PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• REVIEW •

Liver resection for cancer

RW Parks, OJ Garden

Department of Clinical and Surgical Sciences (Surgery), University of Edinburgh, UK
Correspondence to: RW Parks, MD FRCS, Senior Lecturer in Surgery, Department of Clinical and Surgical Sciences (Surgery), University of Edinburgh, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh, EH3 9YW, UK. r.w.parks@ed.ac.uk
Telephone: +44-131-536 3817, Fax: +44-131-226 2881
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HISTORY OF HEPATIC RESECTION

The earliest hepatic surgery was almost exclusively performed for trauma with records from as far back as 1870[1,2]. Among the earliest liver resections performed for tumor were those of Langenbuch in 1888[3], Tiffany in 1890[4], and Lucke in 1891[5]. By 1899, 76 cases of liver resection had been reported with a mortality rate of 14.9%[6], a remarkably low figure for operations of this magnitude, all performed at the end of the 19th century. Wendel undertook the first anatomical resection for liver cancer in 1911 when he performed a right lobectomy. The patient who had a primary hepatocellular carcinoma survived for 9 years following the resection[7]. The earliest methods of achieving haemostasis were by electrocautery, elastic tourniquet, and suturing with flexible blunt needles. In 1902, Pringle described compression of the portal triad as a technique to reduce bleeding. A year later Anschutz described finger fracture although this was popularized much late r by Lin[8]. Over the past 50 years, the basic techniques of liver surgery have been refined and developed. Improved survival and reduced mortality rates associated with hepatic resection have resulted in a broader application of these operations, nonetheless, the majority of procedures are performed with a curative intent, although occasionally a palliative procedure may be considered.

BASIC HEPATIC ANATOMY

Precise knowledge of the surgical anatomy of the liver is essential before embar king on hepatic resection. The liver is supported beneath the diaphragm by the reflections of its visceral peritoneum, namely the right and left coronary ligaments, the left triangular ligament and the falciform ligament. There have been many descriptions of the internal architecture of the liver, but that reported by Couinard in 1957[9] is the most widely recognized and remain s the most clinically useful description for the hepatic surgeon.

The anatomical divide between the right and left liver is not at the falciform ligament but in a plane which runs from the gallbladder fossa to the inferior vena cava and is known as the midplane of the liver (the principal plane or Cantlie's line). Within this imaginary plane runs the middle hepatic vein which drains into the vena cava at a common confluence with the left hepatic vein. The right and left hemilivers are themselves further divided by the right and left hepatic vein and the right and left branches of the portal vein. Couinaud identified eight segments in the liver, each supplied by its own portal venous and hepatic arterial pedicle and each drained by a single bile duct. Terminology for various anatomical portions of the liver and the surgical removal of these portions continues to evolve. The Terminology Committee of the Intern ational Hepato-Pancreato-Biliary Association recently published a description of the newest terminology of hepatic anatomy and liver resections[10]. It had no responsibility to investigate anatomy per se and based its report on accepted internal liver anatomy. Right hepatectomy (or hemihepatectomy) and left hepatectomy (or hemihepatectomy) are the appropriate terms for removal of the right and left sides of the liver respectively. Any individual anatomical segment of the liver can be removed, the procedure being referred to as a segmentectomy. Groupings of segments can also be removed and these procedures may be referred to as sectionectomies (or sectorectomies) (Figure 1 a,b).

