LEADING ARTICLE

Treatment of colorectal metastases: surgery, cryotherapy, or radiofrequency ablation

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The liver is the most common site of metastases from colorectal cancer. There has therefore been growing interest in how liver metastases may be ablated. The most common techniques for ablation of liver metastases are surgical resection, cryotherapy, and increasingly in recent years, radiofrequency ablation.

Colorectal cancer is a major cause of cancer related mortality, accounting for 20 000 deaths per year in the UK alone.[1] Although 80% of patients who develop colorectal cancer will have primary surgery, about half of all patients either have advanced disease at presentation or develop it subsequently.[2] The liver is the most common site of metastases from colorectal cancer and one third of patients who present with metastatic disease apparently have involvement of no sites other than the liver.[3]

NATURAL HISTORY OF COLORECTAL LIVER METASTASIS

The outlook for patients with liver metastases in the absence of treatment is dismal. The median survival of such patients is only 6–9 months although this varies with the extent of disease at presentation with metastases.[4 5] Only a small fraction of patients will survive five years and all will subsequently die if no other condition causes earlier mortality. Although some patients will die with the disease confined to the liver, many will develop metastases elsewhere. While some of these undoubtedly have occult extrahepatic dissemination at the time they present with liver metastases, there is good evidence that these metastases can metastasise by both the bloodstream and lymphatics.[6] The lungs are the most common sites to be affected by this blood borne spread and the lymphatic spread affects intra-abdominal lymph nodes, initially around the hepatic artery. The peritoneal cavity may be affected by both lymphatic and local spread from the liver.

CHEMOTHERAPY

Unfortunately, chemotherapy used to treat metastatic colorectal cancer is purely palliative. 5-Fluorouracil (5-FU), usually combined with folinic acid, is the mainstay of treatment of advanced colorectal cancer and with these regimens the median survival is in the region of 12 months.[4] Much is currently made of the poor overall survival of patients with colorectal cancer in the UK compared with the rest of Europe, and lack of availability in the NHS of the "newer drugs" has been cited as a reason for this by many oncologists. However, although use of the newer and active agents such as irinotecan[7] and oxaliplatin[8] unquestionably results in higher response rates, the improvement in median survival amounts to only a few months and at the cost of a more intensive treatment schedule. In the case of irinotecan, the incidence of toxic deaths has led to suspension of two large US trials.[9] While it is vital that cancer physicians vigorously explore the use of more active regimens, it is clear that even the more active drugs used in isolation will make but a small impact on the survival of patients with colorectal cancer in general. NICE has yet to pronounce on the utility of these drugs.

As most patients with advanced colorectal cancer have liver metastases and as many patients die with liver as the only site of disease, it is clear that the outlook for these patients can only be improved if the disease in the liver can be adequately treated. There has therefore been growing interest in how liver metastases may be ablated. The most common techniques for ablation of liver metastases are surgical resection, cryotherapy, and increasingly in recent years, radiofrequency ablation. However, the volume of prospective data available with respect to surgical resection[10–16] is greatly in excess of that available for the other treatment modalities.

LIVER RESECTION

The liver is a parenchymal organ richly endowed with a blood supply. For this reason it was in the past regarded as a surgical "no go" area and resection was performed relatively infrequently up to the 1960s. It was often a bloody affair and attended by not inconsiderable morbidity and sometimes mortality. As it is easily possible to occlude the blood inflow to the liver by clamping the portal vein and hepatic artery it is clear that much of the bleeding associated with the operation came from the hepatic veins which were less easy to control. Several factors have brought about improvement in the quality of liver surgery in recent years. Firstly, it is now more widely understood that the liver has a segmental structure with eight segments which have their own identifiable portal venous and hepatic arterial supply, bile duct, and hepatic vein.[17] All of these segments can be removed individually, although in some cases, such as segment VIII, this

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Abbreviations: 5-FU, 5-fluorouracil.

