aiming to prevent tumor growth. When there is disease progression during this period, these individuals are not usually considered candidates for the second procedure, and this number could reach 20%. Survival at three years can reach 54% of the costs of morbidity in 30% after the first procedure and 45% after the second^{13,22}.

Re-hepatectomy

After liver resection with curative intent, approximately 60% to 70% of patients will experience disease recurrence, and of this amount, one third will relapse only in liver. Of this group, about 10% to 30% will present new conditions for liver resection, being candidates for re-hepatectomy. Despite the technical difficulties of the procedure, some studies have shown complications and survival rates similar to first resection^{5,21}. In bi-institutional study, median survival of 37 months was achieved. Patients with interval between resections greater than one year have a more favorable prognosis¹⁸. There are few series in which one or more third hepatectomies were necessary, however good results can be achieved selected cases⁴.

Extreme hepatic resections

When there are metastatic lesions involving the confluence of the hepatic veins or invading the superior vena cava, resections are generally not feasible due to risk of intraoperative bleeding and gas embolism. However in some cases, total vascular exclusion can be performed with or without resection and reconstruction of the inferior vena cava with possible prosthesis to replace it. Usually, these situations need to clamping of the inflow (portal and arterial) associated with the control of the vena cava, infra and supra hepatic. When these maneuvers, usually occurs hemodynamic instability and, eventually, the use of venovenous bypass may be necessary. Modifications of this technique can be used as the preservation of caval flow by clamping of the hepatic veins¹⁰. In this condition, there is less hemodynamic changes and resections can be performed more safely.

The normothermic liver ischemia with clamping of the hepatic pedicle and the inferior vena cava above and below the liver can be tolerated for up to 60 minutes making safer resection of these tumors¹². Some authors advocate the use of cold ischemia (hypothermic) with the same clamping associated with liver perfusion with cold preservation solution (used in transplants) in order to reduce the harm to the liver parenchyma during resection complex, which would lead to lower morbidity post surgery and a lower incidence of renal failure. In these extreme situations the rate of operative

mortality in expert hands is 5% to 10%, morbidity 64% and five-year survival of 38%⁸. It should be noted that only is multidisciplinary follow-up and periodic re-evaluations together with the team can lead to better treatment of this group of patients.

CONCLUSIONS

The various strategies used in patients with liver metastases, initially unresectable seem to aim at curative resection, leaving 30% to 40% of functional liver parenchyma. Treatment should be individualized and the involvement of professionals from various areas of medicine should be encouraged. The initial chemotherapy (neoadjuvant) is essential in treating these patients, and after initial chemotherapy and lesions response (decreased or remained stable), some strategies can be employed, namely: 1) whether the unilateral resection of the lesions will leave liver remnant of less than 30%, hold portal embolization; 2) if three to five lesions up to 3 cm in diameter will remain after hepatic resection containing the greatest amount of metastatic liver disease, it can be associated to it ablative techniques (radiofrequency) or enucleation; 3) if more than five lesions or single lesion greater than 3 cm will be left in the remnant liver, perform hepatectomy in two stages usually associated with selective embolization or ligation of the portal vein.

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