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Outcome and morbidity of liver surgery in children: a single-centre, 47-year experience

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Abstract

Background: The outcome and survival of children with both benign and malignant liver tumours, over a 47-year period was recorded at The National Paediatric Cancer Centre, Our Lady's Children's Hospital (OLCHC), Crumlin. The retrospective study documents the impact of improved chemotherapy, multidisciplinary team approach and specific paediatric hepatobiliary surgical training on morbidity, outcome and survival.

Methods: A retrospective review of the hospital records of all children who presented with a primary liver tumour (benign or malignant) or a primary malignancy significantly involving the liver was undertaken. A review of the management of all such patients at OLCHC, between 1964 and 2011 was performed. This retrospective study reports on two distinct periods, group 1 (1964–1990, $N=21$ patients, previously reported) and group 2 (1994–2011, $N=33$). Follow-up for all group 2 patients ended in November 2014.

Results: A marked difference in survival was noted between the groups with 91% overall survival in group 2 patients as compared to 28% in group 1. Significant complications were documented in group 1 but were uncommon in group 2.

Conclusion: The improvement in mortality and morbidity reflects improved staging and chemotherapy in all patients with a malignant disease but also improved surgical strategies and multi-disciplinary team management (MDT). Specialist training in liver surgery had a significant impact on post-operative morbidity. The results suggest that in certain circumstances, rare and complex liver surgery may be performed in small centres if the necessary supports and experience co-exist.

Keywords: Hepatoblastoma, Paediatric liver resection, Neoadjuvant chemotherapy, Liver tumours, Morbidity and survival

Background

Primary liver tumours and malignant abdominal tumours with direct extension into the liver, are rare in children with an overall incidence of approximately 0.6 to 1.2 per million. Although uncommon, malignant liver tumours are the third commonest solid abdominal malignant neoplasms in childhood but account for only 0.5–2% of all paediatric solid neoplasms [1]. Malignant tumours are more common than benign tumours and are most commonly hepatoblastoma. The relative rarity of these tumours, both benign and malignant, in this young population presents unique surgical challenges to the paediatric surgical oncologist and raises significant issues concerning the level of appropriate training and experience needed to perform these challenging procedures. This assumes not only a logistical problem for an institution or jurisdiction, on the delivery of such a service but also presents ethical considerations when dealing with such a small critical mass. In particular, the question

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of where such surgery should be performed is debatable especially in the era of outcomes linked to clinical volume.

The experience gained at the National Cancer Centre at Our Lady's Children's Hospital, Crumlin (OLCHC), Dublin, Ireland, over a 47-year period in dealing with this rare problem has provided a unique opportunity to detail outcomes as measured against such variables as adjuvant and neoadjuvant chemotherapy, multidisciplinary team management and the availability of surgical expertise with specialty training in paediatric hepatobiliary disease.

Improved survival in the management of liver tumours is not only the result of progress in chemotherapy and attendant supportive care but also in specialised surgical training that facilitates safe and complete resection. Complete macroscopic resection is a significant predictor of survival [2] but requires specific training in Paediatric Hepatobiliary Surgery. This retrospective study reports on the impact of such training and neoadjuvant therapy on the outcome of hepatectomy for both benign and malignant liver tumours in the era of multi-disciplinary management.

Aims

To document the morbidity, outcome and survival of children with both benign and malignant liver tumours, over a 47-year period and observe the impact of improved chemotherapy, multidisciplinary team approach and specific paediatric hepatobiliary surgical training on that outcome and survival.

Methods

A retrospective review of the hospital records of all children who underwent resectional surgery, biopsy only or liver transplant, for both benign and malignant liver tumours, including tumours infiltrating the liver and requiring en bloc resection of liver and tumour, at OLCHC between 1964 and 2011 was undertaken. The report is based on an analysis of two distinct periods, group 1 from 1964 to 1990 (previously reported [3]) and group 2 from 1994 to 2011. Both periods under review are functionally separated by modern pre-operative chemotherapy regimens, utilisation of multi-disciplinary tumour boards and the appointment of a subspecialty paediatric surgeon trained in both surgical oncology and hepatobiliary disease from 1994 onwards. This surgeon and his team were responsible for all liver resectional surgery from that time to November 2011. Prior to 1993, liver surgery was performed by different surgeons and there was no tumour board panel for MDT review.