can be difficult. The technology has also improved greatly. Virtually all liver surgeons use ultrasound parenchymal dissection and argon diathermy as routine and the old fashioned finger fracture has rightly been relegated to history. The ultrasound dissector allows the liver parenchyma to be aspirated leaving the fibrous structure, including the blood vessels, intact. Argon diathermy allows the argon gas plasma to be sprayed on these structures coagulating them and this device will seal holes on the side of veins. Lastly, and possibly most importantly, as the bleeding during the parenchymal dissection comes from the hepatic veins, anaesthetic techniques have been developed to lower the patient's central venous pressure with a dramatic effect on bleeding. In previous years, anaesthetists tended to fill patients pre-emptively with blood and other fluids in anticipation of massive losses. This raised central venous pressure and established a vicious circle of bleeding and transfusion, which nowadays is seldom seen. Presently, for a routine major liver resection, blood losses in the region of a few 100 ml should be the norm with no necessity for blood transfusion.[18] These technical advances have had a marked effect on morbidity and mortality.

> "A large number of substantial prospective and retrospective case series consistently show five year survival rates following liver resection of 30–50%"

Perioperative mortality is now very rare, in the region of 2%.[10–16 19–21] This is approximately half of the mortality rate associated with colonic resection which is in the region of about 5% overall.[2] Mortality, when it occurs, is usually as a result of comorbidity, with liver insufficiency being the second most common cause of death. Postoperative morbidity is still present, with biliary complications being most common.[10–16 19–21]

Outcome of surgical treatment

As it is proved that liver resection can be safely carried out, what is its utility? It may seem counterintuitive that cancer may be cured by resection of metastatic disease and, further, no randomised controlled trial has ever compared liver resection with chemotherapy alone. Indeed, the time when such a trial could ethically be performed has long passed. A large number of substantial prospective[10–16] and retrospective[19–21] case series consistently show five year survival rates following liver resection of 30–50% depending on selection criteria. Recurrence after five years is very unusual and hence the vast majority of patients who survive five years are cured of the disease. It is sometimes suggested that patients with liver metastases that are suitable for operation are a self selected good prognosis group, in that they have well circumscribed and less aggressive disease. To some extent this is true. Patients identified in historic series who fulfilled the criteria for liver resection but on whom the surgery was not performed faired better than the average patient with metastatic disease in terms of median survival.[15] However, by five years virtually all of these patients had died of the disease and so the benefit of resection is now difficult or impossible to refute.

Selection of patients for operation

Which patients benefit from resection can, to some extent, be determined from the published series.[10–16 19–21] This said, the indications for resection are changing to include patients previously thought to be unsuitable. Additionally, neoadjuvant chemotherapy may be impacting on this by extending the scope of surgery and this will be discussed further below. To benefit from liver resection patients should, in general, have circumscribed hepatic disease. Traditionally, this has been interpreted as being four metastases or less but there is little evidence that the number of metastases is of great importance as long as they can all be removed. In order for patients to survive, at least two segments of liver, preferably in continuity, should be preserved. It is very important that all of the disease is removed at operation. Studies show that incomplete resection has little, if any, impact on survival.[15] At present, the consensus is that patients with extrahepatic disease should not be treated surgically unless it can be radically resected, for instance a lung metastases.[22] This would include patients with peritoneal disease and lymph node involvement of the hepatic artery chain.[10] The position of the metastases may also be important. Involvement of all three hepatic veins or the portal vascular structures bilaterally is at present a contraindication to surgery, although techniques are being developed which may overcome these difficulties. It is important that wherever possible a margin of at least 1 cm is obtained as prognosis is worse in the case of smaller margins.[10–16 19–21] Bilateral involvement of the liver with metastases has no adverse impact on outcome, provided all of the disease can be resected.

