Colorectal cancer is one of the most common cancers in Western society. Although it is not as common in India, the incidence of colon cancer has been rising in both men and women. For the year 2001, it was estimated that the incidence of colorectal cancer in India would be 18,427 in men and 13,092 in women. This is similar to the number diagnosed annually in the UK.

At presentation, 15%-25% of patients will have liver metastases, and the liver will be involved in as many as 50%-75% of patients who develop metastatic disease. Importantly, metastases are confined to the liver in about 20%-35% of patients with advanced disease, and the liver is the only site of recurrence in about half of the patients who relapse after resection of the primary cancer. Without treatment, the median survival with liver metastases is 6-9 months, depending on the extent of disease at the time of diagnosis.

Resection of colorectal cancer liver metastases (CRLM) results in 5-year survival rates of 25% to 44%, with operative mortality of 0%-6.6%. Unfortunately, only about 15%-20% of patients with liver metastases are suitable for liver resection, although this may increase with introduction of newer techniques and better chemotherapeutic agents. Given that approximately 18,000 patients develop CRLM annually in the UK, approximately 3600 patients may be suitable for liver resection.

This review focuses on present challenges in the treatment of CRLM.

Pre-operative staging

Pre-operative staging is mainly based on imaging techniques. In most places, a contrast-enhanced CT scan remains the modality of choice. This has improved considerably with the advent of helical CT scanning, in terms of resolution and ability to image with greater precision during various phases of contrast enhancement. Contrast CT scan has detection rates for CRLM of 68%-91%. Limitations include the need for high radiation dose and low sensitivity for detection and characterization of lesions less than 1 cm. It is important to also perform a chest CT to look for lung metastases.

Magnetic resonance imaging (MRI) provides high lesion-to-liver contrast. Limitations include low sensitivity for detection of disease in the peritoneum and chest. Its main role is complementary in lesions that are difficult to characterize on CT.

Positron emission tomography (PET) is highly sensitive, so any focal area of hypermetabolism can give a false-positive result. Other disadvantages are high cost, poor lesion localization, and low sensitivity for lesions less than 1 cm. PET-CT combines the advantages of CT with the functional ability of PET, by the fusion of PET images with CT images acquired at the same time.

Patient selection

The variables that are most consistently associated with poor outcome and tumor recurrence are tumor-positive resection margins and extrahepatic disease at surgery. In patients with positive resection margins, survival after resection hardly differs from the natural history of the disease. Although this is difficult to assess pre-operatively, surgeons should think carefully prior to planning surgery to ensure that there is a fair chance that all tumor tissue can be adequately removed.

The presence of extrahepatic disease is generally considered a contraindication to hepatic resection, especially with peritoneal or abdominal lymph node metastases, where hepatic resection does not seem to improve survival at all. An exception is the presence of potentially resectable lung metastases; 5-year survival rate of more than 20% has been reported after combined resection of lung and liver metastases.

Other factors related to survival after resection are the number and size of metastases, synchronous presentation of metastases with primary tumor, time between primary tumor and metastases, original staging of the primary tumor, and high pre-operative carcino-embryonic antigen (CEA) levels. In a scoring system using five variables (size of metastases >5 cm, disease-free interval <12 months, number of metastases >1, lymph node-positive primary tumor, and preoperative CEA >200 ng/mL), Fong and colleagues showed 5-year survival of >40% after resection in patients with up to two of these criteria. Five-year survival
was <20% in those with three or more variables.

In recent years there has been a realization that the traditional criteria of ‘resectability’ (1-3 unilobar tumors, <5 cm in size) were too restrictive. Experience has demonstrated that patients with the traditional adverse factors can also experience long-term survival following liver resection. A shift has therefore occurred from morphological criteria to criteria based on whether a macro- or microscopically complete (R0) resection of the liver can be achieved. The American Hepato-Pancreato-Biliary Association 2006 consensus conference concluded that CRLM should be considered resectable if the disease can be completely resected, if two adjacent liver segments can be spared with adequate vascular inflow and outflow and biliary drainage, and if the volume of the liver remaining after resection (‘future liver remnant’; FLR) will be adequate.

Pre-operative biopsy of liver lesions has no place in the management of CRLM. In fact, biopsy is harmful due to the risk of tumor seeding along the tract, which adversely affects resectability as well as long-term survival, even when resection of hepatic metastases is undertaken.

Methods of improving resectability rates

Neoadjuvant chemotherapy

In many patients in whom metastatic disease is confined to the liver and who have good performance status, resection is not possible either because of extensive liver involvement or because of unfavorable distribution of the lesions. In some of these patients, combination chemotherapy may convert unresectable lesions into resectable ones. In most series, 15%-30% of patients who initially had unresectable disease underwent macroscopically curative resection. In one study, 5-year survival rate after chronomodulation chemotherapy followed by resection was 40%. Most of these chemotherapeutic regimens use a combination of 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX) and/or irinotecan (FOLFIRI). Trials currently evaluating bevacizumab, a monoclonal antibody directed against the angiogenic factor, vascular endothelial growth factor (VEGF) and cituximab, directed against epidermal growth factor receptor, provide some hope that even more initially unresectable lesions might become suitable for resection.

