European Journal of Cancer 106 (2019) 126–132

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Microscopically positive resection margin after hepatoblastoma resection: what is the impact on prognosis? A Childhood Liver Tumours Strategy Group (SIOPEL) report

Daniel C. Aronson [a,*], Víola B. Weeda [b], Rudolf Maibach [c], Piotr Czauderna [d], Patrizia Dall'Igna [e], Jean de Ville de Goyet [f], Sophie Branchereau [g], Giorgio Perilongo [h], Penelope Brock [i], Joszef Zsiros [j], Michaela Semeraro [k], Christophe Chardot [l], Barbara Wildhaber [m], Bruce Morland [n], Laurence Brugières [o] for the Childhood Liver Tumour Strategy Group (SIOPEL)

[a] Department of Paediatric Surgery, University Children's Hospital Zürich, Zürich, Switzerland
[b] Department of Surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
[c] IBCSG Coordinating Center, Berne, Switzerland
[d] Department of Surgery and Urology for Children and Adolescents, Medical University of Gdansk, Gdansk, Poland
[e] Department of Pediatric Surgery, University Hospital of Padua, Padua, Italy
[f] Department of Pediatric Surgery and Transplantation, ISMETT – UPMC, Palermo, Sicile, Italy
[g] Dept. of Pediatric Surgery, APHP Bicêtre Hospital, Le Kremlin-Bicetre, Paris, France
[h] Department of Pediatrics, University Hospital of Padua, Padua, Italy
[i] Department of Pediatrics, Great Ormond Street Hospital for Children, London, United Kingdom
[j] Department of Pediatric Oncology, Máxima Medisch Centrum, Utrecht, the Netherlands
[k] Clinical Research Unit, Paris Centre Necker-Cochin, APHP, Paris, France
[l] Department of Pediatric Surgery, Hopital Universaire Necker Enfants Malade, Paris, France
[m] Department of Pediatric Surgery, Hopiteau Universitaires de Geneve, Geneve, Switzerland
[n] Department of Paediatric Oncology, Birmingham Children's Hospital, Birmingham, United Kingdom
[o] Department of Children and Adolescents Oncology, Gustave Roussy, Villejuif, Paris, France

Received 14 June 2018; received in revised form 8 October 2018; accepted 22 October 2018
Available online 5 December 2018

* *Corresponding author*: Department of Paediatric Surgery, Universitäts-Kinderspital Zürich, Steinwiesstrasse 75, Zürich, CH- 8032, Switzerland.
E-mail address: dan.aronson@kispi.uzh.ch (D.C. Aronson).

https://doi.org/10.1016/j.ejca.2018.10.013

KEYWORDS
Hepatoblastoma;
Partial liver resection;
Positive margin;
Outcome;
Children

Abstract ***Background:*** To evaluate the impact of a microscopically positive resection margin (microPRM) on the outcome of hepatoblastoma patients pretreated with chemotherapy.
Methods: Local recurrence and survival rates of 431 children treated in the SIOPEL 2 and 3 trials were analysed comparing 58 patients with microPRM with 371 who had a complete resection (CR) and who were then stratified by risk category. The tumour was standard-risk in 312 patients and high-risk (PRETEXT IV and/or extrahepatic disease and/or α-fetoprotein [AFP]<100 ng/ml) in 117 patients. All received cisplatinum-based neoadjuvant and postoperative chemotherapy as per protocol. Apart from one microPRM patient who went on to transplant, none received any additional local treatment.
Results: With a median follow-up of 67 months, local relapse occurred in 3/58 patients with microPRM (5%) and in 23/371 (6%) patients with CR. The 5-year overall survival (OS) was 91% (95% confidence interval [CI] 80%–96%) for the microPRM and 92% (95% CI 89%–95%) for the CR group. The 5-year event-free survival (EFS) was 86% (95% CI 74%–93%) for the microPRM and 86% (95% CI 82%–89%) for the CR group. Neither OS nor EFS was statistically significantly different between the two groups, neither overall nor when risk group stratified.
Conclusions: In the context of cisplatin-based chemotherapy, the presence of microPRM did not influence the outcome even without additional local treatment. Although CR remains the aim, microPRM does not necessitate mandatory second look surgery. A 'wait and see policy' is warranted if postoperative chemotherapy is administered and AFP levels and imaging become normal.

