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New techniques in liver surgery

by

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List of articles

The thesis is based on the following papers, which will be referred to by their Roman numerals.

- I.** Ulf Jersenius, Fredrik Granath, Dag Arvidsson, Paul Blomqvist.
Liver Operations in Sweden in 1987-99.
Scandinavian Journal of Surgery 2005;94:25-30. *Reprinted with permission from The Finnish Surgical Society.*
- II.** Ulf Jersenius, Dag Arvidsson, Johan Lindholm, Seppo Anttila, Anders Elvin.
Radio-Frequency Ablation in the liver close to the bile ducts. Can intraductal cooling offer protection? *Surgical Endoscopy* 2005;19(4):546-50. *Reprinted with permission from Springer-Verlag.*
- III.** Ulf Jersenius, Diddi Fors, Sten Rubertsson, Dag Arvidsson.
The effects of experimental venous carbon dioxide embolisation on hemodynamic and respiratory variables. Accepted for publication in *Acta Anaesthesiologica Scandinavica*. *Reprinted with permission from Blackwell Publishing.*
- IV.** Ulf Jersenius, Diddi Fors, Sten Rubertsson, Dag Arvidsson.
Laparoscopic parenchymal division of the liver in pig. Comparing efficacy and safety of three different techniques. *Submitted.*

Abstract

The development of liver surgery has a long history and through the years, much knowledge has been gathered concerning various aspects of the liver. The exploration and understanding of liver anatomy and liver regeneration and development of surgical techniques are important landmarks. Liver surgery today is a demanding field in which accumulated knowledge has fused with modern perioperative care to the benefit of the patients. In recent years simultaneous developments in radiological liver imaging, chemotherapeutic regimens and ablative treatment options further increased our ability to treat patients with liver disease. Liver surgery is the only treatment that can offer the patients long term survival or cure from malignant liver disease, but new treatment options are being developed and introduced in the clinic. To ensure patient safety these techniques have to be experimentally evaluated. Two rapidly expanding techniques are Radio Frequency Ablation and laparoscopic liver surgery.

The aim of this study was to evaluate recognised risks during Radio Frequency Ablation (bile duct injury caused by heat), and laparoscopic liver surgery (carbon dioxide emboli).

To give an overview of liver surgery in Sweden, Paper I is a registry study where liver surgery in Sweden recent years is described. All patients operated by liver resection in Sweden during 1987-1999 were included from the Inpatient Registry. Additional data were collected from the Swedish Cancer Registry and the Cause of Death Registry. Analyses of the patients, indications, mortality and causes of death are presented. In Sweden, 21 persons per million and year have been operated on and the patient selection criteria have probably been strict. Paper II is an animal experimental study evaluating a new technique for bile duct protection during Radio Frequency Ablation. With this technique, called intraductal cooling, cooled saline is infused in the bile ducts and supposedly protects them from heat injury. A protective effect was not proved in this study but the technique has been tested in patients with promising results, and it may need to be evaluated further. Importantly, we observed no negative effect of the cooling procedure on the ability of the Radio Frequency Ablation procedure to create the desired heat necrosis in the target tissue. Paper III and IV are animal experimental studies and focus on laparoscopic liver surgery. During pneumoperitoneum with carbon dioxide and liver parenchymal transection, embolisation to the pulmonary circulation is a recognised risk. Emboli may theoretically increase the morbidity among the patients. In paper III we have demonstrated changes in cardiopulmonary circulation persisting for hours after an experimental embolisation, an observation not earlier reported. In Paper IV we found differences in the risk of such emboli when different devices were used during laparoscopic parenchymal liver transection in pig. Influence on blood gases was apparent and indicates negative influence on the pulmonary gas exchange. The findings in Paper III and IV have clinical implications and have to be further evaluated.

In conclusion, we have pointed out that liver surgery is relatively infrequent in Sweden and that future expansion is probably. The new techniques we evaluated are feasible but have recognised risks, confirmed and further described in this study. As we maximise the potential of the techniques, patient safety must have the highest priority.

Abbreviations

CCC:	Cholangiocellular cancer
CO:	Cardiac output
CO ₂ :	Carbon dioxide
CRM:	Colorectal metastases
ETCO ₂ :	End-tidal carbon dioxide
HBV:	Hepatitis B virus
HCC:	Hepatocellular cancer
HCV:	Hepatitis C virus
HR:	Heart rate
IDC:	Intraductal cooling
LLS:	Laparoscopic liver surgery
MAP:	Arterial blood pressure
MPAP:	Pulmonary artery pressure
PaCO ₂ :	Arterial carbon dioxide tension
PaO ₂ :	Arterial oxygen tension
PCWP:	Pulmonary capillary wedge pressure
PIP:	Peak inspiratory pressure
PVE:	Portal vein embolisation
RFA:	Radio frequency ablation
T:	Temperature
TEE:	Transoesophageal echocardiography
V _d /V _t :	Physiologic dead space