Index cases were readily identified from a patient and surgical database, using laboratory and Hospital Inpatient Enquiry (HIPE) sources for the first reported period, where possible, (1964–1990) and in addition, follow up for the second period (1994–2014) by outpatient ambulatory clinic review and telephone interview. All patients were less than 16 years of age and had been diagnosed with a primary liver tumour. Patients in group 1 ($N=21$, 1964–1990), were not discussed at a formal tumour board and had undergone either resectional surgery or biopsy ($N=5$) alone with surgery performed by three different surgeons. Group 1 outcomes are described in a previous report [3]. All patients in group 2 ($n=33$, 1994–2014) were discussed at an MDT Tumour Board panel. All had undergone biopsy (if malignancy suspected), and received neo-adjuvant chemotherapy followed by definitive resectional surgery performed by a single surgeon (MTC), appointed to the consultant staff in 1993. By comparison neo-adjuvant chemotherapy was given to 9 patients only in group 1. Two patients in group 2 were considered to have non-resectable hepatoblastoma and who underwent successful reduced cadaveric liver transplantation were considered relevant to the discussion and are included in the survival analysis.

Statistical analysis was descriptive and survival analysis by Kaplan–Meier with significance determined using a log rank regression (Mantel–Cox log rank regression). Data was censured as days to death with analysis of group 1 patients ending as of June 1990 and group 2 as on November 2014.

Results

Patient demographics notably age, sex and clinical presentation are detailed in Table 1. Of the 21 patients in group 1, 12 were males and 9 were females. The mean age at presentation in this group was 2.86 years with a range of 3 to 127 months. Twenty patients in group 2 were males and 13 were females, with a mean age at presentation of 3.65 years and a range of 1 to 192 months. The most typical presentation in both patient cohorts was with an abdominal mass (16 in group 1 and 33 in group 2) which was usually associated with anaemia (16 in group 1 and 21 in group 2). Other symptoms included abdominal distension, fever and anorexia. All patients in group 1 underwent an open biopsy and in 5 patients no further surgery (other than liver biopsy) was performed. Tumour biopsy in group 2 was by way of a Tru-cut biopsy, generally under ultrasound guidance. In group 1, 15 patients (71%) had a hepatoblastoma (HBL), 2 (9%) had hepatocellular carcinoma (HCC), 2 (9%) had embryonal sarcoma (ES) and 1 each had haemangioendothelioma (HE) and non-Hodgkin's lymphoma (NHL). A similar range of pathology was seen in group 2 with 18 HBL (55%), 1 HCC (3%), 4 ES (embryonal-sarcoma) (12%), 6 mesenchymal hamartoma (18%), 2 focal nodular hyperplasia

Table 1 Patient characteristics and histological subtypes (%)

	Group 1 ($n=21$)	Group 2 ($n=33$)
Age		
Mean	34 months	44 months
Range	3–127 months	1–192 months
Sex		
M	12	20
F	9	13
Presentation		
Mass	16	33
Anaemia	16	21
*Other	2 (9)	4 (12)
Histology (%)		
HBL	15 (71)	18 (55)
HCC	2 (9)	1 (3)
ES	2 (9)	4 (12)
MH	0	6 (18)
FNH	0	2
NBL	0	2
HE	1	0
NHL	1	0

HBL hepatoblastoma, *HCC* hepatocellular carcinoma, *ES* embryonal sarcoma, *MH* mesenchymal hamartoma, *FNH* focal nodular hyperplasia, *NBL* neuroblastoma, *HE* hemangioma, *NHL* non-Hodgkin's lymphoma

*Fever, anorexia and abdominal distension

(FNH), (9%), and 2 neuroblastoma (NBL) (9%) primaries invading the liver.

Neoadjuvant chemotherapy was given to all patients in group 2 but it is not possible to document the type and duration of chemotherapy (neo-adjuvant or adjuvant) given to group 1 patients.

Radiological investigations

Thirty-two patients in group 2 underwent a CT scan and 16 cases had MRI imaging. An MRI scan was not considered mandatory for most cases in group 2 and utilised only following MDT tumour board panel meetings at the surgeon's request, when there was uncertainty around resectability. All patients in group 2 had an ultrasound and this was the sole imaging in a single patient with a FNH. A CT scan was performed in 9 of the group 1 patients, angiography in 9, ultrasound in 10, and a Technetium 99 m (Tc99) scan in a single patient with hemangioendothelioma (HE). Angiography was not used in any group 2 patient but an MRI angiogram was helpful in the diagnosis of portal vein thrombosis in 1 patient following resection due to a kinked and redundant portal vein. This was successfully treated by excision of the redundant portion and primary repair.

