ELSEVIER

European Journal of Cancer 41 (2005) 1031–1036

European Journal of Cancer

www.ejconline.com

Guidelines for surgical treatment of hepatoblastoma in the modern era – Recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL)

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Received 8 January 2004; received in revised form 11 February 2005; accepted 17 February 2005

Abstract

Cisplatin-containing chemotherapy and complete surgical resection are both crucial in the cure of hepatoblastoma. Radical resection can be obtained either conventionally by partial hepatectomy or with orthotopic liver transplant, but the surgical approach to hepatoblastoma differs considerably across the world. Our main aim in this paper is to present the surgical recommendations of the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL), as well as to stimulate international debate on this issue. We discuss biopsy, verification of resectability, resection principles, indications and potential contraindications for orthotopic liver transplant, as well as thoracic surgery for pulmonary metastases. We suggest that heroic liver resections with a high probability of leaving residual tumour should be avoided whenever possible. In such cases primary orthotopic liver transplant should be considered. Superior survival rates in hepatoblastoma patients who have received a primary transplant after a good response to chemotherapy support the strategy of avoiding partial hepatectomy in cases where radical resection appears difficult and doubtful. We recommend early referral to a transplant surgeon in cases of: (i) multifocal or large solitary PRETEXT IV (PRE Treatment EXTent of disease scoring system) 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 improved survival. We advise the more frequent use of orthotopic liver transplant, as well as the standardisation of techniques for partial liver resection. These 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.

Keywords: Hepatoblastoma; Children; Surgery; Treatment; Liver transplant; Guidelines

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doi:10.1016/j.ejca.2005.02.004

1. Introduction

In the management of hepatoblastoma, complete tumour resection is a crucial step on the route to cure. Therefore, a main goal of treatment for hepatoblastoma is to achieve complete tumour resection; the presence of lung metastases at diagnosis is not an absolute contraindication for partial liver resection or liver transplant because many lung metastases respond very well to chemotherapy and can disappear completely or become resectable by the end of pre-operative chemotherapy [1,2]. Residual pulmonary disease should be removed and the primary tumour subsequently resected. Radical tumour resection can be either by conventional hepatic surgery (partial or total hepatectomy) or with orthotopic liver transplant [2].

The current surgical approach to hepatoblastoma differs significantly among various international collaborative groups. Our main aim in this paper is to present the surgical recommendations adopted by the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL), as well as to stimulate debate on these issues. From its inception, the SIOPEL group recommended pre-operative chemotherapy for childhood hepatoblastoma [3]. In the SIOPEL 1 study, 28% of patients (32/115) were 'downstaged' by PRETEXT criteria after pre-operative chemotherapy, there was tumour shrinkage in >90% of patients, resulting in less extensive liver resections than were initially anticipated. Eight of these children had initially unresectable tumours due to involvement of all liver sectors [4]. North American study groups (the Children's Cancer Study Group (CCSG) and the Pediatric Oncology Group first, and the Intergroup Hepatoma Study, thereafter) promoted immediate surgery for localised tumours [5]. The hepatoblastoma group of the German Cooperative Pediatric Liver Tumour Study was initially positioned between these two strategies, advising primary surgery for those tumours confined to just one lobe of the liver, but it has recently modified its approach by recommending pre-operative chemotherapy for every hepatoblastoma, because of the significantly higher incomplete resection rate (by 50%) for patients in whom primary tumour resection was attempted. In the German experience, there was micro or macroscopic residual disease in 30% of patients (14/48) undergoing primary resection *versus* 19% (15/78) in patients who had all received pre-operative chemotherapy [6]. Contrary to a commonly held belief, pre-operative chemotherapy has not led to more intra- and peri-operative complications, at least in the extensive SIOPEL experience [3] and, in contrast to the American experience with cisplatin- and doxorubicin-treated patients, no chemotherapy-related deaths occurred in the SIOPEL 1 study [4,5]. Furthermore, in the SIOPEL 1 study, in only four patients (3% of the total) were tumours thought to increase in size during pre-operative chemotherapy. Just one of these tumours became 'unresectable' during pre-operative chemotherapy, whereas it had been potentially resectable at diagnosis. Even this patient was subsequently salvaged with total hepatectomy and orthotopic liver transplant [4].

