Liver transplantation in colorectal metastases. Is there an indication for this procedure?

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Colorectal cancer (CRC) is the third most frequent form of cancer and the second most frequent cause of death from cancer (1, 2). It is estimated that there are 1.9 million new cases and 935 000 deaths from the disease each year (1, 2). Approximately 25% of patients with CRC present liver metastases (CRLMs) at the time of diagnosis (11.8%-14.1% in colon cancer and 9.5%-12.5% in cancer of the rectum) and 50% of patients will go on to develop metastases in the course of their illness (2).

Surgical resection in combination with preoperative neoadjuvant or adjuvant chemotherapy is the only curative treatment provided that resection is performed
with strict oncologic criteria (3, 4). Unfortunately, only 20-30% of patients present resectable (M1a) or potentially resectable (M1b) metastases (2, 3).

Generally speaking, overall survival (OS) rates of resected patients at 5 and 10 years are 44% and 25%, respectively while in patients with unresectable metastases treated with systemic chemotherapy the survival rate is 5-10% (2, 5).

Sixty to seventy percent of patients experience recurrence of the tumor in the liver remnant and given that very few of these tumors can be resected again, most patients die from tumor progression and liver failure (6). Given this component of “local failure”, in the 90s some authors performed liver transplantation on unresectable CRLMs but with very poor results with survival rates of between 0-18% at 5 years post-transplantation (7). With such a background, it was considered that transplantation was contraindicated for CRLMs. However, a pilot study (Secondary cancer, SECA-I; Clinical Trial.gov: NCT 01311453) initiated in 2006 in Oslo, with 23 patients with a mean number of metastases of 8 (range: 4-40), Hagness et al (8–10) reported overall survival rates of 95%, 68%, 43.5% and 26.1% at 1, 3, 5 and 10 years post-transplant which led to a renewal of interest in transplantation for CRLMs(11).

The authors reported a prognostic score (an “Oslo score”) of 1-4 points based on the size of the largest lesion (>5.5 cm.), plasma levels of carcinoembryonic antigen (CEA) (>80 µg/L), the delay between resection of the primary tumor and transplantation (<2 years) and assessment of response to chemotherapy, giving 1 point for each variable (8). In spite of its simplicity, the score expresses two dynamic clinical variables directly related to tumor biology such as the time interval between resection of the primary tumor and the indication for transplantation (lead-time bias) and response to systemic chemotherapy (11, 12).

When the authors analyzed the impact of the “Oslo score” on survival, they observed that in patients with a score of 0-2, 5- and 10-year overall survival rates were 64.3% and 42.9% while in those patients presenting two risk factors the 5- and 10-year
overall survival rates were 50% and 33%. These selection criteria have been confirmed by other authors. For example, Toso et al (13) in the Compagnons Hépato-Biliaires series, a retrospective study of 12 patients, reported OS and recurrence free survival (RFS) of 50% and 38% five years post-transplant.

These results were corroborated in a second trial by the same group (SECA-II, Clinical Trials.gov NCT01479608; Norway) in 15 patients with stricter inclusion criteria where an “Oslo score” of 0-1 yielded 5- and 10-year overall survival rates of 83% and 50% and a 5-year RFS of 35% (10, 14). Curiously, in both studies the most frequent distant failure were metastases in the lungs, slow growing tumors which in some cases were liable to pulmonary resection. These selection criteria have been confirmed by other authors such as Toso et al (13), who in a retrospective study of 12 patients reported OS and RFS rates of 50% and 38% at 5 years post-transplant.

In a recent analysis comparing transplantation (n=56) with liver resection (n=128) in patients with a high tumoral load, five-year OS was 69% and 14%, respectively (15).

Given the scarcity of organs, Hernández-Alejandro and Rajendran (16, 17) have published the results of a study using live donors in 10 patients - 9 with synchronous metastases and 1 with a metachronous tumor-, conducted in three institutions (Clinical Trial.gov NCT 02864485, Toronto protocol, Canada and NCT 05248581, USA). The median interval between diagnosis and transplantation was 1.7 years (range, 1.1-7.8 years). The patients had a favorable biologic profile with an Oslo score of 1.5 and all had received neoadjuvant chemotherapy. The OS and RFS rates at 1.5 years were 100% and 62%.

**Future perspectives and conclusions**

Although the experience outlined above is based on small and heterogeneous series, there is no doubt that the results obtained with liver transplantation for CRLMs warrant its inclusion among the possible indications for liver transplantation as it offers an overall 5-year survival rate (60%) comparable to that obtained by transplantation in
hepatocarcinoma with the criteria of Milan, the University of California, San Francisco or Tokyo (OS: 60-70% at 5 years), in metastases of neuroendocrine tumors and offers a survival rate above the minimum required (50% at 5 years) in terminal liver diseases (11, 18–21).

