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## 2.1 Introduction

Liver Tumors in children encompass a wide spectrum of entities ranging from benign to semimalignant to malignant (see Chaps. 8 and 14).

Each entity would tend to have its own historical (especially treatment related) perspective and thus make an overview unnecessarily complicated.

So in this chapter, we intend to focus mainly on the two clearly defined malignant tumors. Hepatoblastoma is the most common and relevant in childhood. The other, namely hepatocellular carcinoma has many similarities to the adult variety, though, not in all aspects (especially not the same etiology).

The most dramatic improvement in outcome has occurred in hepatoblastoma since the introduction and use of chemotherapy in the late 1970s. Thus, one can think of and divide the history of progress into three distinct eras.

1. The “dark ages” pre systematic surgery – from the “beginning” to the 1940s
2. The “industrial revolution” in surgery and their pioneers – 1940s to 1970s, predominantly adult surgeons
3. The “enlightenment” – introduction of chemotherapy and collaboration of specialties – from the 1970s onward.

*Neither the terms used nor the dates need to be taken too literally or strictly as the cut offs are not necessarily so sharp.*

We shall try to follow this outline throughout and add some thoughts about the future.

Naturally, the last period is of the most topical interest and actually having lived through and taken part in it, could be biased, but is the most detailed and hopefully informative one.

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In Hepatocellular Carcinoma, the improvements have been mainly due to better and safer surgical techniques based on more accurate anatomical knowledge but far less spectacular (Czauderna et al. 2002). The pioneers in all these fields clearly need to be mentioned in a historical review.

The same applies to a much better and still ongoing refinement of the pathology and the authors of early texts devoted entirely to pediatric tumors deserve the same attention.

Equal merit also goes to the development of national and international cooperative and multidisciplinary groups. (see Sect. 2.8) Collaboration is the key word to the successful management of liver tumors in children.

## 2.2 The Dark Ages

In this protracted period over many centuries, children were hardly considered to be part of society with little attention being given to their plight and especially their diseases. It is therefore not surprising that it is hard to find any reference of their role in medical literature, even in the extensive, early, mostly encyclopedic German literature of the late eighteenth century. Tumors of any organ including liver were recorded as curiosities due to all sorts of mystical or religious causes with corresponding treatments, e.g., exorcism, counteracting bad vapors. Surgery was the realm of barber surgeons who performed dramatic “primitive live” surgery often as a spectacle for curious onlookers.

The advent of printing made it possible to publish extensive illustrated treatises on these curious procedures. (see Sect. 2.3)

An exception to these aberrations is possibly the somewhat more rational approach of some of the early medieval Arab thinkers and also Maimonides (1,135–1,204).

A light in this period was to come from the early “foundling” hospitals and their enlightened benefactors, later to become the first children’s hospitals. (see Sect. 2.4)

## 2.3 Advent of Printing

Histoire de la Médecine et du Livre Médical (1978)  
Paule Dumaitre, Editions Pygmalion, Olivier Perrin.

## 2.4 Early Children’s Hospital

Some selected ones are:

The Great Ormond Street Hospital for Sick Children founded in 1852 by Dr. Charles West, associated with the Peter Pan Foundation and the Coram Trust

Hôpital des Enfants Malades Paris 1802

Anna Kinderpital Vienna 1850

Kinderspital Bern 1862

Pediatric ward in Charité Hospital Berlin 1829

Bambino Gesù Rome 1869

The Children’s Hospital of Philadelphia founded in 1855

The Chicago Hospital for Women and Children 1865

The Boston Children’s Hospital 1869

New York Babies and Children’s Hospital 1887

Alder Hey Children’s Hospital Liverpool 1914.

Kings College Hospital London 1913 has a special hepatology unit and transplant center for children.

None, because of their early founding times, initially specialized in the treatment of liver tumors in children, but it is worthwhile mentioning that later on, many of them developed such services or units that were often associated with distinguished pioneering personalities in relevant specialties (often pediatric surgery or pathology). In order to avoid repetition, these are mentioned under other appropriate headings.

