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S. Pathak, G. Sarno, G.J. Poston

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Authors: S. Pathak, G. Sarno, G.J. Poston

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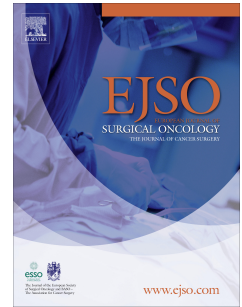
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# **Synchronous resection for colorectal liver metastases:**

## **The future**

**Pathak S, Sarno G, Poston GJ**

### **Background:**

As many as 25% of colorectal cancer patients will have liver metastasis (CRLM) at presentation and a further 20-30% will develop metachronous disease following colorectal surgery<sup>(1)</sup>. Hepatectomy is feasible in 20% of cases and five year survival rates of up to 37-58% have been reported<sup>(2)</sup>.

When hepatic metastases are diagnosed concurrently with the primary colorectal tumour, the timing of surgical intervention remains controversial. Traditionally most centres have adopted a staged treatment with the colorectal primary being dealt with first, followed by hepatic resection. However recently there has been increasing enthusiasm for synchronous surgical management, or in some cases, a liver first approach. The surgical management of patients with synchronous colorectal metastases has not been clearly defined.

The aim of this article is to examine the arguments for these management strategies in patients who present with Stage 4 colorectal cancer.

## **Arguments against synchronous resection**

Traditionally patients who have simultaneous detection of hepatic metastases and primary colorectal disease were regarded as a less favourable group in terms of tumour biology, as metastasis had occurred even before diagnosis<sup>(3, 4, 5)</sup>. Most surgeons have advocated resection of the primary disease first, followed by hepatic resection if the disease has remained operable in the interval time period.<sup>(6)</sup>

R0 resection may appear technically feasible at the time of surgery for the primary, however, partial hepatectomy will not provide additional benefit if occult distant disease is present. Therefore theoretically, delaying the resection of synchronous metastases for approximately 3-6 months may allow occult disease to become clinically overt<sup>(7, 8)</sup>. Using this approach, patients who become unresectable in the interval time period (due to aggressive tumour behaviour) can be spared the morbidity of additional major intra-abdominal surgery and instead undergo focussed palliative chemotherapy to prolong their survival, and increase their overall quality of life. Therefore the interval time period allows for assessment of tumour behaviour as well as selecting those patients most likely to benefit from partial hepatectomy.

Additionally, neoadjuvant chemotherapy administered in this time interval may decrease the likelihood of micrometastases and hence improve overall length of survival.

A concern regarding this approach is that additional metastases may be found at hepatectomy<sup>(8)</sup>. Additionally it is hypothesized that the doubling time of metastases from colorectal cancer is approximately 14 weeks and that at least 30 doubling cycles

are required for a tumour cell to become clinically apparent. Hence, it is more likely that additional disease found at re-evaluation is actually occult disease that was present at diagnosis/ primary surgery<sup>(8,9)</sup>. However, the increasing use of CT-PET, combined with very high quality CT and liver contrast enhanced MRI scanning will significantly reduce the risk of missing small volume occult disease.

Of further concern are metastases that are originally resectable at the time of primary surgery, that become unresectable during the time lag. This concern is more pressing for large hepatic metastases, as though they may be amenable for treatment via chemotherapy initially, chemotherapy cannot be administered during treatment of the primary, during which time it may enlarge. Additionally, rapid growth of metastases after removal of the primary tumour has been described in mouse models. The loss of primary tumour induced inhibition of angio-genesis in the metastases has been described as the model responsible for this phenomenon.<sup>(16,17)</sup>

### **Arguments for synchronous resection**

Several developments over the past few years have challenged the classical strategy of interval hepatic resection. In particular the continuing development of anaesthesia and critical care, improvements in radiological imaging and developments in hepato-biliary surgery have allowed traditional methods to be questioned<sup>(6)</sup>. Increased pressures to decrease health care costs have also contributed to alternative approaches being considered. Clear disadvantages associated with staged resections include the cumulative duration of hospitalisation which is considerably longer and a second

surgical procedure with its additional costs as well as the psychological stress for the patient<sup>(18)</sup>.

Several studies have demonstrated that simultaneous resection increases the morbidity and length of hospital stay<sup>(10, 11)</sup>. This is countered by the fact that a second admission for intra-abdominal surgery is not required. Additional studies have also shown that simultaneous resections are not associated with increased hepatic (perihepatic abscess due to translocation of intestinal bacteria or decreased hepatocyte regeneration) or colonic (increased incidence of anastomotic leakage) complications when compared against staged procedures<sup>(12, 13, 14)</sup>. However, excessive blood loss has been shown to have a deleterious effect on both short and long-term outcomes post hepatectomy<sup>(15)</sup>. Therefore, one should be cautious in offering any patient with expected high blood (complex pelvic surgery, hepatic fibrosis, pre-treatment with oxaliplatin) loss a simultaneous resection

The argument for undertaking simultaneous resections is strengthened by recent studies which demonstrate the potential hepatotoxicity of some of the neoadjuvant chemotherapy regimens now deployed<sup>(19, 20)</sup>. The simultaneous approach essentially eradicates the role of chemotherapy. However, if chemotherapy is required the simultaneous resection may in fact potentiate the effects of systemic chemotherapy by reducing the total volume of tumour present.

Additionally, it has been proposed that post operative infective complications are associated with a poorer long term outlook secondary to excessive pro-inflammatory cytokine release<sup>(21, 22, 23, 24)</sup>. It is therefore possible, that a second major intra-abdominal operation could predispose to a poorer long term outcome, via a similar mechanism. The risk of post-operative infections would still be present and may in fact be higher on re-laparotomies.

## **Recommendations**

We believe that there are certain situations which preclude a synchronous resection. Liver metastases found during emergency colorectal cancer resection (following obstruction, perforation or bleeding) should not be resected synchronously due to the high likelihood of peritoneal and other overt disease<sup>(25)</sup>. Additionally, cases where the probability of postoperative liver insufficiency is increased (cirrhotics or patients in whom a major hepatectomy is being undertaken) should not undergo synchronous resection. Simultaneous hepatectomy should not be performed unless the chance of achieving a negative resection margin is high<sup>(10, 14)</sup>.

Therefore our recommendations are:

- a) Easy primary tumour resection and easy liver resection: synchronous resection
- b) Easy primary tumour resection, borderline/unresectable liver tumours: chemotherapy, followed by hepatectomy, followed by primary resection

- c) Difficult/unresectable primary tumour resection, easy liver resection:  
chemo radiotherapy for primary tumour, primary resection followed by a  
hepatectomy

Most importantly, simultaneous resections should only be considered by surgical teams with considerable experience in both fields. With increasing financial demands on modern health care services and continued developments within surgery and anaesthetics, every patient with synchronous disease should be considered for simultaneous resection via a multi and inter disciplinary approach.

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