Active treatment of colorectal hepatic metastases

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Key points

- New Zealand has a high rate of colorectal cancer, with 2000 new cases being reported each year
- The development of metastatic disease limits the outcome of surgical treatment for the cancer
- Metastases are often confined to the liver for a period of time, allowing opportunity for treatment
- Liver resection, hepatic cryotherapy, hepatic artery chemotherapy and selective internal radiation therapy are some of the treatments available
- These methods can provide prolonged survival times and near normal quality of life
- Dendritic cell immunotherapy may help control systemic spread of the disease

ABSTRACT

Colorectal cancer is one of the commonest cancers seen in New Zealand and through the development of liver metastases is responsible for some 1000 deaths annually.

In many instances metastases are confined to the liver for some period of time and may therefore be amenable to local surgical or other treatment.

It is no longer appropriate to think of colorectal liver metastases as untreatable. Liver resection can be accomplished with safety and in certain circumstances can achieve five-year survival rates of 25-50 per cent. Hepatic cryotherapy and selective internal radiation therapy are new modalities of local treatment which, when combined with hepatic artery chemotherapy, can achieve high rates of local control and probable survival advantage for many patients with non-resectable liver

metastases.

The limitations of these local treatments relate to the development of extrahepatic tumour sites. Further improvement in survival awaits new therapeutic approaches to this problem. Dendritic cell immunotherapy is a promising new candidate.

INTRODUCTION

New Zealand has one of the highest rates of colorectal cancer in the world with some 2000 new cases being recorded each year. Surgery has always been the mainstay of treatment and remains so. However, the results which can be accomplished by this means are limited by the all too frequent development of metastatic disease.

While adjuvant chemotherapy with 5-Fluorouracil (5FU)-based regimens has been shown to provide benefit in this regard, and can reduce mortality in patients with involved lymph nodes (Dukes stage C) by some 33 per cent,[1] some 50 per cent of those presenting with colorectal cancer will still develop recurrent or metastatic disease at some stage.

Perhaps, because of the predominant spread from the bowel via the portal vein, the liver is the most frequent site of recurrence and is often the only site of obvious metastatic involvement at the time of death. Thus, hepatic metastases are already evident in some 20 per cent of patients at initial presentation and will become so with time in a further 30 per cent of those with the disease.[2]

It is therefore important to consider what treatment is available for those with colorectal liver metastases, and for new treatments to be developed and tested. All too often the view is expressed that no meaningful therapeutic options exist. Whereas this view was appropriate 15-20 years ago, it is no longer so.

Liver resection is now an accepted treatment, capable of providing a cure in some situations, but remains underutilised. Unfortunately, however, only 7-10 per cent of patients will be suitable for liver resection,3 either because of the number, size and location of the tumour deposits within the liver, or as a result of extrahepatic disease.[2] Untreated patients have a median survival of less than 12 months, depending on the degree of tumour involvement.[3,4]

Conventionally the only treatment option considered appropriate for those with non-resectable liver metastases has been systemic chemotherapy and this has generally yielded disappointing outcomes with significant toxicity, low response rates of 10-20 per cent and minimal, if any, survival advantage.[5,6]

Because so many patients appear to have metastases confined to the liver, a number of local treatments have been developed and investigated. These include focally destructive methods such as cryotherapy, and regional methods such as hepatic artery chemotherapy (HAC) and selective internal radiation therapy (SIRT).

Such treatments, although not likely to be curative, may provide local control within the liver and the possibility of improved survival.[7-14] While they are not currently widely available, they are being employed and investigated in leading cancer centres around the world.

This article describes the approach taken by the Wakefield Gastroenterology Centre in treating patients with colorectal liver metastases. The centre has been active in both the development and investigation of a number of new treatment modalities including liver resection, hepatic cryotherapy, HAC and SIRT. These have been used

individually or in combination, depending on the pattern of spread of the disease.

METHOD and RESULTS

Liver resection

The development of liver resection as a safe and practical treatment modality has been dependent on improved knowledge of the segmental anatomy of the liver (eight segments) and of the regenerative capacity of the liver. Providing the liver is not seriously damaged by chronic viral infection or other injurious agents (eg, alcohol) up to six of the eight segments may be removed with expectation of full regeneration and restoration of normal liver reserve within six weeks.