Radiological assessment for PreText Staging [4, 5] was possible for all group 2 patients at the time of primary diagnosis but was not routinely reassigned after preoperative chemotherapy. All patients were discussed at tumour board and a decision was made by the MDT team as to resectability or need for further non-operative treatment. Patients with histologically proven malignant disease were treated according to UKCCSG/CCLG (United Kingdom Children's' Cancer Study Group) chemotherapy protocols. All patients considered resectable were confirmed to be so at surgery ($N=31$) but two children with bilobar disease as shown in Table 2 and considered non-resectable at presentation, were biopsied only and ultimately underwent successful liver transplantation (OLTx).

The right liver lobe was most commonly involved with disease in 5 group 1 patients and 22 cases in group 2. Disease was bilobar in 8 and 2 patients, respectively, and involved the left lobe in 3 cases in group 1 and 9 cases in group 2.

Surgery

Surgical details are summarised in Table 3. All patients with malignant tumours in group 2 received preoperative (neo-adjuvant) chemotherapy followed by delayed surgery irrespective of the initial assessment of tumour operability. Of 7 patients in group 1 with HBL who received pre-operative chemotherapy, only 6 showed a response. Two patients in group 1 with ES received and

Table 2 Anatomical site at presentation of malignant and non-malignant disease

	Group 1	Group 2
Bilobar	8	2
Right	5	22
Left	3	9

Table 3 Surgical details

Surgery	Group 1	Group 2
Biopsy only	5	2*
Incomplete resection	2	-
Lobectomy	5	17
Extended lobectomy	9	8
Non-anatomical	–	6**
Mean blood loss	N/A	248 (152–1200 ml)
Liver transplantation	–	2*
Pre-op chemotherapy	9	25
Post-op chemotherapy	5	25

*Denotes 2 patients with unresectable disease biopsied and referred for OLTx

**Includes 2 patients with NBL who underwent en bloc resection of primary disease and the involved liver segment(s) responded to preoperative chemotherapy but the single patient with NHL showed no response. Chemotherapy was continued in the post-operative period in 5 group 1 patients but all group 2 patients with malignant disease received postoperative chemotherapy irrespective of surgical or histological findings.

Surgical technique

No significant detailed information is available of precise surgical techniques used in group 1 patients but all patients in group 2 had surgery performed under full vascular isolation for periods of 20–30 min and parenchymal dissection using the CUSA® or Helix® Jet Dissector. Average blood loss in 33 patients in group 2 was 248 ml (range 152–1200). Surgical margins and clearance were assessed by palpation only in group 2 and considered "safe" when at least a resection margin of 1 cm was achievable. If the margin was judged, by palpation, to be potentially compromised, an extended hepatectomy was then performed.

Excessive blood loss was encountered in 1 HBL patient (1200 ml), owing to higher pressures in the Helix Jet Dissector than expected. Multiple inferior vena cava (IVC) holes were encountered after release of occlusion and repaired with no untoward consequences. Despite this volume of blood loss there was no, on-table hypotension and full vascular control was maintained at all times using continued and intermittent vascular isolation. Histological margins were negative for tumour in all group 2 patients.

Three patients in group 2 died, 1 with metastatic NBL, 1 with unresponsive HCC and 1 with progressive HBL (unfavorable histology). The patient with aggressive HBL had undergone an extended right hepatectomy with portal vein excision and reconstruction (on table frozen section of portal vein margins were negative) using internal jugular vein but subsequently died from progressive pulmonary metastases, without remnant or local recurrence at 6 months post-surgery. In 1, group 2 patient significant ascites developed in the immediate post-operative period but this resolved spontaneously.

Several complications were reported in group 1 patients and these are listed in Table 4. Of these, multiple complications occurred in the same patient; thus, obstructive jaundice developed in 3 patients (1 with subphrenic abscess, 1 with wound dehiscence, 1 with biliary fistula), iatrogenic diaphragmatic hernia in 1 patient (with cholangitis and intestinal obstruction), and a biliary fistula occurred in 1 patient who also had a sub-phrenic abscess. Four patients overall required re-exploration. Other significant complications included coagulopathy and hypoalbuminemia in 7 patients.

