Liver tumours in children: Current surgical management and role of transplantation

A J W Millar, FRCS, FRACS (Paed Surg), FCS (SA), DCH

Emeritus Professor of Paediatric Surgery, University of Cape Town and Red Cross War Memorial Children’s Hospital, Cape Town, South Africa

Corresponding author: A J W Millar (alastair.millar@uct.ac.za)

This article reviews the current surgical management of liver tumours in children in the light of improved chemotherapy, surgical techniques and outcomes from transplantation. It is a principle of management that complete removal of a tumour must be achieved for cure. Neoadjuvant chemotherapy may downstage advanced local disease to enable safe curative tumour resection. When this is not achievable, transplant is indicated. Conventional indications for transplant are unresectable stages 3 and 4 tumours confined to the liver. With the realisation that lifelong immunosuppressive therapy has considerable adverse consequences, there has been a recent trend towards extreme and ‘acrobatic’ liver resection to avoid transplantation, but still obtain a cure. The current literature is reviewed in the light of these trends and our own experience.

Before embarking on any surgical enterprise with regard to the liver, it is essential to become familiar with the normal anatomy, function and regeneration/repair of the liver as well as the common variants in terms of blood supply (portal and systemic), venous drainage and the intra- and extrahepatic biliary anatomy (Fig. 1).\(^\text{3,4}\) Paediatric liver tumours that may require liver transplantation are shown in Table 1.\(^\text{5,6}\)

Disease assessment includes full imaging with ultrasound (US) and Doppler evaluation, computed tomography, magnetic resonance imaging with gadolinium, angiography and cholangiopancreatography. In children who may well receive preoperative chemotherapy, in most cases a diagnostic biopsy is preferred, usually a Trucut needle core, but laparoscopic or open wedge biopsies may be safer with regard to bleeding from the biopsy site. This would seem essential in infants <3 months and in children >3 years of age if there is a normal or near-normal serum α-fetoprotein level.\(^\text{3,4,5}\)

There are a number of ways to assess and prognosticate the possible outcome of children with liver tumours and specifically with hepatoblastoma, the best known of these is the International Society of Pediatric Oncology (SIOP)'s pretreatment extent (PRETEXT) of disease system, which takes into account the extent of involvement of the four sectors of the liver and also notes extrahepatic growth using the letter V for hepatic vein, P for portal vein, M for metastases and E for extrahepatic lymph nodes.\(^\text{6,7}\) This system has shown good reproducibility with a tendency to overstage, but it is an excellent predictor of survival. Additional information from a histopathological examination of the resected tumour, which would include the tumour's multifocality, vascular invasion and cell type, increases the accuracy of prognosis.\(^\text{8}\) Indicators of good prognosis are the presence of differentiating mesenchymal elements (i.e. fetal histology), therapy-related extent of necrosis of the resected tumour and quantity of viable mensenchyme (bone, muscle and cartilage).\(^\text{9}\) An outline of management for hepatoblastoma and other malignant liver tumours is illustrated in Fig. 2.

The principles of surgical management are to remove all of the tumour, and if this cannot be done even after chemotherapy, then transplantation should be considered.\(^\text{5,9}\) In Internationale d’Oncologie Pediatrique – Epithelial Liver Study Group 2 (SIOPEL) the results of this conventional approach in standard-risk patients showed a 96% macroscopic resection rate and a 90% event-free survival rate. In those high-risk cases with metastases, vascular invasion and extrahepatic resection, the resection rates were down to 66% and event-free survival was only 47%.\(^\text{5,6}\) In our own series since 1990 at Red Cross War Memorial Children's Hospital, using the SIOPEL 3 protocol of chemotherapy, 44 of 49 patients underwent surgical resection with 41 survivors (83%). Of the 49, 1 was unresponsive to chemotherapy and 4 relapsed; 3 with lung metastases and 4...
locally, of which 2 were lymph node-positive at surgery; none was transplanted.