Liver resection has become the treatment of choice for those patients with a limited number of deposits confined to a resectable portion of the liver. Whereas this has usually been taken to mean one half of the liver, it may on occasions also include areas in both lobes of the liver. Between April 1987 and December 1997, a total of 70 patients with colorectal metastases were treated by liver resection by the senior author (RSS). Some 53 entailed resection alone, nine were associated with additional cryotherapy and in eight, subsequent HAC was given.[15]

Patients were aged between 29 and 76 years, with a median age of 60 years. Eighty per cent of resections entailed four or more of the eight liver segments.

Four patients died within 30 days of surgery, giving a mortality rate of 5.7 per cent. In the 53 patients who underwent resection alone, the three and five-year actuarial survival rates, including 30-day mortality, were 62.0 per cent and 27.2 per cent respectively and the median survival time was 38 months.

While postoperative morbidity was relatively high, most was minor and the median hospital stay was only 11 days. Our mortality of 5.7 per cent is comparable with other recently published figures which range from 0 to 8 per cent[3,16,17] and the three-year and five-year survival figures of 62.0 per cent and 27.2 per cent are encouraging and in keeping with other published experience.[3,17,18]

Once patients have recovered from the surgery they return to a normal quality of life, without restrictions.

In line with other major cancer centres, the resection policy at the Wakefield Gastroenterology Centre has become increasingly aggressive in recent years.

It is clear from our experience and that of others17-19 that hepatic resection is relatively safe and can achieve extension of life and long term survival in selected patients (see Figure 1).

Cryotherapy and hepatic arterial infusion chemotherapy

Cryotherapy accomplishes in-situ destruction of liver tumour deposits by freezing, with minimal damage to surrounding normal tissue. It entails a major operation for the placement of liquid nitrogen probes into the tumours for intra-operative freezing. Destruction is by both direct cell damage and damage to the microvasculature.

CT scan showing tow large colorectal liver metastases affecting both the right and left sides of the liver. Both lesions were resected and the patient remains alive and disease-free four years later.

It is generally employed in patients with non-resectable metastases, confined to the liver, which are of limited size (up to 4-5cm) and number (up to four-six). However, on occasions it may be employed with liver resection, to freeze resection margins, or freeze one or more lesions in the liver remnant. In these circumstances it may convert a patient with non-resectable (incurable) disease into one with resectable (curable) tumour.[8]

We have always assumed that, in patients with multiple liver deposits, other sites would be present within the liver. For that reason we follow cryotherapy with four-weekly cycles of HAC to treat remaining microscopic or even macroscopic disease within the liver. Because hepatic metastases derive some 95 per cent of their blood supply from the hepatic artery,[20] chemotherapy infused by this route will achieve high concentrations of drug at the tumour site, and by using drugs which are cleared mainly on first pass through the liver (eg, 5FU, FUDR) minimal systemic exposure occurs, with the result that no systemic toxicity is encountered.[2,3]

HAC has been shown to achieve much higher response rates from liver metastases than systemic chemotherapy and can usually be given with few, if any, side effects.[10,11] We use 5FU continuously via a disposable balloon pump for four days every four weeks. During this time patients remain ambulant and can usually continue with normal activities.

Between October 1991 and December 1997, 42 patients with colorectal liver metastases were treated by cryotherapy and subsequent HAC. The number of lesions present per patient varied from two to 30 (median six), with size ranging from 1-12cm. There was no 30-day mortality, and few serious postoperative complications.

Minor side effects related to HAC were observed in 18.5 per cent of cycles but seldom led to a need for alteration in the treatment. Patient monitoring with serum CEA levels and three-monthly CT scanning indicated disease within the liver was usually well controlled for significant periods of time.

Our experience suggested the addition of HAC conferred additional benefit over cryotherapy alone9 and others have reached the same conclusion.[7,21] Median survival following cryotherapy and HAC in these patients was 17.7 months from treatment (range 3.9-64.9), or 22.2 months (range 5.4-78.1) from diagnosis of liver metastases. This compares favourably with expected median survival times in similar untreated patients of less than 10 months from diagnosis.