Portal vein embolization and staged resection

Portal vein embolization (PVE) of the ipsilateral hepatic lobe was first introduced in 1990. Portal vein embolization leads to atrophy of the ipsilateral lobe and compensatory hypertrophy of the contralateral lobe, thereby increasing the FLR. Hepatocyte regeneration starts within a day after PVE and reaches a peak at 12-14 days. The increase in volume of the remnant liver ranges from 7% to 27%. Hepatectomy is carried out after 3-4 weeks. The complication rate of PVE ranges from 0%-10%.

Staged resection can be carried out in patients with diffuse multinodular metastases. During the first operation, the highest possible number of lesions are resected. Postoperatively, the liver remnant regenerates, accompanied by increase in functional capacity. Systemic chemotherapy is administered during this period to hamper the growth of the metastases. A second-stage resection can be carried out after a few weeks. In one series, 3-year survival after two-stage hepatectomy was 35%, with median survival of 31 months.

Ablative and destructive therapies

Cryotherapy

Hepatic cryotherapy using insulated probes containing liquid nitrogen has been used at laparotomy to treat CRLM. It may be indicated in patients with non-resectable liver metastases and to treat small lesions in the contralateral lobe. Median survival time after cryotherapy ranges from 26-32 months; 5-year survival ranges up to 13.4%. Low pre-operative CEA, lesions less than 3 cm, and no extrahepatic disease are associated with favorable outcome. There is a risk of local recurrence after cryotherapy, of up to 33%. Disadvantages are the size of the probes, which precludes a percutaneous approach, and the potential risk of complications such as hepatic bleeding, thrombocytopenia, hypothermia, myoglobinuria, pleural effusions, acute tubular necrosis, hepatic abscess and bile duct injury.

Radiofrequency ablation

Radiofrequency ablation (RFA) can produce response rates of up to 67%. It is also safe, with complication rates of less than 10%. Advantages include its ease of use, safety, and the ability to use it laparoscopically as well as percutaneously. An apparent disadvantage is the high incidence of local recurrence, which ranges from 1.8%-12% with surgical approach and as high as 40% with the percutaneous approach.

There are no prospective randomized trials to show any therapeutic advantage for any of these
destructive therapies over chemotherapy alone in nonresectable disease confined to the liver. The precise effect of local tumor ablative therapy on survival in CRLM remains unclear.

Resection for recurrent liver metastases

Recurrence may occur after liver resection in about 65% of patients, the most common site being the liver. Approximately 20% of these patients may have liver-only recurrence. It is well established that repeat, even serial, hepatectomy for recurrent colorectal metastases is feasible if the performance status of the patient is suitable. In one study of 191 second resections for CRLM, the 5-year survival rate after second resection was 26%, with median survival time of 30 months.46 However, repeat hepatectomy is often more difficult because of dense adhesions and because the liver parenchyma may be more friable and fibrotic.

Postoperative / adjuvant chemotherapy

Two-thirds of patients will develop relapse after liver resection for CRLM and the 5-year survival is 35%-40% at best. Attempts have been made to reduce the risk of relapse with either systemic adjuvant chemotherapy or chemotherapy by hepatic artery infusion (HAI). In one study comparing standard systemic chemotherapy using 5-FU/leucovorin with alternating systemic therapy and HAI, patients receiving HAI showed lower risk of hepatic progression (23% vs 68%), better 2-year (86% vs 72%) and 5-year (57% vs 49%) survival, and better median survival (37.4 mo vs 17.2 mo).47 There was, however, no reduction in the incidence of metastases elsewhere in the body.

Early results using 5-FU-based regimens for adjuvant chemotherapy were disappointing. The hypothesis that oxaliplatin-based neoadjuvant and adjuvant chemotherapy may be of benefit to patients undergoing liver resection for liver-only disease defined as resectable by classical criteria has been examined by the multicenter pan-European EPOC study. The results are due in the near future.

Conclusions

Surgery is the most effective form of therapy for CRLM. Recent advances in imaging modalities have helped in better patient selection for surgery. Newer chemotherapeutic agents and surgical and radiological interventions have meant that an increasing number of patients can now be considered suitable for surgical resection either primarily or after neoadjuvant chemotherapy. It is important that a multidisciplinary approach is undertaken, involving surgeons, radiologists and oncologists, so that every patient gets the benefit of the most suitable treatment option for his/her condition. It is hoped that with the use of these promising modalities, a greater number of patients with CRLM will be given the chance of long-term survival.

References


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