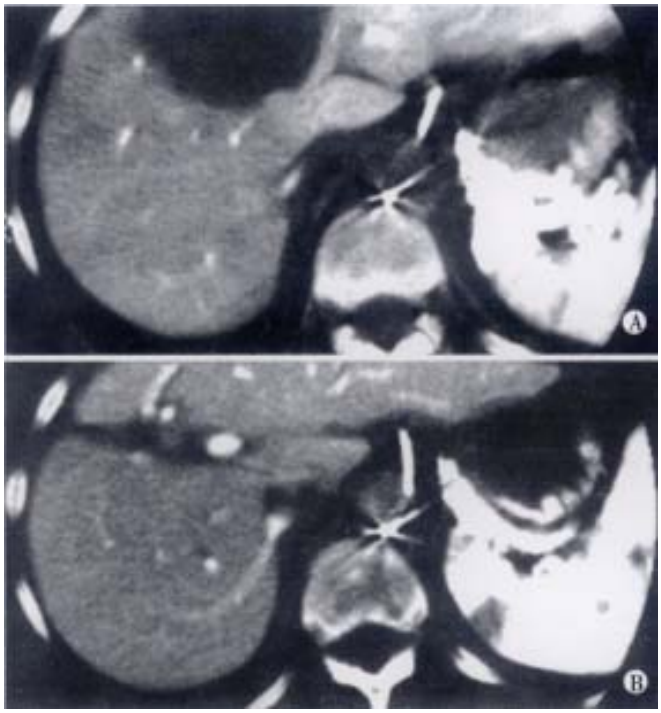

Figure 1 (a) Solitary hepatic metastasis occupying segment 4, 5 and 8, managed by trisegmental resection. (b) CT scan at one year showing hypertrophy of residual left lobe and segments 6/7.

PREOPERATIVE ASSESSMENT

The aim of preoperative investigations should be to determine the nature of the lesion and assess whether it is resectable. Furthermore, the relationship of the tumour to the hepatic vasculature will aid a decision as to the probable surgical procedure.

Liver function tests are frequently abnormal in patients with malignant liver disease and particular attention should be paid to the coagulation profile. Hepatitis B and C antigen screening should be undertaken in view of the associat ion between primary hepatocellular carcinoma and hepatitis. Elevation in tumour markers such as carcinoembryonic antigen (CEA) or alphafetoprotein (AFP) may point towards a diagnosis of colorectal liver metastasis or primary

hepatocellular carcinoma and will serve as a useful baseline for further follow-up.

Characterisation of hepatic lesions is provided by radiological imaging of the liver. Ultrasonography (US) and computed tomography (CT) are the cornerstone of diagnosis and often complement one another. However, magnetic resonance imaging (MRI) is becoming more widely available and may supersede these imaging techniques as the principal radiological investigation. A particular advantage of MRI is its ability to show major blood vessels accurately and demonstrate their relationship to tumour masses. Abdominal ultrasonography gives information regarding the number and size of hepatic lesions and will distinguish liver cysts from solid tumours. If ultrasonography shows multiple solid lesions suggesting incurable malignancy, a biopsy may be performed during the same session to obtain a pathological diagnosis. Duplex ultrasonography may provide additional information regarding involvement of majo r blood vessels and may be particularly useful in the preoperative evaluation of hilar cholangiocarcinoma[11].

Computed tomography may provide more detailed information on the number and size of liver lesions. Most metastases are hypovascular and appear as low attenuation lesions on contrast-enhanced CT scanning. Tumours that may be hypervascular i n relation to normal hepatic parenchyma (e.g. primary hepatocellular carcinoma and metastases from pancreatic islet cell tumour, carcinoid and renal cell carcinoma) may become isodense on a contrast-enhanced CT scan and therefore these patients should undergo both a non-contrast and dynamic contrast study. Dynamic CT scanning ensures enhancement of branches of the portal vein and the hepatic veins so that the relationship of the lesion can be assessed with regard to the hepatic vasculature. This enables determination of resectability and planning of surgical resection. CT arterioportography (CTAP) is a technique whereby the contrast medium is delivered into the portal venous system without prior systemic distribution and dilution. This is achieved by selective catheterisation of the superior mesenteric artery and results in greater hepatic parenchymal enhancement.