Rare hospitals treating only cancer, e.g., Sloan Kettering Memorial Hospital, New York 1884 (founded as the New York Cancer Hospital), The Royal Marsden Hospital London 1851 (founded as The Cancer Hospital) with a Pediatric Branch in Sutton 1962, Institute Gustav-Roussy 1913 (as a development of the Hospice Paul Brousse Paris), and the A.C. Camargo Cancer Hospital Sao Paulo 1934 (as a development from the Antonio Prudente Foundation) did and do have special units for pediatric oncology and surgery.

St Jude’s Childrens Hospital 1962 (initially funded by the Danny Thomas Lebanese Foundation) is the only one known to me as treating solely children with cancer.

Incidentally, Odile Schweisguth, the founding mother of SIOP started a 16 bed pediatric oncology service in 1952 in Paris (Coppes-Zantinga et al. 2000; Schaison and Sommelet 1995).

It goes without saying that this cannot be an exhaustive list, but hopefully a balanced, though personal, selection between various countries and personalities.

## 2.5 Pioneer Pathologists and/or Their Textbooks

One of the first of modern pathologists to devote himself to write a monograph on children's tumors was Willis (1962).

He clearly made the distinction between the embryonal type and carcinoma. Interestingly enough, he mentions the occasional difficulty in making a distinction between the two showing the insight and predating the recently described "transitional type" (Prokurat et al. 2002). Other pioneers are E. Potter (Wiedermann 1994) and J. Keeling (Keeling 1960). Both concentrated on the pathology of the fetus and newborn in their texts, but the latter's particular interest in liver is shown in an article published in 1960 (Keeling 1971).

Another pathologist with foresight was HB Marsden who established the first population-based tumor registry in Manchester and wrote a text on children's tumors (Marsden and Steward 1976). Incidentally, the founder of modern chemotherapy, Sydney Farber was also a pathologist.

The still most widely used classifications of pediatric liver tumors are by Ishak and Glunz (1967), Kasai and Watanabe (1970) and L Dehner Gonzales Crussi. An updated and more unified and internationally accepted system including genetic profiling is necessary.

## 2.6 Pioneers in Surgical Anatomy and Liver Surgery

The techniques of liver surgery are not essentially different in adults and children, and since adult disease is far more common, it is not surprising that "adult" surgeons have taken the lead in these developments, but later on, Pediatric Surgeons, especially in the above-mentioned Children's Hospitals, have also performed liver surgery.

Early reports on liver resections in children are by Howat (1971). Of the 14 malignant ones (out of a total of 19) only 3 survived. Operative mortality due to hemorrhage was 31%. However, in another series by (Price et al. 1982) in a series of 11 resections (6 with hepatoblastoma) in children aged 7 days to 14 years, there were no operative deaths but for 1 tumor-related one at 8 months.

The main risks, as seen above (morbidity, mortality), of liver surgery in the early years, i.e., before an accurate description of the segmental vascular and biliary

anatomy, as described by Couinaud in 1954 (Couinaud 1954, 1957) were bleeding and biliary fistula. A resection mortality of over 10% was described by Exelby 1971/1974 (Exelby et al. 1971, 1975). Various procedures were used to try and reduce and minimize these, e.g., the Pringle maneuver (Pringle 1908) (clamping of the afferent hepatic vascular pedicle); total vascular occlusion (clamping of the aorta and balloon occlusion of the inferior vena cava with +/- hypothermia (Fortner)/(Fortner et al. 1974); preresection ligation of the hepatic artery portal vein and/or hepatic veins; hypotensive anesthesia. Various techniques for dividing the liver parenchyma to reduce hemorrhage were devised, e.g., "finger fracture," water jet, or ultrasound dissection – CUSA.

But as mentioned above, most of the credit must still go to Couinaud for his ground breaking description of the classical eight segments (sectors) now universally accepted as the gold standard in liver surgery (Couinaud 1954, 1957). Before that, the terminology in hepatic resection was confusing and misleading being based on the anatomical right and left lobes and the umbilical fissure which however do not correspond to the vascular supply and biliary architecture. In recent years, the mortality and morbidity in specialized liver centers and by liver surgeons is well below 5%.