Colleagues in the German/Austrian Paediatric Oncology Group (GPOG) have suggested that there is little to be gained from prolonging chemotherapy beyond the planned treatment regimen because of the risk of developing tumour cell chemoresistance [7]. Prolonging chemotherapy beyond the total number of courses, usually 6–8 courses, administered every 3 weeks, is unlikely to result in an unresectable tumour becoming resectable, so other options, including orthotopic liver transplant, should be considered early.

2. Biopsy

Diagnostic biopsy is strongly encouraged in all hepatoblastoma patients for the accurate pathological diagnosis, including histological subtype, as well as for scientific purposes. In the SIOPEL 1 and 2 studies, no life-threatening episodes were recorded after biopsy and there were minor complications in only 7% of cases (7/96), including bleeding from the biopsy site in 4 patients (1 open, 3 closed), abdominal pain in 2 (1 open, 1 closed) and a wound infection in 1 child who underwent an open biopsy. All 7 patients recovered completely within hours or a few days [4].

Due to the risk of formation of adhesions between the tumour and the abdominal wall when an open biopsy is taken, a percutaneous, image-guided control biopsy (under ultrasound or computed tomography) and passing through normal liver tissue is recommended. There were no cases of biopsy-tract seeding in 96 patients registered in the SIOPEL 1 study and other reports of this condition are anecdotal [8]. The limitations of any biopsy in representing a tumour as heterogeneous as hepatoblastoma must be acknowledged.

3. Tumour resection

3.1. General guidelines

At present, the SIOPEL and the German hepatoblastoma groups recommend no attempt at primary surgery for liver tumours [6,9]. 'Downstaging' of tumours by pre-operative chemotherapy, as in the SIOPEL 1 study [4] led to a less extensive liver resection in as many as 25% of cases and allowed a partial liver resection in some cases in which tumours were not thought to be resectable at presentation.

Because of the rarity of primary liver cancer in children, affected patients should have surgery performed in special centres with adequate experience and modern equipment suitable for hepatic surgery. Before the operation, the patient's ventricular ejection and shortening fractions should be assessed by echocardiography if patient has been treated with doxorubicin. Experienced anaesthetists and appropriate postoperative care facilities are of the utmost importance. It is difficult to provide detailed surgical guidelines, due to the variety of techniques of liver resection. Surgeons must keep in mind that complete tumour resection is the cornerstone of cure. They should not adapt their strategies to their expertise but to the anatomical location of the tumour. Mastery of all techniques possibly useful in extensive and complicated liver resections is needed. In general, atypical liver resections should be avoided as they carry higher risk of incomplete tumour removal, as well as a higher risk of postoperative complications [6].

3.2. Resectability assessment

The PRETEXT grouping system, based on imaging findings, was developed to describe the extent of the primary tumour, before and during therapy [3]. The main aim of PRETEXT grouping was to determine whether it would be possible, pre-operatively, to identify the patients in whom complete tumour resection might be performed by partial hepatectomy (Fig. 1). This system is rather different from those developed by the CCSG and the German Cooperative Pediatric Liver Tumor Study [10–14] in which the stage of disease is determined at the initial surgical intervention, undertaken at diagnosis and before chemotherapy. In order to classify the tumour in the PRETEXT system, the patient must undergo imaging with spiral CT followed by contrast administration (including an angio-computed tomography reconstruction of hepatic vessels, when necessary) and/or magnetic resonance imaging with gadolinium. Doppler ultrasound studies are of particular value in children, allowing real-time investigation of the tumour and its relation to the main hepatic veins and portal branches, including an assessment of their patency or possible invasion by tumour. The surgeon is encouraged to be present during Doppler ultrasound studies to facilitate immediate discussion with the radiologist.