Technology now allows three-dimensional modelling of the liver based on spiral computed tomography images[12-14]. Such techniques not only permit detailed reconstruction of the vascular and biliary anatomy of the liver but also offer the potential to measure liver volume before surgery which could be useful in determining the extent and nature of hepatic resection. Accurate assessment of liver volume and an estimate of liver function may also allow prediction of postoperative liver failure in patients undergoing resection, assist in volume- enhancing embolisation procedures, help with planning of staged hepatic resection for bilobar disease and aid in selection of living-related liver donors. Wigmore *et al* have recently demonstrated that virtual hepatectomy of 3-D CTAP reconstructed images provides an accurate prediction of liver mass removed during subsequent hepatic resection[15].

Several techniques have been described for functional assessment of liver capaci ty. These measure drug excretion (e.g. lidocaine clearance[16] or its metabolite monoethylglycinexylidine[17]) or dye excretion (indocy anine green[18,19]). In the future, in patients with impaired hepatic function for whom liver resection is being contemplated, it may be advantageous to combine a functional assessment with an estimation of liver volume to be resected by virtual hepatectomy as described above.

Hepatic angiography is not employed routinely in modern clinical practice to pro vide a specific diagnosis or aid in the planning of surgical intervention, although it may facilitate infusion of lipiodol which may demonstrate “occult” hepatoma in cirrhotic patients being considered for curative resection of primary hepatic malignancy. Laparoscopy is increasingly used to allow direct visualisation of liver lesions and can be combined with laparoscopic ultrasonogr aphy to provide high resolution images[20].

Liver lesions amenable to resection in patients who are fit for surgical intervention should not be biopsied as this may be associated with haemorrhage, sampling error, misdiagnosis and needle-tract tumour seeding. Percutaneous biopsy should only be performed in those patients who are not considered candidates for surgical intervention and only where the results of biopsy might influence further management. In patients with primary hepatocellular carcinoma, it may be valuable to take a biopsy of the uninvolved liver to detect and determine the severity of parenchymal liver disease such as chronic hepatitis or cirrhosis.

Extrahepatic metastases should be sought by means of a chest CT scan before major resection is undertaken, although it is accepted that pulmonary nodules may not always represent metastatic deposits. Upper and lower gastrointestinal endoscopy or barium studies, intravenous urography and mammography (in female patients) may be valuable in patients with a solitary liver metastasis of unknown origin. More recently, positron emission tomography (PET) and isotope scanning using CEA antibodies have been investigated and have shown promising results in demonstration of the hepatic lesions and in determining the extent of extrahepatic disease[21].

Portal vein embolisation (PVE) of the hemiliver to be resected has been proposed to induce homolateral atrophy and contralateral compensatory hypertrophy of the remnant liver and thereby reduce the risk of postoperative liver failure[22]. The concept of PVE appears to be well accepted when performed on healthy liver when extensive resections are being considered[23,24], however, its use in injured liver is also becoming more widely accepted[23,25,26].

PREOPERATIVE PREPARATION

Anaemia and coagulation disturbances should be corrected preoperatively. Administration of vitamin K will improve coagulation disorders secondary to poor nutrition and absence of luminal bile salts in patients with biliary obstruction, but will not reverse coagulopathy secondary to hepatocellular dysfunction. Fresh frozen plasma should be administered to correct the prothrombin time to within 2 seconds of control before surgery if possible.

Patients with obstructive jaundice and portal hypertension have a higher risk of bleeding complications and hepatic decompensation in the postoperative period. Preoperative biliary drainage may improve some of the pathophysiological disturbances associated with obstructive jaundice[27], however placement of biliary endoprostheses may introduce infection and exacerbate subsequent complications[28,29]. The role of preoperative biliary decompression prior to definitive hepatic resection remains unclear.

Surgery in patients with active alcoholic hepatitis carries a substantial risk and abstinence for as little as 3 months will reduce this risk. Patients with active hepatitis who are on long-term steroid therapy may require an increase in steroid cover during the perioperative period. Ascites should be controlled preoperatively by salt restriction and diuretic therapy as ascites increases the risk of impaired wound healing.