1. Introduction

Complete resection (CR) is crucial for cure in the treatment of hepatoblastoma [1–3]. Since the establishment of platinum derivatives and doxorubicin as effective chemotherapy for this primary paediatric liver tumour in the 1980s [4], neoadjuvant chemotherapy, complete delayed resection, and adjuvant chemotherapy became the treatment paradigm for all hepatoblastomas for the Childhood Liver Tumours Strategy Group (SIOPEL) [3,5]. With this strategy, the overall survival (OS) rates have now reached over 90% for patients with standard risk tumours and 80% for patients with metastatic disease [6–8].

Despite the intent of CR with a margin of at least 1 cm of normal liver parenchyma, surgical margins may sometimes be judged as tumour positive by the evaluating pathologist [9]. The prognostic impact of this microscopically positive resection margin (microPRM) is an issue that has been based on observations, but so far it has never been formally studied and fully clarified. The report of the analysis of surgical aspects of the SIOPEL-1 trial described the first observation within the SIOPEL trials that all of 11 patients with microPRM within that trial survived without developing a local recurrence [10]. Since then, repeated incidental observations echoed this finding and seemed to acknowledge that microPRM did not appear to impact prognosis negatively and did not lead to an increased risk of local recurrence in the majority of cases [9,11,12]. To date, none of the four international paediatric liver tumour study groups has formally analysed this issue.

We therefore aimed to analyse the effect of microscopically incomplete delayed tumour resection on long-term outcome, defined as survival and/or local recurrence, in the cohort of children enrolled into the prospective SIOPEL-2 and -3 studies.

2. Material and methods

SIOPEL-2 enrolled patients from October 1995 through May 1998, and SIOPEL-3 ran from June 1998 through December 2004. Protocols were described in detail in previous publications [6,13,14] and are briefly summarised below. The patient accrual of both studies and the exclusion criteria for this analysis are outlined in Fig. 1. The study population is represented by those children who followed the treatment protocol, had either a CR or a resection with a microscopically positive surgical margin as stated by the local pathology report and had a complete follow-up. Patients with a liver transplant were excluded from this analysis. The end-points of analysis were OS, event-free survival (EFS) and local recurrence.

Children aged below 16 years with untreated hepatoblastoma had been eligible for the studies. Measurement of α-fetoprotein (AFP) at diagnosis was obligatory, while surgical biopsy (closed or open) was only mandatory in patients younger than 6 months,