Introduction

Surgery has traditionally been the only potentially curative treatment for primary and secondary liver cancer. These tumours have had a dismal prognosis and most patients are not eligible for surgical treatment. Hepatocellular cancer (HCC) and colorectal metastases (CRM) can be resected in approximately 20% of the patients [1, 2]. This rate is currently improving due to development not only of surgical techniques, but also of new techniques for pre-operative radiological staging, improved strategies for chemotherapeutical treatment and local ablation of malignant tumours. Also, progress in perioperative patient care has contributed. Compared to other highly lethal abdominal cancers, such as pancreatic and oesophageal cancers, the outcome after a resection for a liver malignancy is today relatively favourable. The five-year survival rate is higher than 30% after a resection for HCC [3, 4] or CRM [5, 6].

The surgical technique in liver surgery is challenging and the patients have a high proportion of co-morbidity. Liver resections generate a morbidity around 25% and mortality around 3-5% [7-10], demanding specially trained intensive care units for post-operative care. In the past, these circumstances probably limited the number of liver operations and also hampered the development of treatment for liver malignancies.

One of the most common malignancies worldwide is HCC. The dominant risk factor for HCC is viral hepatitis [11]. Hepatitis infection is a complex field for primary and secondary prevention and efforts have been initiated in different areas with vaccination programs for hepatitis B virus (HBV). Despite this, HBV infection is likely to continue for some time, and thus also HCC. Liver surgery will probably remain the main treatment option for HCC in the coming years.

The liver is a common organ of metastatic disease. The majority of patients with secondary liver malignancies suffer from metastases from colorectal cancer. The risk factors for colorectal cancer are genetic, dietary and other factors. Primary prevention of risk factors of colorectal cancer is unlikely to influence the incidence to any major degree [12]. Liver surgery, supported by chemotherapy in patients with metastatic disease, will probably remain the treatment of choice also in the near future.

With the development of living donor hepatectomy, liver transplantations are increasing in number and this will broaden the therapeutic possibilities for liver malignancies.

In addition, new therapies for local treatment of liver tumours, i.e. without necessitating resection not only of the tumour but also of adjacent healthy liver parenchyma, have been developed and introduced on patients. These techniques include tumour ablation with toxic agents, heating or cooling. These techniques have further improved the possibilities to treat patients with reduced liver function or diminished general health, with promising results.

In Sweden the traditional belief is that there is little to offer patients with liver malignancies. With an increasing awareness of the new possibilities in liver surgery the interest is escalating and demand for surgical treatment is likely to increase. In view of these observations it is important to improve the new treatment options and to take part in the development.

In this thesis we have focused on two new techniques in liver surgery, RFA and laparoscopic liver surgery. These techniques are in clinical use but complications are recognised. The studies in this thesis are aimed to shed light on the potential for these techniques in the field of liver

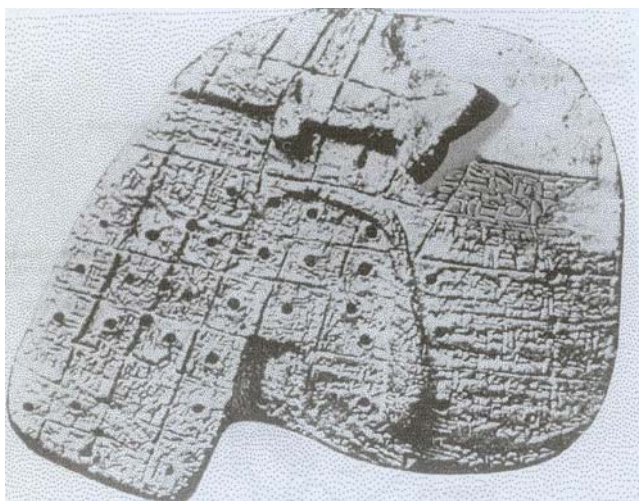
surgery and to increase the understanding of complications associated with the procedures, to secure patient safety.

Historical notes

It is challenging to perform a safe liver resection. The liver is pervaded by a network of arteries, veins and bile ducts and no bloodless planes exist. The liver consists of eight segments, each with a portion of the portal triad – an artery, a vein and a bile duct – branching out from the liver hilus.

The evolution of liver surgical knowledge can be divided in three different periods. First, from ancient times to the late 1800s liver anatomy was the major concern. Later on to the mid 1900s surgical considerations were at the forefront. Most recently, anatomic surgery has been the main focus of research, and it remains so today.