The PRETEXT system has very good reproducibility and an excellent predictive value as regards prognosis [11,15]. However, there are inevitably some limitations. First, difficulties may be encountered in distinguishing between displacement of the anatomical border of a given sector and actual invasion of that sector [2–4,8,11]. Correct PRETEXT grouping is usually easier after pre-operative chemotherapy, when the tumour has shrunk. Second, recent analysis has shown that the use of the PRETEXT system is associated with a moderate

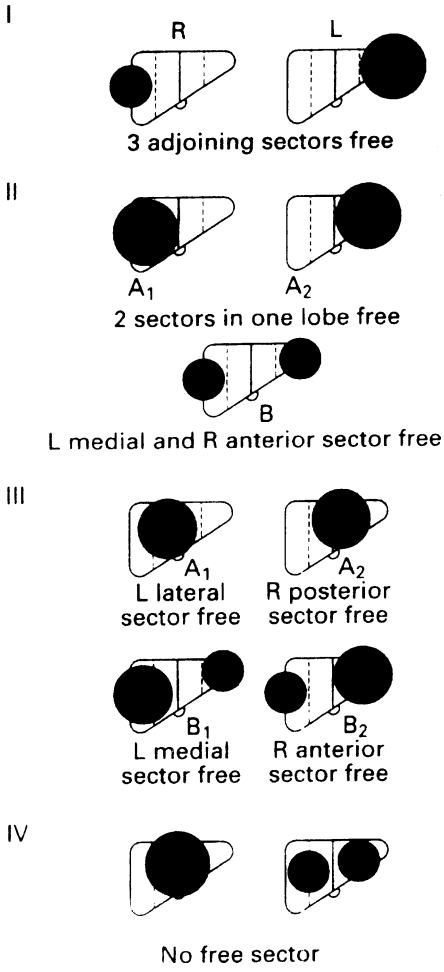

Fig. 1. PRETEXT (PRE Treatment EXTent of disease) staging system.

tendency to 'overstage' some patients, in comparison with postoperative pathological staging [11]. On the other hand, 'understaging', the tumour being more extensive than judged pre-operatively, is unusual; it occurred in 10/91 cases, but incomplete tumour excision resulted in only 4 of these 10 cases. These observations confirm the usefulness of the PRETEXT system for assessing resectability.

Tumour resectability also depends on surgical expertise; for instance, some tumours involving both liver lobes can still be radically resected by either right or left trisegmentectomy when one lateral sector is disease-free. Even tumour encasement or ingrowth into the retrohepatic vena cava does not preclude a radical excision, since the vein can be resected *en bloc* and replaced by a prosthetic graft [16] or, preferably, a venous autograft (internal jugular or external iliac vein) [17].

3.3. 'Difficult' liver resections

A recent analysis of data from the SIOPEL 1 study and a thorough review of the global experience [2] have

shown excellent results with *primary* orthotopic liver transplant compared with those obtained by *rescue* transplant performed for relapse or incomplete tumour resection (87% *versus* 30% long-term, disease-free patient survival). Therefore, it is worth re-emphasising the desirability of avoiding very difficult liver resections that carry a high probability of leaving residual tumour. This recommendation applies mainly to tumours in close proximity to the major hepatic vessels which, in order to be preserved, would have to be peeled off the tumour and/or would require complex vascular resection and reconstruction.

However, when orthotopic liver transplant is not readily available for financial or other reasons, special techniques of hepatic resection can be employed. In these exceptional and difficult cases, total vascular hepatic exclusion (TVE) is of particular value for tumours located very close to the inferior vena cava (IVC), hepatic veins and/or portal vein [18,19] because it allows dissection of the tumour from the vessel or resection of the tumour with a portion of the vascular wall and its subsequent reconstruction in a relatively bloodless field. The duration of TVE should not exceed 45–60 min, although there are some reports of patients tolerating a warm hepatic ischaemia time of up to 85 min [19]. If clamping has to be prolonged, the clamps should be released repeatedly for short periods of time (5 min) [20]. TVE requires appropriate fluid transfusion via a large-bore catheter located in the upper half of the body, as well as careful correction of severe acidosis and electrolyte disturbances immediately after re-perfusion [21]. TVE has been studied extensively and used widely in adults [18–20] but paediatric experience is limited.