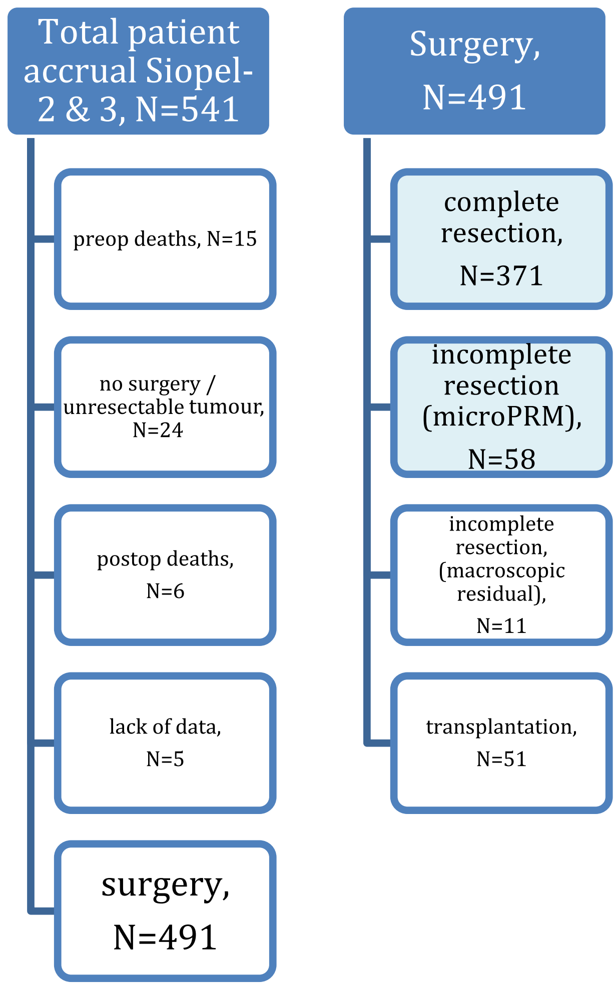

Fig. 1. Overview of the patient selection analysed. The two subgroups in light blue boxes were compared. Note that the lowest box in the first row shows the selection of patients depicted in the second row. Preoperative (preop) deaths were due to early disease progression, postoperative (postop) deaths were due to surgical complications. SIOPEL = Childhood Liver Tumour Study Group; microPRM = microscopically positive resection margins. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

older than 3 years or with AFP less than 100 ng/ml. The PRETEXT (PRETreatment EXTent of disease) staging system was used to evaluate the extent of disease at diagnosis assessed by abdominal ultrasound, computed tomography and/or magnetic resonance imaging for the abdomen and X-ray or computed tomography of the chest for potential lung involvement [15,16].

SIOPEL-2 (pilot) and SIOPEL-3 encompassed two risk groups of hepatoblastoma, standard-risk (SR) and high-risk (HR) groups. SR was defined as hepatoblastoma entirely confined to the liver and involving no more than three hepatic sectors (PRETEXT I-III), HR hepatoblastoma were those tumours involving all four sectors (PRETEXT IV) and/or with vascular invasion (PRETEXT P+ or V+), lung metastases (M+), intraabdominal extra hepatic spread (E+) or AFP levels less than 100 ng/mL at diagnosis.

In SIOPEL-2 and -3, both SR and HR patients were treated with platinum-based chemotherapy. Regimens were similar in the two trials. SR patients received neoadjuvant cisplatin alone, in four courses of 80 mg/m2 every 14 days and two more courses postoperatively. HR patients were treated with seven courses of neoadjuvant cisplatin alternating every 14 days with carboplatin at a dose of 500 mg/m2 and doxorubicin at a dose of 60 mg/m2. Two courses of carboplatin/doxorubicin and one of cisplatin were given after surgery. After the first seven cycles, feasibility of surgical resection was evaluated, and if deemed impossible, three additional courses were then administered, after which feasibility of resection was re-evaluated. If resection remained impossible, orthotopic liver transplantation was considered. HR patients were treated with a maximum of 10 courses of chemotherapy in total. No further surgery nor additional courses of chemotherapy was advised, even in case of microPRM. Therefore, all patients with microPRM were treated the same way as patients with CR, and therefore their actual therapy was equal to the intended therapy.

Central radiologic review was not performed routinely, but a rapid review at diagnosis was available and was recommended in difficult cases. Central review of the histopathology slides derived from tumour biopsy and from a resection specimen was required. The diagnosis of a microPRM was based on local pathology reports as it was not expected to be influenced by central review.

2.1. Statistical analysis

The Kaplan–Meier method was used to analyse the survival curves. OS was the interval between time of diagnosis and time of death, and EFS was the interval between time of diagnosis and time of the first occurrence of progression, relapse or death. The 95% confidence intervals (CIs) were calculated by using the Greenwood formula for survival estimates and by using the exact binomial distribution for rates. All statistical evaluations were done with SAS, version 9.4 (SAS Institute, Cary, NC). The log-rank test was used to compare time-to-event curves, and statistical significance was set at $p < 0.05$. Since this is an unplanned retrospective evaluation, p values should be interpreted as descriptive rather than confirmative.

2.2. Outcome definitions

Complete remission was defined as no evidence of disease on imaging and normal AFP. OS was defined as the time interval between the date of diagnosis and the date of death (from any cause) or the date of the last follow-up. EFS was defined as the time interval from the date of diagnosis to the date of progression, relapse, death or last follow-up, which ever occurred first.