Our experience, and that of others, indicates cryotherapy with subsequent HAC is both safe and well tolerated.21 Local control within the liver is certainly achieved and there appears to be a beneficial effect on the survival of patients with non-resectable liver metastases judged suitable for this treatment. Most patients, however, go on to develop other extrahepatic sites of metastatic disease (eg, lungs, bone, local recurrence) and will die as a result. It is reasonably clear that before further survival benefit will be achieved for this group of patients a means of controlling or preventing the development of extrahepatic disease must be found.

Selective internal radiation therapy

The majority of patients with colorectal liver metastases have more disease than is amenable to either resection or cryotherapy. Many cancer centres around the world have employed HAC in these patients in preference to systemic chemotherapy and this approach almost certainly achieves a modest survival advantage.[10,11] Prior to January 1997, this was our approach, but since that date we have been utilising SIRT followed by HAC and have been very impressed with the ability of this combination of treatments to bring even large amounts (eg >50 per cent liver replacement) of liver tumour under control.[14]

The use of radiotherapy to the liver has conventionally been limited by the poor tolerance for radiation of normal liver tissue. Radiation doses as low as 30-35Gy are associated with a substantial risk of fatal radiation hepatitis.[22] Unfortunately at least twice this dose is needed to achieve tumour cell destruction.

SIRT with 90yttrium microspheres (SIR-spheres®, Paragon Medical Ltd, Perth, Australia) is a new approach which employs a novel delivery system of radioactive microspheres (25-35µm in size) infused into the hepatic artery which permits high doses of radiation to be delivered selectively to liver tumours, with much lower doses being delivered to normal liver tissue. Encouraging results have been achieved in the treatment of both hepatocellular carcinoma[13] and colorectal metastases.[12,14]

Because liver metastases derive some 95 per cent of their blood supply from the hepatic artery,[20] and normal liver only 25-30 per cent, SIR-spheres® injected into the hepatic artery are preferentially trapped in the arterioles of liver tumour tissue. This selective uptake by tumour can be enhanced by the prior administration, into the hepatic artery, of angiotensin II which has a vasoconstrictive action on normal blood vessels, but not on the relatively unreactive neovasculature of hepatic meta-stases.[23,24] Using this technique, radiation doses in excess of 200Gy can be delivered to metastases, with much lower and non-harmful doses being given to the normal liver.[25]

During the period February 1997 to November 1998, we treated 38 patients with extensive colorectal liver metastases by SIRT and subsequent HAC. This involved patients in having a laparotomy for the placement of an hepatic artery Porta-cath for delivery of the treatment. Liver involvement was <25 per cent in 19 patients, 25-50 per cent in nine, and >50 per cent in 10. SIRT was well tolerated and no serious in-hospital morbidity occurred.

Median hospital stay after the SIRT was two days and no treatment-related mortality was seen. All patients experienced lethargy and some anorexia for up to five or six weeks following the treatment, before returning to a normal or near normal quality of life.

Responses to SIRT as indicated by falling tumour markers and serial three-monthly CT scans were seen in over 90 per cent of patients. Some 19 patients (50 per cent) had, or developed, extrahepatic disease (EHD) within nine months of receiving SIRT and have been called Group 1. The remaining 19 patients (50 per cent) still had liver-only disease nine months after SIRT and have been called Group 2.

Estimated survival at six, 12 and 18 months was 69.7, 45.9 and 45.9 per cent respectively and was principally determined by the development of extrahepatic metastases. For Group 1 patients the estimated survival at six months is 59.6 per cent, at 12 months is 13.4 per cent and median survival is 6.6 months.

For Group 2 patients the estimated survival at six, 12 and 18 months is 81.6 per

cent and median survival is 9.2 months, although only three of the 19 have so far died and the median survival for this subgroup of patients is likely to exceed 18 months, which compares very favourably with the expected median survival for similar untreated patients, of six to eight months.

Our experience with SIRT and HAC is in keeping with that of Gray et al 12 who reported a high rate of tumour regression following SIRT in patients with colorectal liver metastases. The treatment is well tolerated and safe and almost certainly results in improved survival for at least those patients whose disease does not progress outside the liver at an early stage. Definitive proof of this must, however, await the outcome of further study (see Figure 2).

CT scans of a patient with multiple colorectal liver metastases; (a)three months before receiving SIRT (b)immediately prior to receiving SIRT and (c) six months after SIRT and six cycles of HAC. Excellent control of the liver involvement was obtained by this treatment.