An exhaustive historical review of all these issues is given by Fortner and Blumgardt (2001).

## 2.7 Liver Transplantation

Liver and other organ transplantation came into their own after the basic research on rejection and its prevention by immunosuppression, was originally done by R. Calne. In children there remained two barriers for a wider use: Organ shortage and the presumed lifelong immunosuppression thought to be necessary. When these were solved, especially with the introduction of the living donor and split liver techniques, overcoming some of the moral dilemmas due to organ scarcity, liver transplantation became more and more important and amenable to children for cure and survival, in HB (basically as an extension of total resection) (Finegold et al. 2008; Otte et al. 2004). All these are rather recent developments and have little place in a historical review, so the details are better left to others (Chap. 10).

## 2.8 International Oncology Groups

### 2.8.1 COG

At the outset in North America, there were a number of interrelated institutions treating only leukemia. An NCI panel was responsible for promoting their integration into a more structured entity with L. Murphy as chair in 1958: CALGB (Cancer and Leukemia Group B) and SWOG (South West Oncology Group). Eventually, solid tumors were also included; CCG (Children's Cancer Group) was established in 1968 chaired by D. Hammond and POG (Pediatric Oncology Group) was founded in 1980 by Theresa Vietti and J. Ternberg by merging CALGB and SWOG. The CCG had special tumor-related groups earlier, namely the NWTs (National Wilms' Tumor Study, chaired by G. D'Angio and H. Wolff) and IRS (Intergroup Rhabdomyosarcoma Study, chaired by H. Maurer). At the same time in 1972, the first cooperative study of combination treatment of liver tumors in children was embarked upon.

In 2000, all these amalgamated to become COG (Children's Oncology Group) under one chair (G. Reaman). COG has a liver subcommittee chaired by M. Malogolowkin followed by R. Myers. Representatives of this group participate actively in all other international liver groups "to come and work together" for exchange of information and plan future generation studies.

Although, strictly speaking, initially, all the above were national American societies, other countries could also become associate members – the beginning of international cooperation (O'Leary et al. 2008).

*(This is an attempt to give a simplified version of a complicated summary of the early formation years which may not be as accurate as the founders would wish.)*

### 2.8.2 SIOP

In Europe, SIOP (Société Internationale d'Oncologie Pédiatrique) was officially founded in 1969 by Odile Schweisguth from Paris (hence the French name) after, a group of pediatric oncologists met in Madrid (1967) initiated by J. Monoreo and recognizing the need for a special international pediatric cancer organization in

Europe also. From this first group, all of them became the founding members. The society has prospered and had some years ago, over 1,000 members. It meets annually alternating between a European and one of the other member countries.

Under the umbrella of SIOP, newer entities and committees were formed (1987), these being SIOPEL, and IPSO, SIOP Asia (including China/Japan/India/Africa/Australasia), and PODC (Pediatric Oncology in Developing Countries).

In their individual ways all of them especially SIOPEL, have made significant contributions nationally and internationally to the management of liver tumors.

### 2.8.3 SIOPEL (SIOP Epithelial Liver Tumors)

1987 – Jerusalem. A preliminary gathering by a small band of oncologists interested in forming a future cooperative liver tumor study group and attending the annual SIOP meeting was convened by J. Plaschkes and J. Pritchard. A short questionnaire was designed and distributed to find out if there was enough common ground and the possible number of patients who could be recruited to take part a trial.

1988 – There followed three informal meetings with most of the original "working party" members and countries represented previously: In London (GOS), Paris (I Gustav Roussy), and Trondheim (Annual SIOP meeting). A caretaker core committee chaired by J. Plaschkes and a protocol writing committee were formed.

1989 – The first "official" formal meeting was held in Padua where the details such as the administrative structure, and other committee members were finalized. Consensus on a study strategy (preoperative chemotherapy and pretext staging) (Roebuck et al. 2007) was reached.

A draft treatment protocol (six pages!!) was written and sent to the SIOP scientific committee as well as to most national pediatric oncology societies by J. Plaschkes (with approval of the writing committee) for evaluation.