Table 4 Summary of clinical outcomes of all patients-benign and malignant disease

Outcome *N* (%)	**Group 1 (*n* = 21)**	**Group 2 (*n* = 33)**
Overall survival	6 (28)	30 (91)
Mortality		
Mortality at 1 month	6 (28)	0
Overall mortality at 1 year of follow-up	12 (57)	1
Mortality beyond 1 year of follow-up	3 (14)	2
Death due to surgical issues	5 (24)	0
Morbidity		
Local relapse	7 (33)	0
*Biliary fistula	2 (12.5)	0
Abscess	3 (14)	0
Intestinal obstruction	3 (14)	0
Jaundice	3 (14)	0
Cholangitis	1 (4.7)	0
Dehiscence	1 (4.7)	0
Ascites	0	1 (3)
Portal vein kinking	0	1 (3)
OLTx survival	0	2/2 100)

*Refers to the incidence of biliary fistula in the 16 patients in group 1 who underwent resection

Overall survival was 28% in group 1 and 91% in group 2. Survival for HBL patients in group 2 was 94% (including 2 patients who underwent successful OLTx. Survival of all patients in group 2 with a malignant liver tumour was 92% (23 of 25 patients) and includes the 2 patients from with un-resectable HBL who underwent successful OLTX. Excluding transplanted patients, overall survival for surgically resectable lesions was 90% (28/31) in group 2 and 25% (5/20) (excluding 1 patient with an haemangioendothelioma) in group 1. Two patients in group 1 were noted to have suffered a distant relapse (lung) at 8 months and 8 weeks. Both patients were noted to be alive and well at time of writing of group 1 results in 1992 but no further follow-up information is available. One patient in group 2 died of pulmonary HBL metastases 6 months post-extended right hepatectomy and planned portal vein resection and reconstruction.

Survival for *all* patients and for those with malignant disease is presented in Fig. 1 and Fig. 2 respectively. Significant differences were seen between group 1 and 2.

Discussion

The management of benign and malignant liver tumours in children is complex. Surgery is demanding and requires specific training and support to achieve good outcomes with minimal morbidity. Evidence from adult hepatectomy series [4] suggests that such surgery should