Prognostic factors

Various prognostic features have been identified other than those stated above. Some workers believe that patients with synchronous metastases fair worse than those with metachronous presentation[21] but other studies do not support this.[12] The carcinoembryonic antigen (CEA) level appears to have prognostic significance as does the presence of more than three metastases.[21] Patients with lymph node involvement or serosal extension with the primary tumours have a worse outlook.[21]

There are few prospective data to determine what percentage of patients with metastatic colorectal cancer will benefit from liver resection. One prospective series suggested that it may be as high as 20%[14] although 10% may be a more conservative estimate.[23] What is clear however is that it is the ability to perform an Ro resection (a complete resection with a histologically negative margin) that matters. If this can be achieved, five year survival is in the range quoted above.

The adverse consequences of percutaneous biopsy are now recognised. A reflex exists among many radiologists, gastroenterologists, oncologists, and even some surgeons that a lesion, even an obvious metastasis, identified on imaging the liver must be biopsied. This is despite the fact that this is virtually never necessary to make a diagnosis. It is now known that about 20% of patients being subjected to a needle biopsy will develop tumour seeding of the biopsy tract.[24] Some of these patients die as a result of the biopsy associated recurrence alone. Routine biopsy of metastases in a patient who has operable disease is therefore indefensible. The optimal management of all patients identified as having colorectal liver metastases on imaging should be discussed with a multidisciplinary team that includes a specialist liver surgeon.

Improving the outcome of surgical treatment

Although as many as 20% of patients with colorectal liver metastases may benefit from surgical treatment, clearly there are a large number of patients who are beyond the scope of surgical treatment. Further, the majority of patients who achieve an Ro resection will still relapse. Are there any means by which the outcome in these patients may be improved? Several studies have evaluated the place of neoadjuvant chemotherapy in patients felt to be conventionally inoperable. In general, these studies have used a combination of 5-FU/folinic acid and oxaliplatin, often chronomodulated.[23] The results suggest that a significant percentage of patients with so-called inoperable disease become operable and the outlook after surgical treatment in these patients compares well with a conventional surgical series. The problem in evaluating this work is the definition of inoperable. It is clear that many, but not all, patients described in these series would be considered conventionally operable by some liver surgeons. It seems possible however that neoadjuvant chemotherapy may extend the role of resectional surgery.

Currently, an EORTC study, supported in the UK by the Cancer Research Campaign, is examining the role of pre and postoperative chemotherapy with 5-FU/leucovorin/oxaliplatin in patients who have operable colorectal liver metastases. This is a good place to start in the assessment of combined treatment protocols as it will allow us to determine whether chemotherapy may extend the survival of such patients. A positive result will allow more patients to benefit from surgery performed for conventional indications. It will also allow the development of study protocols for the treatment of patients with conventionally inoperable disease.

ABLATIVE THERAPIES

In contrast with liver resection, the case for ablative therapy is less convincing. Ablative therapy takes numerous forms. Cryotherapy, radiofrequency ablation, and laser hyperthermia all use thermal energy of some kind to ablate tumour and liver substance. Other methods include direct injection of alcohol or even chemotherapeutic substances into the metastases. Of these methods, the best evidence comes from studies of cryotherapy or radiofrequency ablation.[25–38] The data concerning laser hyperthermia are less convincing,[39] and ethanol injection[40] does not appear to work well for colorectal metastases although it may have a role in the treatment of the small hepatocellular carcinoma.[41] Injection of chemotherapeutic substances is insufficiently studied.[42]

Cryotherapy

Cryotherapy uses a probe perfused with liquid nitrogen to produce an ice ball within the liver. Freezing disrupts the cell membranes and destroys the tissue being treated. The ice ball takes time to form with the probe in situ and realistically it is difficult to treat lesions much bigger than 4 cm in diameter. Most cases have been performed at laparotomy, often combined with liver resection, or laparoscopy. This is because the probes used for cryotherapy are often too large to use percutaneously. Smaller probes are available which can be used percutaneously but the flow of liquid nitrogen is much less and the formation of the ice ball is much slower.