3. Results

3.1. Study population and baseline patient characteristics

Of a total of 541 patients entered into the SIOPEL 2 and 3 studies, 58 patients had a resection with microPRM and were compared to a group of 371 patients with a CR (Fig. 1). Baseline patient characteristics are summarised in Table 1. Both groups were well comparable as there were no significant differences with regards to age, AFP, tumour size, risk assessment and stage.

3.2. Surgery

The type of surgical resections performed in both patient groups are shown in Table 2. In both groups, right hemihepatectomy and right extended hepatectomy were the most frequently performed types of resection. In approximately 20% of cases, a non-anatomic resection was performed, although this kind of resection is not recommended by the surgical guidelines of both studies. The proportion of microPRM per type of resection was not significantly different according to the type of surgical procedure: for right hemihepatectomy 15/134 (11.2%); for right extended hepatectomy 18/98 (18.3%); for left hemihepatectomy 5/67 (7.5%); for left extended hepatectomy 5/28 (17.8%) and for non-anatomic resection 11/87 (12.6%).

Table 1
Baseline patient characteristics of the patient group with microscopically positive resection margins (microPRMs) and those with completely resected (CR) tumours.

Trial, patient and tumour characteristics	microPRM (n = 58)	CR (n = 371)
SIOPEL-2 (n; %)	19 (33%)	85 (23%)
SIOPEL-3 (n; %)	39 (67%)	286 (77%)
Male	32 (55%)	219 (59%)
Female	26 (45%)	152 (41%)
Age in months; median (range)	12 (.4–159)	17 (.2–183)
Ex-premature	6 (10%)	23 (6%)
AFP at diagnosis; median (range)	177980 (24–4700000)	72600 (3.5–8425300)
SR (n; %)	41 (71%)	271 (73%)
HR (n; %)	17 (29%)	100 (27%)
PRETEXT		
I (n; %)	4 (7%)	22 (6%)
II (n; %)	21 (36%)	169 (46%)
III (n; %)	23 (40%)	142 (38%)
IV (n; %)	10 (17%)	38 (10%)
V+	1	18
P+	3	26
E+	4	11
M+	6	48
F+	7	37
R+	5	2

SIOPEL = Childhood Liver Tumour Study Group; AFP = α-fetoprotein; HR = high-risk; SR = standard-risk; PRETEXT = pretreatment extent of disease system; V+ = venous involvement (inferior vena cava and/or hepatic veins); P+ = portal vein involvement; E+ = extrahepatic abdominal disease; M+ = extra-abdominal metastasis; F+ = multifocal disease; R+ = preoperative or intraoperative tumour rupture.

Table 2
Type of surgery.

Type of resection	microPRM	CR
Right hemihepatectomy	15 (26%)	119 (32%)
Extended right hepatectomy	18 (31%)	80 (22%)
Left hemihepatectomy	5 (9%)	62 (17%)
Extended left hepatectomy	5 (9%)	23 (6%)
Non-anatomic resection	11 (19%)	76 (20%)
Type of resection not mentioned	4 (7%)	11 (3%)
Total	58	371

CR = completely resected; microPRM = microscopically positive resection margins.

3.3. Outcome and local recurrence

At a median follow-up of 67 months, in the microPRM group, 53 patients (91%) were alive and disease-free, and in the CR group, 344 patients were alive and disease-free (92.7%). A local recurrence occurred in 3 (5%) patients in the microPRM group and in 23 [18 + 5] (6%) in the CR group. Four patients in the microPRM group later developed distant recurrence versus 26 [21 + 5] in the CR group (Table 3).

3.4. Survival

The OS at 5 years was 91% (95% CI 80%–96%) for the microPRM group and 92% (95% CI 89%–95%) for the CR group, respectively. The EFS at 5 years was 86% (95% CI 74%–93%) and 86% (95% CI 82%–89%) for the microPRM group and for the CR group, respectively. Neither EFS nor OS were statistically significantly different between the two groups. In a separate analysis in both risk categories—SR and HR—no differences in the local recurrence rate, in the OS and in the EFS were observed between the microPRM and the CR group (Table 4 and Fig. 2).

4. Discussion

The results represent the first in-depth analysis related to the issue of the prognostic implication of microPRMs in

Table 3
Overview of local and distant recurrences with outcome per patient group.