Such an indication requires a very carefully thought out clinical, pathologic and surgical assessment as ethical and technical aspects converge, for example, the availability of organs from cadavers, the accredited experience of the center in complex liver surgery, in liver transplantation and the need to work in close cooperation in multidisciplinary units in the treatment of advanced colorectal cancer (2, 3, 11, 18). For this reason, the International Hepato-Pancreato-Biliary Association has published some recommendations for the indication of transplantation in CRLMs (18). A schematic algorithm of principles for patient selection is shown in figure 1.

From the oncologic point of view, it is crucial that patients be selected according to the prognostic and predictive factors such as the location (right-sided vs left-sided) and histology (poorly differentiated, signet ring cell-mucinous-adenocarcinoma) of the primary tumor, the genomic profile of the tumor: the presence of microsatellite instability (MSI), mismatch repair (MMR), mutations in the RAS gene (KRAS, NRAS, HRAS), BRAF-V600E and HER2 mutations which allow ineffective treatments to be avoided and in turn the use of targeted treatments such as HER2 antagonists of tyrosine kinase receptor (e.g. trastuzumab, pertuzumab) (22) or the use of immunotherapy in tumors with high microsatellite instability (23).

The most widely used systemic neoadjuvant therapy used is based on 5-fluouracil (5-FU) /folinic and oxaliplatin (mFOLFOX) or 5-FU/ folinic acid plus oxaliplatin and irinotecan (FOLFOXIRI), with or without bevacizumab o cetuximab (anti-epidermal growth factor receptor inhibitors) depending on sidedness and molecular profile (5). As has been mentioned, a very important prognostic factor is the degree of response to the neoadjuvant treatment, via radiologic or nuclear medicine assessment and/or via the determination of markers derived from tumor cells: circulating tumor cells, cell-
free DNA and mRNA (2, 3, 11, 14).

From the surgical point of view, it will be necessary to optimize the availability of organs for transplantation for example by using normothermic perfusion in suboptimal donors, organs from donors in “circulatory death”, the “Split transplant” technique, living donor transplant or the development of innovative techniques such as the auxiliary transplant of a partial graft (segments 2 and 3) and subsequent hepatectomy, once the partial graft has regenerated, known as the RAPID technique. (18, 24, 25).

In this case some doubt still remains concerning the possible pro-proliferative effect on the metastases that the regenerative stimulus of the liver may have, although this may be temporary, in addition to the immunosuppression (18, 24, 25).

Another controversial aspect is the effect of the immunosuppressants on possible tumor recurrence long-term as the appearance of “de novo tumors” in patients who have received transplants is well known. The initial combination of calcineurin inhibitors with mTOR inhibitors (mammalian target of rapamycin) is recommended, with a gradual reduction of the calcineurin inhibitors (11, 18).

**Conclusion**

Although a few years ago liver transplantation was contraindicated in patients with unresectable metastases from colorectal cancer, currently transplantation may be a valid option in highly selected patients in centers with experience in liver surgery and the multidisciplinary management of advanced colorectal cancer. The development and refining of prognostic scores will allow patients to be better selected for liver transplantation. In line with this, several clinical trials looking into the different aspects of transplantation for CRLMs are currently ongoing (Clinical Trial.gov NCT Toronto Protocol, 02864485, LIVERT (W) O HEAL, Germany 03488953, TRANSMET, France 02507348, Norway 02215889, and Spain 05398380).
Abbreviations: CRLMs Colorectal liver metastases, OS Overall survival, RFS Recurrence free survival
References


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PATIENT SELECTION

- Diagnosis of CRLMs
- Extrahepatic disease
- NR CRLMs

**Fulfils histology Molecular profile**
- **YES**
  - Appropriate transplant candidate
  - **NO**
    - Palliative Therapy

**Synchronous disease**
- Asymptomatic
  - Systemic chemotherapy
    - 4-6 months
      - No response
        - Palliative Therapy
      - Good response

**Symptomatic**
- Tumor pathology
  - Grade response
    - Molecular profile
      - Therapy to transplantation
        - No response
          - Palliative Therapy
        - 6 months minimum
          - Stable disease (Oslo score 0-2)
          - **TRANSPLANT**

**Metachronous disease**
- Palliative Therapy

**At least 1 year**

CRLMs: colorectal liver metastases. NR CRLMs: non-resectable colorectal liver metastases. * No BRAF V600E mutation, microsatellite stable and mismatch. Adapted from Bonney G et al (Reference 18)