Application for Funds was made to the Swiss Cancer League for a workshop/symposium in Bern and for the first trial office YRGO (Yorkshire Regional Cancer Office) in Leeds.

The approved protocol was activated in July 1989.

1990 – A full 2 day international Liver Study Symposium was held in Bern (Plaschkes 2001). A Newsletter (L. Shafford) and Budget were presented for the first time. Previous to and after this international workshop, others, under the acronym CELTIC (Common Epithelial Liver Tumors International Criteria), were held in 1990 in London (St. Bartholomew's Hospital hosted by J. Kingston), in 1991 in Athens (hosted by H. Kosmides), and in 1992 in Hannover (hosted by D. von Schweinitz), to try and standardize definitions and mostly sponsored by the local hosts and J. Pritchard.

After all these initial activities, regular biannual SIOPEL meetings in a European host country as well as the annual SIOP meetings followed.

What followed is not history anymore.

### 2.8.4 IPSO

The “International Society of Pediatric Surgical Oncology” originally brought together, in 1989, the small band of pediatric surgeons committed to oncology by J. Plaschkes and D. Hays at the Prague SIOP meeting hosted by J. Snadjauf, where, aptly, the main topic was surgery. Eventually, these preparatory contacts led to the formation of IPSO, officially founded in 1991 in Rhodes with a constitution written by Antonio Gentil-Martins and J. Plaschkes elected as first president. The society runs a rare tumor registry and has a discussion forum for difficult cases. The president and another representative each have a seat on the scientific committee of SIOP. The main annual meetings are held at the SIOP meetings but other ad hoc ones have also taken place.

Their regular meetings have enhanced the surgical inputs and answered questions raised in clinical trials.

### 2.8.5 SIOP ASIA

It was formed to encompass and include not only the original European founder countries, but also continental Chapters with their own presidents and representatives in all annual meetings. Regular separate meetings are also held in these continents sponsored by SIOP mainly for educational purposes.

### 2.8.6 PODC (Pediatric Oncology in Developing Countries)

Similarly, to bring in an even wider membership and assist these countries in developing their own oncology services, the Pediatric Oncology in Developing Countries committee was formed in 1996 and regularly sponsors scholarships “for individuals to attend SIOP meetings.”

The PODC committee of SIOP (HP Wagner) and its activities also contribute greatly to further the aims mentioned below.

### 2.8.7 EONS (European Oncology Nursing Specialists)

One must also not forget to mention the nurses (mostly fully integrated into the European Oncology Nursing Specialists societies) whose care and knowledge are important in maintaining the high safety standards required for the often elaborate chemotherapy regimes.

## 2.9 National Pediatric Oncology Societies

UK (UKCCSG) later (CRUK) 1977 (Hammond 2003)  
 France (SFOP) (Schaison and Sommelet 1995)  
 Germany (GPOH) (1991). Formed by the fusion of GPO (1993) with DAL (German working party for Leukemia) (Hertl 1995)  
 Austria 1974 (Gadner 1992)  
 Italy (AIEOP) 1974  
 Switzerland (SPOG) (1964) (Wagner 1994)  
 Australia/New Zealand (ANZHOG) (1986)  
 Latin America (SLAOP) (1979)  
 Japan (1950) (Evans et al. 1973; Bessho and Kobayashi 1993)  
 America (ASPHO)/COG (see Sect. 2.8.1)

One of the principal aims and efforts of these societies was to enroll sufficient numbers of patients to enable clinical trials to be conducted scientifically with sufficient statistical power. (Most have organ-related studies and trials.) Obviously, because of the relative rarity of pediatric malignancies (even more so, liver tumors) sufficient numbers of children can be enrolled only by national and international cooperation.



## 2.10 Clinical Liver Trials

Since the introduction of antineoplastic therapy by Sydney Farber in 1948 (Farber et al. 1948) for leukemia, chemotherapy has taken on an increasingly important role for solid tumors in children.

Liver tumors, in particular hepatoblastoma, was, because of its relative rarity, one of the last of the specific pediatric ones to be investigated in prospective clinical trials.