Completeness of tumour resection should be assured by all possible means. If there is any doubt, frozen sections of the resection margin should be obtained both from the tumour side of the specimen and from the liver remnant. When microscopic residual disease is identified, the surgeon should consider re-resection of the margin, taking an 'extra slice' of the liver, where applicable and reasonable. The final judgement on the anatomical completeness of the resection depends, of course, on the pathology report. After surgery, it is crucial that serum alpha-foetoprotein (AFP) concentration has returned to normal before declaring the child in complete remission. This may take up to several weeks and one must keep in mind that a transitory rise in AFP can be observed shortly after surgery as a result of liver regeneration, especially in very young children. This transitory rise can be delayed by chemotherapy given after surgery or transplant.

When a difficult hepatic resection is anticipated or when orthotopic liver transplant has to be delayed, hepatic artery chemoembolisation (HACE) may be considered [22,23]. There is very little experience of this technique in children, but HACE may induce a decrease in tumour size, even when the tumour has not responded to systemic chemotherapy. However, the complications of HACE such as fatal pulmonary embolism, deterioration of liver function, septicemia, injury to extra hepatic organs, should not be underestimated, and whether it is able to convert anatomically unresectable lesion into a candidate for partial hepatectomy remains controversial.

4. Liver transplant

In the SIOPEL 1 study, 12 patients (8% of all patients enrolled) underwent orthotopic liver transplant as the primary surgical option, after appropriate pre-operative chemotherapy. This was carried out in 7 children as a 'primary' procedure and in 5 who had already undergone partial hepatectomy. The median follow-up at 31st December, 2001 was 127 (range 10–135) months since diagnosis and 117 (range 52–125) months since liver transplant for patients who were still alive. Disease-free survival was 75% at 5 years and 66% at 10 years after liver transplant. Survival after primary liver transplant was 85.7% (6/7 patients) compared with 40% (2/5 patients) after 'rescue' transplant [2]. Incomplete tumour resection and intrahepatic recurrence after partial hepatectomy were the usual indications for rescue transplantation.

A review of the global experience [2] collected 147 cases transplanted in 24 centres. Primary and rescue liver transplants were performed in 106 cases (72%) and 41 cases (28%), respectively. Twenty eight patients (19%) received a live related liver transplant and 119 (81%) received a post-mortem liver graft. Additional chemotherapy was given post-transplant in 65 (44%) cases. Disease-free survival at 6 years post-transplant was 82% for the primary liver transplant and 30% for the 'rescue' liver transplant [2]. Multivariate analysis performed for primary liver transplant showed that the only parameter related to overall survival was venous invasion ($P = 0.04$). The significantly better survival rate obtained in patients who received a primary transplant after a good response to chemotherapy supports the strategy of avoiding any attempt at partial hepatectomy when radical resection seems difficult and unlikely, as in the case of a PRETEXT III tumour in close proximity to the main hepatic vessels.

Patients with multifocal PRETEXT IV tumours also benefit from primary liver transplant, even if one of the liver sectors has apparently cleared by pre-operative chemotherapy. In such cases, recurrence after partial liver resection is very probable, due to the persistence of small, viable tumour deposits after chemotherapy, which are not shown by present imaging techniques. In some multifocal PRETEXT IV hepatoblastoma, invading all four sectors, 'downstaging' to PRETEXT III can apparently be achieved when one sector seems

to clear completely after chemotherapy, possibly allowing partial hepatectomy. On the other hand, the identification of microscopic tumour in resected liver when primary liver transplant was performed [24] suggests that liver transplant may still be the optimal choice for this subcategory of PRETEXT IV patients, whatever the result of chemotherapy.

Should liver transplant be proscribed in patients with lung metastases at presentation? Such is the policy in some centres but not others if the lung deposits clear after chemotherapy. Of the 12 patients who received a liver transplant in the SIOPEL 1 study, 5 had multiple lung metastases at presentation but their lungs cleared after chemotherapy. Four of the 5 (80%) were alive and disease-free at a follow-up of 52–99 months after liver transplant [2]. Twelve patients (8%) in the collected global material presented with lung metastases. Their long-term survival was 58%; similar to the SIOPEL 1 experience. These data suggest that liver transplant is a reasonable option if lung metastases have been eradicated by chemotherapy. Whether surgical resection of residual pulmonary metastases before the time of liver transplant is a valid therapeutic possibility is still unclear. In the SIOPEL 1 study, all 4 of the 22 patients with pulmonary metastases at presentation, in whom a metastatectomy was performed, survived without residual disease [4,25]. However, in the SIOPEL 2 study, 8 patients out of 25 had surgery following chemotherapy for residual lung metastases but only 3 survived (data not shown). As regards surgery for lung deposits, exploration of both lungs is required through either a median sternotomy or bilateral thoracotomies. Wedge resection, with wide margins, is the preferred technique for removing pulmonary deposits in order to preserve as much pulmonary tissue as possible.