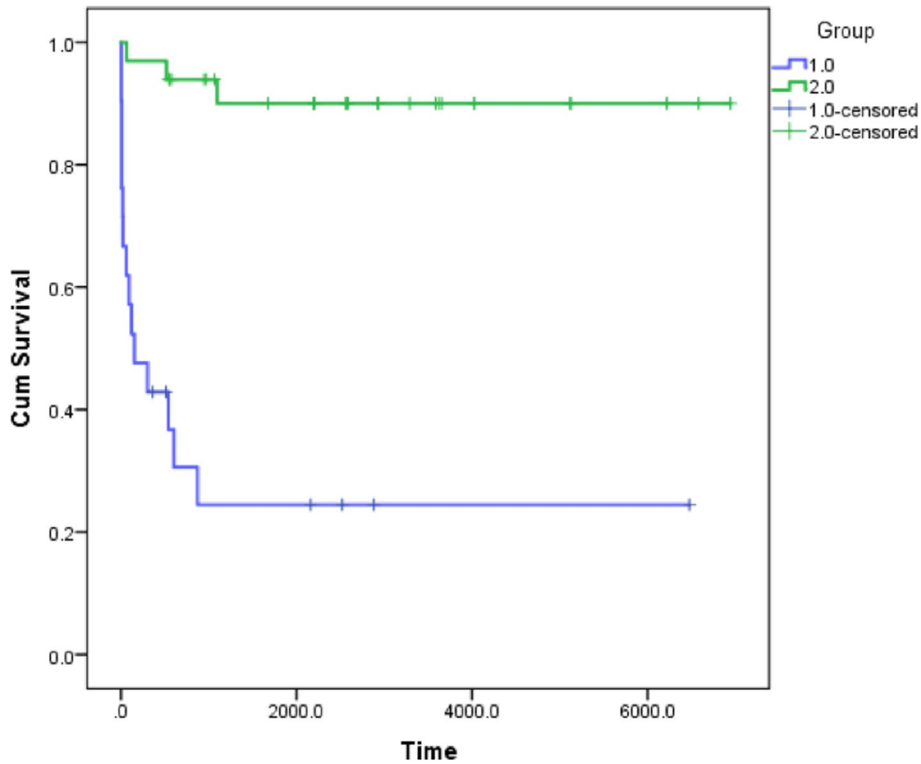

Fig. 1 Cumulative survival plot for all patients

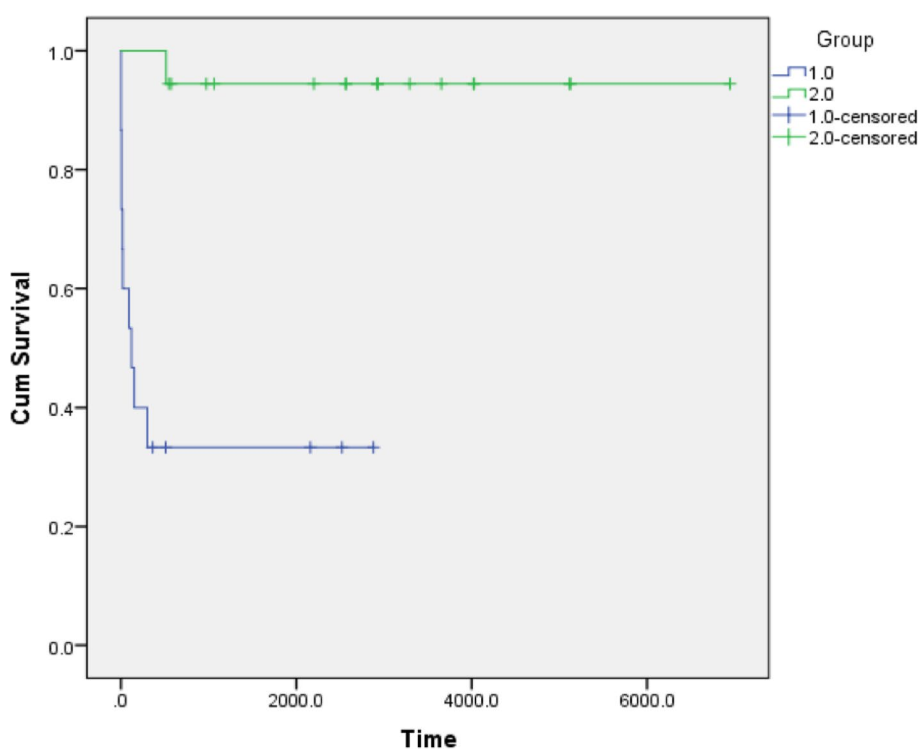

Fig. 2 Cumulative survival plots for hepatoblastoma

only be performed in high volume centres and generally by surgeons appropriately trained in these techniques. This is logical given the complexity of such surgery and the potential for morbidity, effect on quality of life and overall survival. However, while this concept of centralisation for rare conditions or specialised surgery is for the most part accepted in adult surgical practice, it may not always be a good fit for specific paediatric surgical conditions [6]. Examples of this include rare neonatal congenital anomalies such as oesophageal atresia-fistula where a single surgeon may repair only one or two each year and yet most paediatric surgical centres will undertake this surgery [7]. By contrast, conditions such as bladder extrophy, biliary atresia, oesophageal replacement and the surgery of complex solid tumours (including liver tumours) are generally regarded as outside the "comfort zone" or skill set of most paediatric surgeons. For these patients, referral to a super-specialist quaternary centre is the norm [8]. This makes overall sense as it is not just the surgery that matters but the multidisciplinary team infrastructure that is key to better outcomes. These vital services include, paediatric intensive care, skilled anaesthesia, medical (paediatric) oncology and the myriad other resources that can be needed for challenging cases. Critical mass may equally influence a centre's outcome but the argument is not always so simple or practical for all patients and families. Overseas referral to super-specialist centres may not always be feasible for a variety of reasons, including financial, social and cultural displacement of families which may direct that care be delivered "closer' to home, albeit, in low volume centres. In these situations, it is important that outcome metrics of small volume centres are regularly audited and referenced against an international benchmark.

The standard measurable outcomes reported for liver resectional surgery in both adults and children are mortality and morbidity. Significant immediate and short-term mortality rates have been reported and may be as high as 40% but more recent studies have reported an overall operative mortality as low as 3% [9]. In our series, 57% (12/21) of group 1 patients died within 1 year of follow-up and of these 6 patients had died by 1 month and a further 6 by 1 year. Progressive disease is the commonest cause of death in most series but in group 1 of this series, 5 (24%) patients died as a result of surgical issues while 3 succumbed to progressive local disease. Specific information is lacking as to the precise cause of death in group 1 patients but in 5 patients this was the result of haemorrhage and cardiac arrest, and in 1 patient, death was secondary to pneumonia 3 weeks after surgery. Three patients suffered progressive disease and the remaining 7 relapsed. Mortality in group 2 patients was 9% (3/33) and was due to progressive disease (1 patient with unresponsive HCC, 1 with progressive HBL and 1 with metastatic NBL), between 6 and 24 months. There were no deaths due to surgical complications.