Group	Recurrence	Alive	Deceased	Total
microPRM (n = 58)	Local	1	2	3 (5%)
	Distant	2	2	4 (7%)
CR (n = 371)	Local	10	8	18 (4.9%)
	Distant	13	8	21 (5.7%)
	Both	0	5	5 (1.4%)

CR = completely resected; microPRM = microscopically positive resection margins.

Table 4
5-year event-free and overall survival rates by risk group (SR versus HR) and by completeness of resection (microPRM versus CR).

Risk strata	Group	N pts	N events	5-year EFS and 95% CI	Pp	N deaths	5-year OS and 95% CI	Pp
Standard-risk	microPRM	41	3	93% (79%–98%)	.41	1	98% (84%–100%)	.46
	CR	271	32	88% (83%–91%)		14	94% (90%–97%)	
High-risk	microPRM	17	5	71% (43%–87%)	.27	4	76% (49%–90%)	.25
	CR	100	18	82% (73%–88%)		13	88% (80%–93%)	

HR = high-risk; SR = standard-risk; CR = completely resected; microPRM = microscopically positive resection margins; EFS = event-free survival; OS = overall survival; CI = confidence interval.

hepatoblastoma patients who underwent definitive surgery after neoadjuvant chemotherapy. Outcome results of patients with microPRMs and long-term follow-up, as compared with those after CR of the tumour, showed no statistically significant differences in the appearance of local recurrence nor in OS nor in EFS. Owing to the low number of events in the microPRM group, this retrospective evaluation is not however powered to