Incidentally, hepatocellular carcinoma, although inherently of a very different nature and being even more rare, was, for practical reasons, also subjected to the same treatment as HB in most studies.

At the outset, the strategy and staging systems chosen by SIOPEL were different from that in the United States. In the USA, traditionally, primary surgery, wherever possible, was the initial step, whereas in SIOPEL preoperative (neoadjuvant) chemotherapy was the rule. (It was chosen for the simple reason that if the tumor became smaller difficult liver surgery would be safer.) This is not the place to repeat or mention all other advantages and even possible disadvantages for this choice.

Some other countries chose their own individual ways, i.e., Germany followed the USA example, whereas Japan mostly preferred preoperative chemotherapy.

Because the overall results of the different strategies were, broadly speaking, similar, each group has continued to adhere to its own original concept. It must however also be said that the chemotherapy agents used were and are quite substantially different as well.

In addition, the various staging systems used can make comparisons questionable and replete with pitfalls.

For that reason, SIOPEL introduced its own system (PRETEXT) specially designed and conceived to reflect the surgical anatomy of the liver (complete surgical resection still being the most important prognostic factor). This system is now being used by all in conjunction with the others, i.e., the classical Stage I–IV, allowing direct comparison of outcomes.

Below is a concise list of most of the past trials and their results (Tables 2.1–2.4)

## 2.11 Conclusions and Future Outlook

Unless and until a “magic bullet” is discovered or some treatable genetic profile can be identified and screened for, it seems likely that surgical resection will still remain an integral treatment option in the near future. Since the dawn of effective chemotherapy, the demise of surgery has often been predicted, but so far, this has not happened. Laparoscopic and Robot and computer-assisted surgery from “afar” will, theoretically, make specialized surgery available to all (Koffron et al. 2006).

Scientific international multidisciplinary trials with their logical stepwise improvements will probably, for some time, remain the aim and gold standard, but some serendipitous unexpected discovery (as in many medical instances, see Cisplatinum) (Rosenberg et al. 1965; Rosenberg et al. 1969) cannot be discarded either.

Because of the ever increasing stratification and differentiation of risk groups, both histologically and genetically, “personalized” treatment will become the rule. For that reason, with the smaller study cohorts, international cooperation will be even more essential to be able to fulfill valid statistical criteria. The large populations in India, China, and other developing countries (see PODC above) will all play an increasingly important role in enhancing future developments more rapidly. They will and can initiate their own trials and still be able to participate in the already established ones.

HCC prevention by hepatitis B immunization will substantially reduce the incidence.

Although trying to end on an optimistic note, one cannot fail to mention that the increasing burden of national and international administrative regulations and directives will severely hamper the possibility of international cooperation, and delay, if not make impossible, the development of scientific trials especially in very rare pediatric liver tumors. Future historical reviews will give us an answer to this prediction.

**Table 2.1** Pediatric liver trials, North America

Study	Chemotherapy	Number of patients	Outcome	Author
CCG 862/SWOG 7.695 1976–1978	VCR + CPM + DOXO alternating with VCR + CPM + 5FU	61 patients All liver tumors	3 year OS Group I - 94% Group II - 57% Group III - 20% Group IV - 14%	Evans [49s]
CCG 823F 1986–1991	CDDP + DOXO	33 patients All liver tumors	2 year OS Stage II - 86% Stage III - 58% Stage IV - 32%	Ortega et al. (2000)
POG 8.697 1986–1989	C5V	60 patients Hepatoblastoma	4 year OS Stage I/PPFH - 100% (surgery only) Stage I/II - 90% Stage III - 67% Stage IV (8 pts) - 12%	Douglass et al. (1991)
INT-0098 (CCG-8.881/ POG-8.945) 1989–1992	C5V vs. CDDP + DOXO	Stage I/II: 50 patients Stage III: 83 patients Stage IV: 40 patients All liver tumors	4 year OS I/II = 100% versus 96% III = 68% versus 71% IV = 33% versus 42%	Ortega et al. (2000)
P9545 <sup>a</sup> 1993–1995	C5V vs. CDDP + CARBO	Stage I PPH: 17 patients Stage III: 38 patients Stage IV: 50 patients Hepatoblastoma	3 year OS Stage I PPH: 100% Stage III/IV: 74% versus 56%	Malogolowkin et al. (2008)
COG-P9645 1999–2003 <b>Preliminary results</b>	Stage I/PPFH surgery only Stage I/II randomized to C5V + -amifostine; Stage III/IV randomized CDDP + CARBO versus C5V +/- Amifostine	270 patients Hepatoblastoma	Stage I/PPFH (n 16) Stage I/II +/- Ami Stage III OS 4 year Stage III/IV CC (n 56) EFS 3 year C5V(n53) EFS 3 year Stage IV (n10) OS 4 year 100% 96% 88% 38% 60% 67%	Malogolowkin et al. (2008)