What then is the role of transplantation in our setting of a developing economy and uneven healthcare delivery? Accepted criteria for transplant should be an anatomically unresectable tumour, where complete removal can only be achieved by total hepatectomy (i.e. no extrahepatic residual intra-abdominal tumour).

The tumour should be chemosensitive and all PRETEXT metastases should be cleared by chemotherapy. SIOP recommends early referral to a transplant surgeon in cases of: (i) multifocal or large solitary PRETEXT IV hepatoblastoma involving all four sectors of the liver; and (ii) unifocal, centrally located tumours involving main hilar structures or main hepatic veins. Because complete tumour resection is a prerequisite for cure, any strategy leading to an increased resection rate will result in an improved survival rate. SIOP advises the more frequent use of orthotopic liver transplant in those patients with tumour burden as described above, as well as the standardisation of techniques for partial liver resection.\[9\] Although SIOP’s guidelines should not be seen as final, but rather as a starting point for further discussion between the various national and international liver tumour study groups, it is indeed a moot point as to whether transplantation in our setting should be recommended so precipitously. The short-term results from transplantation are good, with >70% survival in most series (Table 2).\[8\]\[10\] Clearly, transplantation should not be considered lightly, as it condemns a child to lifelong immunosuppressive therapy and the risk of graft dysfunction and rejection.\[10\] One should be reminded that the consequences of lifelong immunosuppressive therapy include impairment of renal function owing to a combination of chemotherapy and calcineurin inhibitor drug toxicity, dyslipidaemia, lymphoproliferative disease and other malignancies, e.g. Kaposi sarcoma, leiomyosarcoma, and skin, breast and gastrointestinal cancers.\[10\] It is therefore a reasonable discussion point as to how far one should go in order to avoid transplantation. There is of course the potential for rescue transplant after a failed resection with local recurrence, but the outcomes are less favourable than primary transplantation.\[10\] One can push the limits of surgery to the extreme in order to completely remove all tumours, even when in conventional terms the tumour may be considered unresectable. Examples include resecting a tumour with adjacent hepatic vein involvement and replacing the vein with a graft.

On occasions where the main tumour involves most of the liver but segments 6 and 7 are clear, if there is a large accessory right hepatic vein as described by Baer et al., an extended left hepatectomy including segments 1–8 can be performed with preservation of adequate venous outflow via this vein (Fig. 3).\[12\] Another extreme surgical concept is extending the hepatic resection with transplantation as an immediate back-up or safety net should a complete resection, having been embarked on, turn out not to be possible. We did this in a 10-year-old boy with a large central fibrolamellar tumour, performing an extended left hepatectomy with Roux-en-Y drainage of an obstructed right segment 6,7 bile duct with long-term success; the patient was healthy 17 years post resection.\[16\]

In chemosensitive tumours, this strategy of resection can be extended to patients with multicentric tumours where satellite tumours in residual liver segments can be separately...
will remain and consider staged surgery with staged removal of a residual tumour. Preoperative imaging and intraoperative US is essential to identify all residual tumours. Good curative resection.

recurrence following a previous attempt at chemotherapy or angioembolisation.

include some benign tumours, such as a very extensive haemangioendothelioma not responding to treatment with β-blockers, chemotherapy or angioembolisation.

Causes of death in children transplanted for liver tumours are predominantly tumour recurrence (60% for hepatoblastoma and 86% for hepatoellular carcinoma); technical or immunosuppression/rejection-related complications are similar to those in children receiving liver transplants for other diseases.

Conclusion

The best results are achieved by a combination of elective resection in well-selected cases, transcatheter and rescue transplantation. Centres of hepatobiliary surgery should offer both extended hepatic resection and transplantation.

Extensive resections should be considered as an option, particularly where access to transplantation is suboptimal and where access to diligent long-term follow-up is challenging. If transplantation is the only option, then timing of the transplant is crucial. Ideally transplantation should be between courses of chemotherapy, with some post-transplant chemotherapy possible. Living donor transplant is preferred, because the timing of the transplant can be planned and the graft is usually of superior quality when compared with a deceased donor graft.

References