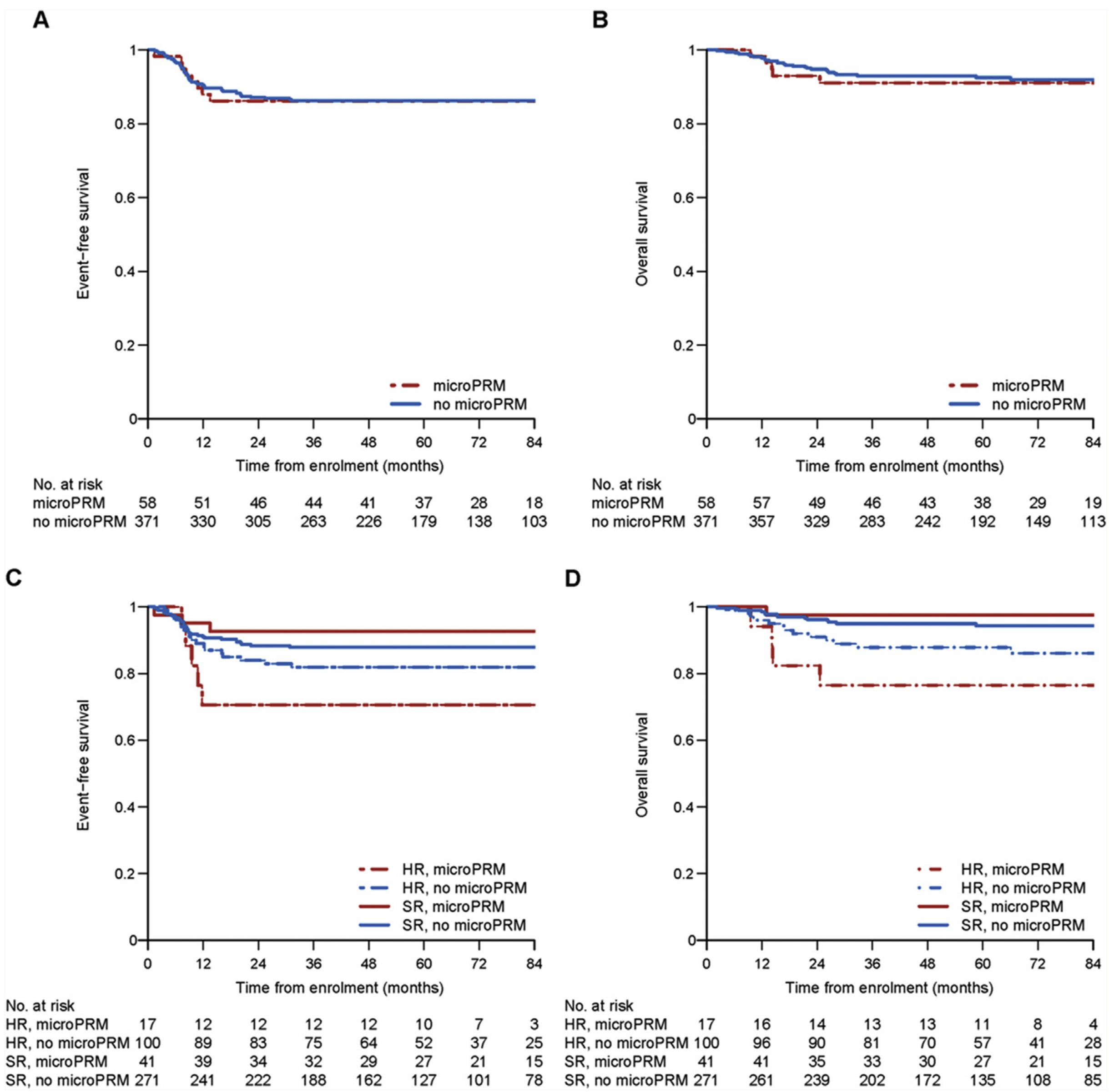

Fig. 2. Kaplan-Meier estimates. (A) Event-free survival (EFS), whole cohort. (B) Overall survival (OS), whole cohort. (C) EFS, stratified by standard-risk and high-risk patients. (D) OS, stratified by standard-risk and high-risk patients. microPRM = microscopically positive resection margin; HR = high-risk; SR = standard-risk.

allow firm conclusions. Yet, the data presented are the best currently available to address this question.

The results seem to contradict earlier reported observations of outgrowth of residual disease after incomplete resection of metastatic tumour deposits, in view of which a negative impact of microscopic residual tumour on prognosis would be expected [17,18]. Also, microscopic spill due to preoperative tumour ruptures has recently been recognised as a bad prognostic factor [19]. The first observations within the SIOPEL studies regarding microPRM were made in the SIOPEL-1 trial, where 11 of 128 patients (8.5%) undergoing surgery had a resection with microPRM. None of them had a re-resection nor suffered from local recurrence [10]. One patient died of progressive distant disease, and one died due to a non–tumour-related cause (Budd-Chiari syndrome). All others had no evidence of disease at a mean follow-up of 5.5 years (range 2–8 years) [10]. This observation was from a too small series to allow a formal comparison of outcome with the patients who had a completely resected tumour.

The same conclusion could be drawn from the observation within the first intergroup hepatoblastoma trial run in North America [INT-0098 trial]. The trial comprised seven patients with positive resection margins (stage II) who showed equally good survival as the 43 patients who had a CR (stage I) without receiving further surgical exploration or re-resection [20]. Regretfully, the stage III and IV patients cannot be taken into account as this article does not report R1 versus R2 incomplete resections for stage III and IV and that therefore cannot be compared to the patients with CRs in these two staging groups. These small data did not allow a firm statement regarding the prognostic value of positive resection margins either. Obviously, the SIOPEL studies cannot be compared with INT-0098 as the latter used primary surgery at diagnosis (resections for smaller tumours and biopsy only for larger tumours) and different chemotherapeutic regimens [20].

There are few older similar observations in the literature. King reported 10 (22% of the described series) patients with microscopic residuals (stage II). The recommended second-look procedure was only performed in five, in four of whom no evidence of tumour was found, while in one microscopic foci of residual hepatoblastoma were identified. Seven patients remained in complete remission [21]. In a personal communication, Mahour stated in the discussion following King's paper that as far as he was aware, based on the experience of the Children's Hospital of Los Angeles, a second-look surgery in all cases of positive margins was not mandatory but should be based on postoperative AFP levels and imaging results [21].