Assessment of underlying liver disease is vitally important because, although ex tensive hepatic resection may be well tolerated when the remaining liver has nor mal function, even minor resections in cirrhotic patients may be poorly tolerate d. The use of clinical and biochemical parameters (using the modified Child-Pugh classification) in the assessment of surgical risk in cirrhotic patients is well established and correlates well with surgical risk.

OPERATIVE TECHNIQUES

Hepatic resection is performed under general anaesthetic with a controlled central venous pressure of less than 5 mmHg. For the majority of hepatic resections, the initial incision should be a bilateral

subcostal incision. Exposure may be further improved in some patients with a narrow costal margin by extending the incision in the midline upwards to the xiphoid process.

In patients with hepatic malignancy, a thorough search is made of the peritoneum and regional lymph nodes to exclude extrahepatic dissemination of malignancy. The liver is carefully palpated and intraoperative ultrasound is undertaken to confirm the position of the tumour and its relationship to the hepatic vasculature.

All major hepatic resections mandate control of the inflow vasculature and hepatic venous outflow to and from the portion of the liver to be resected with maint enance of good hepatic arterial and portal venous blood supply to the remnant. This may be done by dissection of the relevant portal pedicle at the hilus and outside the liver substance as is the authors' preference, or alternatively, the major branches may be secured within the liver following division of liver tissue. We have not found it necessary to consider the use of total vascular exclusion[30] in the last 10 years and have favoured "classical" hepatic resection in preference to segmental resections particularly for metastatic tumours[31]. Detailed descriptions of these various techniques are outwith the scope of this article but can be referred to in many major texts[32,33]. The liver parenchyma can be transected in a number of ways, but it is the authors' preference to employ a Cavitron ultrasonic surgical aspirator (CUSA) which skeletonises the vessels within the hepatic parenchyma, allowing their identification before they are damaged. Small vessels (<2 mm) can be secured by diathermy before division, although larger vessels and branches of the hepatic veins are best secured by ligation or application of clips. The relevant hepatic vein(s) may be divided using a vascular stapler or clamped, divided and oversewn with a continuous non-absorbable suture.

The exposed raw surface of the transected liver, vena cava and retroperitoneum are carefully inspected for any bleeding which should be controlled with diathermy or suture. An argon beam coagulator can be applied to the raw surface to ensure haemostasis. Thrombin glue can also be sprayed on these areas to minimize the risk of postoperative bile leakage. It is the authors' preference to place routinely a large tube drain connected to a closed drainage system before wound closure.

POST-OPERATIVE MANAGEMENT

High dependency nursing care is required to provide adequate observation of vital signs and conscious level in the postoperative period. Monitoring includes regular measurement of heart rate, blood pressure, central venous pressure, oxygen saturation, urine output and drain losses.

Patients undergoing major hepatic resection and those with poor preoperative liver function are at particular risk of developing postoperative hepatic decompensation. Maintenance of adequate liver function can be judged by regular assessment of conscious level, acid base status, blood glucose levels, blood lactate levels and prothrombin time.

COMPLICATIONS

Despite improvements in surgical technique and perioperative care, major complications and death may occur following major hepatic resection and the risks to the patient should not be underestimated. In a series of 133 hepatic resections in 129 patients published from our own unit[34], the overall operative mortality was 4.7%. Major early morbidity occurred in 20% of patients and resulted in unplanned radiological or repeat operative intervention, transfer to the intensive care unit in some patients and prolongation of hospital stay. Other major series report similar morbidity and mortality rates[35,36].

Postoperative liver failure from inadequate functional residual liver tissue is the leading cause of death after hepatectomy[37,38]. It has been previously reported that patients with a postoperative residual volume of 35% with good function are at low risk of developing liver failure[39]. However, in patients with impaired liver function, smaller resections may be hazardous.