> "Cryotherapy uses a probe perfused with liquid nitrogen to produce an ice ball within the liver"

There are complications with the technique. Following thawing of the ice ball there may be cracking of the frozen liver and this, and the hole made by the probe, can result in very significant bleeding. Secondly, there is a systemic response related to the thermal injury and the necrotic tissue left within the liver. The hospital stay associated with extensive cryotherapy may be longer than that associated with resectional surgery in some cases.

Radiofrequency

Radiofrequency ablation uses radiofrequency radiation to produce local heat in the tissues. An electrode or electrodes are placed in the lesion and the heat produced causes tissue necrosis. The advantage is that unlike cryotherapy there is no difficulty in making the probes small enough to be used easily percutaneously. However, there is a limit to the volume of tissue that can be treated by a single electrode and as with cryotherapy treating larger volumes of tissue can be problematic. For this reason manufacturers have devised a variety of electrode designs which consist of arrays of electrodes or single electrodes which open in situ to produce a number of tips to increase the volume of liver treated. Because of the simplicity in performing this technique percutaneously and the relative cheapness of the devices, radiofrequency ablation is increasingly being practised, in contrast to cryotherapy. Indeed, virtually any radiology department in a hospital without specialised liver services and one semiskilled interventional radiologist could theoretically set up such a service. It seems unlikely that this would result in an overall improvement in the care of patients with colorectal liver metastases.

Assessing the benefit of ablative treatments

The questions that must be asked of interventional therapy are essentially the same as those asked of liver resection. Firstly, can it reliably ablate liver metastases; secondly, can it result in improved survival; and thirdly, is it safe. In attempting to answer these questions it is important also to outline the problems in interpreting the results which are far greater than for liver resection. It is important to be aware that there are few trials that are useful in making an objective assessment of the worth of the various techniques.

What then are the answers to the questions posed above? Firstly, it seems likely from the various studies that ablation of a targeted metastasis can be achieved 55–90% of the time.[30–32] These results are worse than after liver resection but the less satisfactory results may relate to the type of lesions being treated. Ablative therapies are often used for the treatment of metastases that are considered too ill placed to be able to accomplish a resection with a 1 cm margin. Often this would include lesions which are very close to the major vascular structures in the liver, which it may not be possible to sacrifice. Treating such lesions is going to be difficult for any technique. Just as a surgical margin is likely to be compromised, the presence of flowing blood will conduct away the thermal effects and lead to incomplete ablation. Although it is difficult to determine why failure occurs in the various reports it seems likely that not including all of the tumour in the zone of destruction and the heat conducting effects of nearby blood vessels presumably play a part. Distinguishing between radiofrequency and cryotherapy is not possible at present as studies claim superiority of one or other technique.[33 37]

Secondly, with respect to overall survival, unlike liver resection there is no evidence to suggest that ablative treatment alters long term survival compared with chemotherapy alone.[25] This is not to say that it does not nor could not do so given appropriate patients, but at present doubt remains. It is important to realise that in general, patients included in trials of ablative therapy are different from those in surgical series. The ideal patient for ablative therapy would be the patient who, several years after a curative colonic resection for an early stage well differentiated cancer develops small metastases in the middle of a lobe of the liver. Such a patient is however also ideally suited to surgical treatment and for such a patient the long term results of surgery are excellent. Interventional therapy tends to be used in patients who are otherwise considered to be beyond the scope of conventional surgical treatment. It is also an observation that the more technically accomplished the liver surgery unit the fewer patients there are that are considered suitable for ablative therapy.

When a metastasis is removed by surgical resection, most commonly the affected lobe or at least a segment is removed. This achieves in most cases not only a 1 cm margin but also removes the liver which may contain satellite metastases that may have spread within the portal circulation but are not yet detectable on imaging. It is therefore theoretically possible that ablative treatments may be intrinsically inferior. Lastly, when patients have surgical treatment a laparotomy is performed and on occasions small volume peritoneal disease is found that was not identified using imaging. Such patients are not subjected to liver resection, as it is known that the results of surgery are poor if there is residual disease.[15] Not all patients having ablative treatment will have laparotomy or laparoscopy and so certainly a proportion of patients (probably approximately 12%[37]) will be subjected to ablative treatment although they have no hope of long term survival. This will serve to make the results of percutaneous interventional treatments appear worse.