Significant morbidity was noted in group 1, 66% (14/21), but was unusual in group 2, 9% (2/33). While morbidity is an important outcome measure and contributes not only to quality of life, it can also impact on survival. No specific information is available from group 1 about the severity of complications and their impact on survival but complications such as intra-abdominal abscess, biliary fistula and jaundice, coagulopathy could well decrease survival or at least interfere with the delivery of adjuvant therapy. The relationship between survival and morbidity is not always well developed in the literature and few studies have reviewed morbidity as a separate entity even though reported rates are as high as 39% [10].

In a review of 53 centres from the USA, Zwintscher et al. reported that the frequency of hepatectomy varied from 1 to 5 per year/centre (including patients up to 20 years old). While they concluded that this surgery could be performed safely in low volume centres they suggested that complex surgery could be referred to high volume centres. However, even in high volume centres, morbidity was significantly higher at 30% overall (39 of 126 patients) and four-fold higher than in low volume centres. High volume centres (defined as greater than 5 cases per year) had no mortality compared with 3.7% in low volume centres [11]. The authors suggest that this may reflect referral of more complex cases to the high volume centres. Although the study does not present detail of patients who underwent primary or rescue liver transplantation, a key recommendation is the ready availability of a transplant service. This seems especially relevant if extended hepatectomies are routinely performed. An extended hepatectomy was performed in 8 patients in group 2 but none required a rescue transplantation. Nine patients in group 1 underwent an extended hepatectomy but no information is available on whether or not an emergency OLTx would have been indicated (if available at that time). In this current study such a relationship and advice was readily available for all group 2 patients, if needed.

It is generally accepted that the treatment of rare and difficult to treat, paediatric surgical conditions should be centralised in specialised centres or quaternary hospitals. Concepts of critical mass and focused resources underscore this concept and are widely accepted in developed countries. However, considerations of available expertise, disruption to family, cultural issues and the financial cost of international referral, are variables that should also form part of the overall discussion. If complex paediatric liver surgery is to be performed in a setting of relatively low case volume, it is essential that outcome measures are on a par with international standards. This study has shown that it is possible to achieve this but also, that this outcome is possible only when all necessary resources and expertise are readily available. These resources have been presented above but the availability of a trained hepatobiliary/oncology surgeon and an oncology service is key to reduce morbidity and achieve excellent survival. Institutions who facilitate this service must ensure that all aspects of such care are in place and that there is easy access to, and communication with, a paediatric liver transplant centre as is necessary for unresectable tumours and the rarely needed, emergency transplantation.

Summary and conclusions

This study was undertaken to critically report the outcome metrics of all paediatric patients with a liver tumour (primary or infiltrating) and who underwent resectional liver surgery in a single, National Referral Oncology Centre in Dublin, Ireland over a 47-year period. An earlier published report from our institution has illustrated the many significant difficulties encountered treating children with liver tumours during that past era not only in Ireland but in many other centres worldwide at that time [3, 12, 13]. Marked differences in survival and reduction in morbidity were observed in group 2 patients as compared to group 1 and reflect advances in medical oncology, MDT tumour board discussions, standardised neoadjuvant chemotherapy, skilled anaesthesia, intensive care support and hepatobiliary surgery. Crucial to these improved outcomes was the recruitment of surgical personnel skilled and trained in oncology and hepatobiliary disease.

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Author's contributions
MC and HZ conceptualised and designed the study, with MC playing a role as the main surgeon of the participants. Literature review, the consolidation of references and the manuscript write-up were performed by MC and HZ. AA, HS and AM conducted patient review, medical follow-ups and performed the data collection. As for the "Result" section, MC carried out the statistical construction, and was assisted by HS and AM regarding the chart review. Multiple re-writes, as well as editorial and manuscript advice were offered by HZ and NH.

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Availability of data and materials
All the data will be available upon request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained by the research and ethics committee of Our Lady's Children's Hospital Crumlin. Consent was obtained from all participants agreeing their data to be used in research, their information is anonymised and this is a retrospective review.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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