How can these unexpectedly good findings be explained, whereas microscopic residuals after tumour rupture or after incomplete lung metastasectomies are usually regarded as prognostic for poor EFS? Several arguments have already been put forward in our analysis of the small cohort of patients described in the SIOPEL-1 analysis [10]. First, a positive margin on the surgical specimen side does not necessarily mean that there are remaining viable tumour cells on the resection plane of the patient's liver remnant. Specifically with the use of surgical dissecting instruments like the CUSA dissector that cuts and aspirates, part of the healthy liver tissue margin on the resection specimen may have been aspirated by the instrument. The haemostatic cautery of the resection surface in the patient that is often applied may also account for further tumour cell clearance. Because the liver remnant surface is not routinely biopsied, it can therefore not be convincingly stated that we deal with a microscopic residuum on the patient's side of the resection margin. For these reasons, we have used in our article the safer and more accurate term 'microscopically positive resection margin'. Second, one must realise that these findings happened in the context of very successful platinum-based neoadjuvant chemotherapy that makes large tumours shrink and may lead to disappearance of (micro) metastatic lung disease [14]. It may well be that the postoperative continuation of chemotherapy took further care of eliminating microresiduals. Obviously, the above-mentioned explanations are hypothetical and cannot be ascertained in this study.

A larger set of trial patients with substantial follow-up time is needed to theoretically question the long-proclaimed paradigm that 'complete tumour resection is the corner stone of hepatoblastoma treatment', as is echoed in almost every hepatoblastoma paper ever published. Preliminary data regarding this issue have been discussed in smaller specialist forums and meetings [22,23]. Based on these shared experiences, gradually, even non-peer reviewed abstracts have led to references in the literature despite the inconclusive status of evidence [2,11,12]. Based on our findings, we propose that microPRMs after partial hepatectomy for hepatoblastoma do not necessarily call for a mandatory re-operation to re-resect the margin of the liver remnant. If the surgeon suspects a positive margin during the resection, the liver remnant could be carefully biopsied opposite the site that seems at risk to gain insight in the true status of the resection. However, based on our limited findings, a wait and see policy seems to be warranted if postoperative chemotherapy is administered and if subsequent AFP level monitoring and imaging studies remain normal.

It must be stressed, especially as a guide to local physicians who might only see this disease relatively rarely, that the goal of surgery in hepatoblastoma remains a complete tumour resection with negative margins. A resection with a microscopically positive margin should therefore not be regarded as a therapeutic alternative but would still be the 'wrong' surgery. We continue to encourage a wide spread use of a conservative surgical approach in highly experienced centres trained for complicated liver resections, as opposed to primary liver transplantation [24,25]. Because the outcome of salvage liver transplantation seems inferior to primary complete tumour resection, macroscopic residual disease has to be avoided by all means [26].

Funding

No specific funding.

Conflict of interest statement

No conflict of interest disclosures from any authors.