Abbreviations: VCR: vincristine; CPM: Cyclophosphamide; DOXO: doxorubicin; 5FU: fluorouracil; CDDP: cisplatin; C5V: cisplatin, fluorouracil and vincristine; CARBO: carboplatin; OS: overall survival.

<sup>a</sup> Final study analysis is still pending.

**Table 2.2** Germany

Study	Strategy	Number of patients	Chemotherapy	Stage	Outcome	References
CGPOH-HB89 1988–1993	Primary surgery	72	Ifosfamide Cisplatin Doxorubicin	I II III IV	DFS 75% median FU 64 month 100% 50% 71% 29%	Von Schweinitz et al. (1997)
CGPOH-HB94 1994–99	Primary surgery	48	Ifosfamide Cisplatin Doxorubicin	Standard risk	OS Median FU 58 months 77%	Fuchs et al. (2002)
		18	Etoposide Carboplatin	Advanced or recurrent		Fuchs et al. (1999)
HB99 1999–2008	Mixed		IPA/ Carboplatin- VP16		Preliminary results only	Häberle et al. (2003)

**Table 2.3** JAPAN

Study	Strategy	Number of patients	Chemotherapy	Stage	Outcome	References
JPLT-1 1991–1999	Mixed PRETEXT	145 HB	Cisplatin THP Adriamycin <sup>a</sup>	I II IIIA IIIB IV	3/6 year OS 77.8%/73.4% 100%/100% 100%/95.7% 76.6%/73.8% 50.3%/50.3% 64.8%/38.9%	Sasaki et al. (2002)
JPLT-2 1999–2004	All preop done except PRETEXT 1	144 HB	PRETEXT 1 PRETEXT 2 PRETEXT 3	I II III IV	3 year OS 100% 88% 68% 42%	Preliminary results

<sup>a</sup> Japanese Adriamycin THP=Tetrahydropyranil



**Table 2.4** SIOPEL

Study	Strategy	Number of patients	Chemotherapy	Stage	Outcome	References
SIOPEL 1 1990–94	Primary Chemotherapy <sup>a</sup>	154	Cisplatin Doxorubicin	I II III IV and metastases	3 year OS 79% 3 year EFS 67% 3 year EFS by PRETEXT 100% 83% 59% 44% 28%	Pritchard et al. (2000)
SIOPEL 2 1995–98	Primary Chemotherapy	Standard risk 77 High risk 58	Cisplatin Alternating Cisplatin, Carboplatin/Doxorubicin		3 year OS 91% PFS 89% 3 year OS 53% PFS 48%	Perilongo et al. (2004)
SIOPEL 3 Standard Risk (SR) 1998–2006	Primary Chemotherapy Randomized SR versus HR	SR126:HR129	CDDP vs. CDDP + DOXO	All Stages	3 year EFS/OS CDDP 83%:85% CDDP + DOXO 89%:93%	Perilongo et al. (2009)
SIOPEL 3 High risk (HR) 1989–2004	Primary Chemotherapy	151	Alternating CDDP + Carbo- platin + DOXO	All Stages	3 year EFS/OS 65%:69%	Zsiros et al. (2010)

<sup>a</sup> PRETEXT I were eligible for primary surgery

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