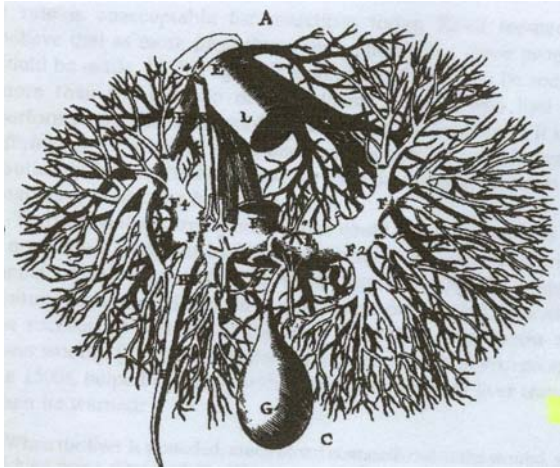
The liver has been considered to have particular significance in many historical cultures. In the Assyrian and Babylonian cultures in Mesopotamia, 2000-3000 BC, the liver was believed to be the organ of fate. The liver hosted spirits and was the seat of life force. The liver from sacrificed animals, usually sheep, was used for divination, hepatoscopy. Clay models of the normal animal liver were used for interpretation and teaching, **picture 1**.



Picture 1. Clay model of a sheep's liver (ca. 2000 BC).

Later, the Egyptians also considered the organ significant; they removed it and placed it in a container beside the embalmed Pharaoh. An interesting parallel to the ablative techniques used today is that that early Egyptians and Greeks used heat to cauterise ulcer and superficial neoplasm. The earliest recognisable description of the anatomy of the liver came from Alexandria, from Herophilus (334-280 BC) and Erasistratus (310-250 BC) who coined the term “parenchyma” (“to pour in beside”). Galen (ca.130-200 AD), a Greek who went to Rome to become the physician to the emperors, further described the liver anatomy and also referred to the work of Herophilus and Erasistratus. Galen suggested that the liver lobes spread out like the fingers of the hand, but did not specify the number of liver lobes. He also described the internal liver tissue and vasculature. His description of the liver dominated the medical literature until the fifteenth century. Leonardo da Vinci (1452-1519) later accurately illustrated the portal vein and intrahepatic venous system in several anatomic drawings.

During the Middle Ages further knowledge of the liver anatomy was obtained. At this time in Europe, the heart was considered the pre-eminent body organ and Harvey described the blood circulation in 1628. The place of the liver in his scheme is somewhat unclear. A colleague of his in England, Francis Glisson (1592-1656), described the intrahepatic vasculature. He also redescribed the vasculobiliary sheath first described by Johannis Walaeus in 1640. Glisson was credited with the discovery of the sheath and the Glissonian capsule is still referred to in modern liver surgery. The Glissonian capsule covers the portal triad and forms a natural border used for dissection when anatomical liver resections are performed. In modern times, Couinaud and others have emphasised the importance of this structure. Glisson was one of the first to describe the intrahepatic topography, **picture 2**.



Picture 2. *Intrahepatic vasculature as illustrated in Francis Glisson's Anatomia Hepatis (1654).*

Over the years surgeons performed and described many liver operations, mainly for wounds sustained in combat. The first successful liver resection is considered to have been performed by Carl Langenbuch in 1887 [13]. He removed a 370 g pedicled tumour from the liver of a 30 year old woman. To overcome the problems of uncontrolled bleeding J. Hogarth Pringle in 1908 reported how the inflow to the liver and excessive bleeding could be controlled by occluding the vessels in the extrahepatic portal triad with the fingers [14]. This method is still used to control vascular inflow during liver surgery and the eponym “Pringles Pinch” is still in use today. Walter Wendel reported in 1911 the first attempt at an anatomical liver resection, a right sided hemihepatectomy, respecting major intrahepatic vascular structures [15]. In 1952, Jean Louis Lortat-Jacob reported the first extended right hemihepatectomy, the most extensive liver resection up to that time [16]. A thoracoabdominal approach was then used for the first time. Thomas Starzl attempted in 1963 the first human liver transplantation [17]. The patient, a boy with biliary atresia, died during the operation of continuous haemorrhage. In 1968 Starzl reported a series of seven liver transplantations where all the patients

survived the operations [18]. One patient survived more than a year.