References

[1] Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck DJ, et al. 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). Eur J Cancer 2005;41:1031–6.
[2] Meyers RL, Tiao G, de Ville de Goyet J, Superina R, Aronson DC. Hepatoblastoma state of the art: pre-treatment extent of disease, surgical resection guidelines and the role of liver transplantation. Curr Opin Pediatr 2014;26:29–36.
[3] Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: its evolution and the current status as per the SIOPEL trials. J Indian Assoc Pediatr Surg 2014; 19(4):201–7.
[4] Quinn JJ, Altman AJ, Robinson HT, Cooke RW, Hight DW, Foster JH. Adriamycin and cisplatin for hepatoblastoma. Cancer 1985;56:1926–9.
[5] Pritchard J, Brown J, Shafford E, Perilongo G, Brock P, Dicks-Mireaux C, et al. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach — results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 2000;18:3819–28.
[6] Perilongo G, Maibach R, Shafford E, Brugieres L, Brock P, Morland B, et al. Cisplatin versus cisplatin plus doxorubicin for standard risk hepatoblastoma. N Engl J Med 2009;361:1662–70.
[7] Hishiki T, Matsunaga T, Sasaki F, Yano M, Ida K, Horie H, et al. Outcome of hepatoblastomas treated using the Japanese study group for pediatric liver tumor (JPLT) protocol-2: report from the JPLT. Pediatr Surg Int 2011;27:1–8.
[8] Zsiros J, Brugières L, Brock P, Roebuck D, Maibach R, Zimmermann A, et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. Lancet Oncol 2013; 14:834–42.
[9] Dicken BJ, Bigam DL, Lees GM. Association between surgical margins and long-term outcome in advanced hepatoblastoma. J Pediatr Surg 2004;39:721–5.
[10] Schnater JM, Aronson DC, Plaschkes J, Perilongo G, Brown J, Otte J-B, et al. Surgical view of the treatment of patients with hepatoblastoma. Results from the first prospective trial of the international society of pediatric oncology liver tumor study group (SIOPEL-1). Cancer 2002;94:1111–20.
[11] Lautz TB, Ben-Ami T, Tantemsapya N, Gosiengfiao Y, Superina RA. Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. Cancer 2011;117:1976–83.
[12] Perilongo G, Malogolowkin M, Feusner J. Hepatoblastoma clinical research: lessons learned and future challenges. Pediatr Blood Cancer 2012;59:818–21.
[13] Perilongo G, Shafford E, Maibach R, Aronson DC, Brugieres L, Brock P, et al. Risk-adapted treatment for childhood hepatoblastoma: final report of the second study of the International Society of Paediatric Oncology SIOPEL 2. Eur J Cancer 2004;40: 411–21.
[14] Zsiros J, Maibach R, Shafford E, Brugieres L, Brock P, Czauderna P, et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 2010;28:2584–90.
[15] Aronson DC, Schnater JM, Staalman CR, Weverling GJ, Plaschkes J, Perilongo G, et al. Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the international society of pediatric oncology liver tumor study group SIOPEL-1 study. J Clin Orthod 2005;23:1245–52.
[16] Roebuck DJ, Aronson DC, Clapuyt P, Czauderna P, de Ville de Goyet J, Gauthier F, et al. 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol 2007;37:123–32.
[17] Von Schweinitz D, Faundez A, Teichmann B, Birnbaum T, Koch A, Hecker H, et al. Hepatocyte growth-factor-scatter factor can stimulate post-operative tumor cell proliferation in childhood hepatoblastoma. Int J Cancer 2000;85:151–9.
[18] Fuchs J, Rydzynski J, Von Schweinitz D, Bode U, Hecker H, Weinel P, et al. Pretreatment prognostic factors and treatment results in children with hepatoblastoma. Cancer 2002;95: 172–82.
[19] Meyers RL, Maibach R, Hiyama E, Haberle B, Krailo M, Rangaswami A, et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 2017;18:122–31.
[20] Ortega JA, Douglass EC, Feusner JH, Reynolds M, Quinn JJ, Finegold MJ, et al. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 2000;18:2665–75.
[21] King DR, Ortega J, Campbell J, Haas J, Ablin A, Lloyd D, et al. The surgical management of children with incompletely resected hepatic cancer is facilitated by intensive chemotherapy. J Pediatr Surg 1991;26:1074–81.
[22] Brugières L, Plaschkes J, MacKinlay G, Cecchetto G, Czauderna P, Aronson DC, et al. Hepatoblastoma with microscopic residual disease after surgery: data from SIOPEL 1 and 2 studies. Med Pediatr Oncol 2000;35:177 (Abstr O-33).
[23] Aronson DC, Brugieres L, Maibach R, Childs M, Otte J-B, Gauthier F, et al. Hepatoblastoma with microscopic residual tumor after surgery: results from SIOPEL-2 and 3 trials. Pediatr Blood Cancer (SIOP abstracts – 2008) 2008;51:25 (Abstr O.024).
[24] Guérin F, Gauthier F, Martelli H, Fabre M, Baujard C, Franchi S, et al. Outcome of central hepatectomy for hepatoblastomas. J Pediatr Surg 2010;45:555–63.
[25] Fuchs J, Cavdar S, Blumenstock G, Ebinger M, Schäfer JF, Sipos B, et al. POST-TEXT III and IV hepatoblastoma: extended hepatic resection avoids liver transplantation in selected cases. Ann Surg 2017;266:318–23.
[26] Czauderna P, Otte J-B, Roebuck DJ. Comments on surgical treatment of locally advanced hepatoblastoma. Cancer 2012; 118(16):4092–3 [letter to the editor; author reply 4094-5].