Should patients with initial, macroscopic intravascular involvement be excluded from orthotopic liver transplant? Twenty eight patients (19%) in the collected global material presented with macroscopic venous invasion and their long-term survival was 54% *versus* 78% for patients without venous invasion [2]. Multivariate analysis performed separately for primary liver transplant group showed that venous invasion was the only statistically significant adverse prognostic factor, but in the SIOPEL 1 study, 5 of 7 patients with vascular invasion became long-term, disease-free survivors. Similar observations were made by the Pittsburgh group: 7 out of 9 tumour-node-metastasis (TNM) IVA or IVB (8 of whom had major intrahepatic venous invasion) were alive and disease-free 21–146 months after liver transplant [26]. Hence, initial involvement of the portal or hepatic veins/vena cava involvement does not seem to be a definite contraindication for liver transplant.

For the sake of complete tumour excision, some experts recommend that total hepatectomy for hepatoblastoma should include the removal of the retrohepatic vena cava [17] because, in most cases, one cannot be sure on the basis of imaging, that the wall of the IVC and the ostia of the hepatic veins are completely free, with a safe margin of tissue between the tumour and the veins. Moreover, resection of the major venous drainage of the organ bearing the tumour in continuity with the organ itself is a basic principle of surgical oncology. This approach does not preclude a cadaveric liver transplant provided with the vena cava. In live related liver transplant not provided with the vena cava, reconstruction can easily be achieved with a venous allograft procured from a post-mortem donor or, preferably, from the parental donor (internal jugular vein).

The persistence of viable extrahepatic deposits not amenable to surgical excision is an absolute contraindication to liver transplant. It also seems logical to propose that non-response to pre-operative chemotherapy is a contraindication to liver transplant because of the high likelihood of systemic dissemination of the tumour.

We propose the following guidelines for early referral to a liver transplant surgeon:

1. Multifocal PRETEXT 4 hepatoblastoma.
2. Large, solitary PRETEXT 4 hepatoblastoma, involving all four sectors of the liver, as confirmed by state-of-the art imaging. Unless tumour 'downstaging' is clearly demonstrated after pre-operative chemotherapy, as may be the case when the anatomical border of an uninvaded liver sector is compressed without true malignant invasion, primary liver transplant seems to be the best option.
3. Unifocal, centrally-located tumours involving main hilar structures or main hepatic veins, which would presumably not become free of tumour even after an overall good response to chemotherapy and, therefore, are not amenable to a partial hepatectomy.

When tumour resection by partial hepatectomy is macroscopically incomplete or when intrahepatic recurrence is observed after a previous partial resection, the indication for rescue liver transplant is controversial, because of the disappointing results observed both in the SIOPEL 1 study and in the global experience.

The liver transplant should not be delayed for more than a few weeks after the last course of chemotherapy. Entry on to the waiting list for a cadaveric transplant is a good option if access to a donor graft can be expected within this time; otherwise an intrafamilial, live related liver transplant should be considered.

5. Conclusion

These considerations constitute an attempt to standardise surgical guidelines for the treatment of hepatoblastoma. They are already the surgical cornerstone of

the SIOPEL 4 protocol, which opened in September 2004.

Because complete tumour resection is a prerequisite for cure, any strategy, including new chemotherapy schedules, that leads to an increased resection rate should result in improved survival for hepatoblastoma patients. We propose that orthotopic liver transplant should be considered more actively in specific patient categories. These guidelines should not be viewed as a final statement but as a starting point for further discussion between national and international liver tumour study groups.

Conflict of interest statement

None declared.

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