INDICATIONS FOR HEPATIC RESECTION

The main indication for hepatic resection is primary or secondary hepatic malign ancy. (Figure 2 a,b). Primary malignant hepatic lesions include hepatocellular carcinoma, and less common tumours such as cholangiocellular carcinoma and haem angiosarcoma. Liver resection for metastatic disease is predominantly undertaken for patients with colorectal metastases, however, resection has been performed for non-colorectal liver metastases. Hepatic resection is also undertaken for contiguous tumours involving the liver, such as in selected patients with gallbladder carcinoma or cholangiocarcinoma involving the extrahepatic biliary tree. The indication for hepatic resection for malignancy in our own unit is shown in Table 1.

Hepatocellular carcinoma (HCC) is one of the world's most common malignancies and is particularly challenging because it usually develops on a background of chronic inflammatory liver disease[40]. The mean overall survival of patients with untreated HCC is generally reported to be 3 to 4 months after symptom s appear, however, in Japan and other parts of the world where HCC is being detected earlier, median survival times are nearly 6 months. Surgical resection is the treatment of choice for HCC if the resection can be performed safely and will not leave gross residual disease, however, unfortunately only a small proportion of HCC's are amenable to surgical removal. In non-cirrhotic patients, the tumour has often reached a substantial size by the time of presentation, whereas cirrhotic patients frequently have compromised liver function sufficient to preclude even segmental resection. The average survival time of patients who have undergone resection is about 3 years. Five year actuarial survival rates of 60%-70% have been reported in patients with Stage I/II disease compared with corresponding survival rates of 20%-30% in patients with more advanced disease (stage III/IV)[41,42]. Although the operative mortality rate from liver failure after hepatectomy for patients with HCC has decreased with experience[43], it still ranges from 0%[44,45] to 32%[46-48].

Table 1 Indication for hepatic resection for malignancy in Edinburgh (1988-2001)

Indication	Number
Primary liver tumor	
Hepatocellular carcinoma	30
Intrahepatic cholangiocarcinoma	8
Angiosarcoma	1
Clear cell carcinoma	1
Metastatic liver tumor	
Colorectal adenocarcinoma	131
Stromal tumor	8
Carcinoid tumor	7
Breast metastases	2
Appendiceal metastases	2
Metastatic melanoma	2
Contiguous tumor involving liver	
Hilar cholangiocarcinoma	29
Gallbladder carcinoma	7
Adrenocortical tumor	1
Total	230

Figure 2 (a) Large solitary metastasis resected by extended right hepatectomy. (b) CT scan showing hypertrophied left and caudate lobes with no evidence of recurrence at one year.

Resection if possible is the treatment of choice for colorectal metastases and offers the only potential for cure[35,49]. Several studies have document ed the unfavourable prognosis of untreated hepatic metastases from colorectal cancer. Without treatment, 60%-75% of patients are dead at 1 year and the mortality rate at 3 years is almost 100%[50,51]. Five year survival rates in patients undergoing hepatic resection for colorectal metastases range between 25%-40% in most major centres[35,52,53]. Figures from the authors' unit demonstrate a 3-year survival rate of 65% in patients who underwent resection of colorectal liver metastases[34]. The number of metastases is no longer considered to be as important a predictor of long-term survival as previously[53,54]. Complete excision of all demonstrable tumour with clear resection margins has been shown to be of much greater importance[35]. Segmental-based resection allows excision of bilateral or multiple liver lesions that previously might have been deemed irresectable. Staged resection is another technique whereby large volumes of liver parenchyma may be resected without inducing hepatic insufficiency. There is increasing evidence that selected patients who develop recurrent hepatic tumour following previous resection of colorectal liver metastases will benefit from re-resection[55,56].