Thirdly, in terms of safety, mortality from treatment itself is approximately 1% with an additional 2% of patients dying of other causes.[34] This is similar to mortality following liver resection in the best series. The use of thermal injury close to the bile ducts and blood vessels may potentially lead to a catastrophic injury, and lethal Budd-Chiari syndrome has been personally observed. Morbidity is approximately 30% with cryotherapy,[29] and liver cracking and the need for transfusion[27] is a particular problem (13%). Radiofrequency appears safer and generally well tolerated.[33] Major morbidity appears uncommon. Many patients are able to leave hospital shortly after the procedure and exhibit few side effects. As mentioned above, percutaneous needling of liver metastases is associated with a significant incidence of needle track recurrence.[24] In theory, the ablative treatments, because they aim to destroy the tumour, should not result in this complication. However, on the contrary, the limited evidence that is available suggests that the incidence of neoplastic seeding may be as high as 25%,[43 44] similar to that following percutaneous biopsy. This must remain a major concern and at present may preclude the use of the technique in healthy patients with conventionally operable disease.

Future of ablative treatments

Looking to the future, how can the role of ablative treatment be established? It is currently difficult to justify a trial comparing ablative and surgical treatment in the most optimal cases. The results of surgical treatment in these patients are good and operative mortality is very low. A patient understanding the facts outlined above would be unlikely to consent to randomisation. It certainly would be possible to perform a trial on elderly and less healthy patients, randomising them to surgical treatment or ablation, but this would require a very large multicentre trial to achieve sufficient patient numbers. A better approach is to adopt a stepwise procedure towards evaluating ablative therapies by performing a randomised trial on patients who are unsuitable for surgical treatment. In the EORTC protocol currently being developed, patients will be randomised to chemotherapy alone with 5-FU/leucovorin/oxaliplatin or to chemotherapy plus ablative treatment. Although few of these patients will ultimately be curable, a significant improvement in survival in the ablation group would be strong evidence that the technique is of value. Such a result would allow protocols including patients with more favourable disease to be confidently produced, providing the issue of tumour implantation can be dealt with.

CONCLUSION

In conclusion, liver resection is established and is a safe and effective treatment with the ability to cure a subgroup of patients with colorectal liver metastases. It is currently certain that in the UK not all patients who could benefit are being referred, although anecdotally it would appear that referral for surgery of this type is more common and the utility of the treatment better accepted by oncologists. If the outcome of patients with advanced colorectal cancer is to be improved, in the view of this author, it is essential that all patients with colorectal liver metastases, and not just the fortunate, are reviewed by a team that includes a specialist liver surgeon.

The role of ablative treatments is at present not established. However, there is a possibility that at least radiofrequency ablation will have a role in the treatment of colorectal liver metastases but a definitive answer on this must await the results of large well conducted trials. The widespread use of these treatments on patients who have otherwise potentially curable disease and no contraindications for resectional surgery must be avoided. I have witnessed an interventionalist spending all day ablating one of three metastases in a patient under general anaesthetic when the entire tumour burden could have been easily removed in half the time using a conventional surgical approach. It is essential, at least for the present, that interventional ablation should only be carried out in experienced hepatobiliary units with multidiscipline teams who also offer high quality liver surgery. Wherever possible patients having ablation should be included in clinical trials. Only in this way will the utility of the technique be determined while allowing patients to be protected from the enthusiasm of inexperienced interventionalists.

Conflict of interest

Professor Primrose has served on an advisory board for Sanofi-Synthelabo, the manufacturers of oxaliplatin.

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