Surgical resection of hepatic metastases from neuroendocrine tumours is curative in some cases and is usually effective in relieving symptoms[57]. Palliative debulking or cytoreductive surgery is often worthwhile as it offers a chance of prolonged survival and may cause complete or partial relief of the incapacitating symptoms related to hormone production. McEntee *et al* reported the outcome of 37 patients (24 carcinoids and 13 islet cell tumours) who unde rwent hepatic resection for metastatic neuroendocrine tumours[58]. Seventeen resections were considered curative and in this group, results were encouraging in terms of survival and symptom relief, however in patients undergoing palliative resection the mean duration of symptom relief was only 6 months. Thompson *et al*, however, reported that half their patients with islet cell tumours had symptomatic improvement with a mean duration of 39 months after noncurative resection[59].

The role of hepatic resection for non-colorectal non-neuroendocrine metastases is less well defined. Most studies report small numbers of patients and must be regarded as anecdotal. Schwartz' review of the literature concluded that little improvement could be anticipated for resection of metastases from tumours of the oesophagus, stomach, small intestine or pancreas[60]. Similarly, there was little evidence to support routine resection of metastases from gynaecological or breast carcinomas, however, resection of metastases from primary renal cell carcinoma, Wilms' tumour, and adrenocortical carcinoma was indicated. Harrison *et al* reported a single centre experience of 96 patients who underwent liver resection for non-colorectal, non-neuroendocrine metastas es with no perioperative deaths[61]. The overall survival rate at 1, 3 and 5 years was 80%, 45% and 37% respectively (median survival, 32 months), with 12 actual 5 year survivors. Patients with genitourinary primary tumours exhibited the best outcome followed by patients with primary soft tissue tumours (breast, melanoma and sarcoma). Hepatic resection for non-colorectal gastrointestinal primary tumours was generally associated with a poor survival. Similar results have been reported from other centres where long-term survival was only seen in patients with non-GI-origin metastases[62].

Contiguous cancer arising from the extrahepatic biliary tree or gallbladder may also be amenable to hepatic resection. A more aggressive approach to the management of hilar cholangiocarcinoma in recent years has been associated with improve d long-term survival and quality of life[63-65]. In a recently reported series of 114 patients who presented with hilar cholangiocarcinoma, 98 patients had a radical resection, three underwent palliative resection and only 13 were not treated surgically[66]. The operative mortality rate was 4% and the 5-year survival rate was 28%. This report supports the widely held view that radical resection provides the best prognosis for selected patients with hilar cholangiocarcinoma. A number of recent studies have reported long-term survival after radical surgery for gallbladder cancer[67,68]. Radical regional lymphadenopathy may have survival benefits for patients with node-positive disease[69,70]. Aggressive reresection has been shown to be beneficial for patients with gallbladder cancer discovered during or after laparoscopic cholecystectomy for patients other than those with T1 tumours[71].

SUMMARY

Recent reports have highlighted consistently improved perioperative morbidity and mortality rates following hepatic resection. Operative mortality rates, even in cirrhotic patients, are less than 5% in most recent series. The commonest indication for hepatic resection is primary or secondary hepatic malignancy and therefore appropriate preoperative assessment of such tumours is vitally important. Accurate radiological imaging, including the use of three-dimensional reconstruction, will indicate if lesions are resectable and will aid the decision regarding the likely surgical procedure. Portal vein embolisati on is becoming a more widely accepted technique to induce contralateral hypertrophy reducing the risk of postoperative hepatic impairment and therefore increasing the indications for liver resection. The selection and subsequent management of patients with primary and secondary hepatic malignancy requires a multidisciplinary team approach invo lving hepatologists, radiologists, anaesthetists and surgeons and therefore the care of such patients should be undertaken in specialist hepatobiliary centres. Whilst accepting that hepatic resection offers the only prospect of cure for many patients, it is evident that future efforts will also be focused on determining the role of adjuvant treatments to reduce the inevitable recurrence of tumour which occurs in the majority of patients.

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