Many scientists have contributed to the development and refinement of the techniques for resectional liver surgery. In the search for the intrahepatic course and distribution of the arteries, veins and ducts, the Frenchman Claude Couinaud published



Picture 3. *Claude Couinaud.*

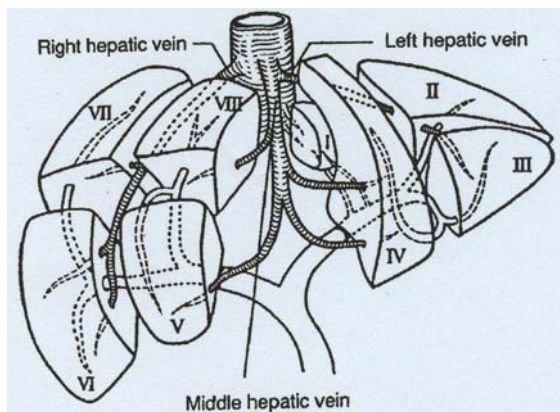
a report in 1954 [19], **picture 3**. He proposed that the liver could be divided into eight segments, each supported by an artery, a vein and a bile duct. Other classifications have been proposed but the Couinaud classification has since then been most extensively used when describing anatomical liver resections. Another controversial subject in liver surgery is techniques and instrumentation for liver transection. Several researchers have contributed. Ton That Tung applied the techniques of blunt anatomical resection with instruments or the fingers and described his controlled resection technique when dissecting anatomic planes [20]. The “finger fracture technique”, digitoclasia, was extensively used for safe dissection without rupturing the vascular structures. The rationale for this is that the portal structures offer greater resistance to pressure than the liver parenchyma. In this way the vascular structures could be identified and secured.

Thus, the surgical procedures used today are based on a long history of discoveries by scientists and surgeons based on understanding of the liver anatomy and haemorrhage control.

Anatomical implications for liver surgery

The increasing knowledge of hepatic anatomy and surgical techniques has led to a shift of hepatic surgery towards segment-oriented, or anatomical, resections [21, 22]. This technique involves the resection of isolated anatomic and functional units, segments. Segment-oriented resection allows maximal conservation of normal liver parenchyma. More patients can be offered surgical treatment and the operations are safer and cause less morbidity.

Liver resections can be divided into anatomical resections involving removal of one or more segments at the same time, and atypical or wedge resections when the segments are not respected. As described by Couinaud in 1957, the liver can functionally be divided in eight different parts called segments [23], **picture 4**.



Picture 4. *The segmental anatomy of the liver.*

Additional studies that helped pave the way for the acceptance of anatomical liver surgery are those by Ton That Tung, Hjortsjo, and Goldsmith and Woodburne [20, 24, 25].

The segments are distinguished based on the portal venous arrangements and the location of the three main hepatic veins. These veins divide the liver into four sectors, each receiving a portal pedicle. Each portal pedicle is further subdivided to define the eight functional units, segments. The middle hepatic vein divides the liver in a right and a left part. The middle hepatic vein is delineated on the liver surface of the main portal scissura. This scissura (Cantlie's line) runs from the centre of the gallbladder fossa and to the left of the inferior vena cava. The two functional hemilivers are separately supported by their portal supply, arterial supply and bile drainage. Each hemiliver is further subdivided into two different sectors by the left and the right hepatic veins. The left is found behind the ligamentum teres. The right is less well defined, but is approximated as including tissue from the anterior border at a point between the gallbladder fossa and the right angle of the liver to the confluence of the inferior vena cava and the right hepatic vein. Thus, the left hemiliver is divided in anterior and posterior sectors, the former including segments III, IV and the latter segment II. An exception is segment I, which has an independent blood supply, with separate connections to the portal or hepatic veins. The right hemiliver is divided in the anteriomedial and the posteriolateral sectors, including segments V, VIII and VI, VII, respectively.

Uni-, bi- and pluri-segmentectomies can be performed after a preoperative tumour staging. It is considered appropriate to resect up to six segments (approximately 80% of the liver) in one resection. Several approaches for anatomical resections have developed to divide the liver parenchyma, the pedicles and the veins. The vascular structures can be divided from outside the liver or within. These techniques are called extrahepatic, anterior or posterior intrahepatic approaches and will not be further discussed here.

The goal of a resection is to remove the entire tumour or all of the metastatic sites. A margin of one cm is preferred to obtain a R0 resection that leaves no malignant cells [26, 27], although use of a smaller margin may have only a minor impact on the overall survival [26, 28].

In order to minimise blood loss, intermittent vascular control is usually applied. For the same reason the central venous pressure is preferably maintained below 5 cm H₂O [29]. Also, the technique used for parenchymal transections is crucial to minimise blood loss and will be discussed later.

Liver tumours

Different malignant and benign tumours may develop in the liver. Liver resections necessitated by malignant disease are the most common and demanding operations in liver surgery. The most dramatic advances have been made in this field and the techniques evaluated in this study are mainly used for resection of malignancies. Therefore, benign disease is not further commented on.

Hepatocellular cancer

Hepatocellular cancer (HCC) is the most common malignant liver tumour and accounts for approximately 85% of all diagnosed primary liver tumours.

HCC is the sixth most common cancer tumour in the world and accounts for approximately 6% of all human cancer. More than 600,000 new cases are estimated per year [30]. Because of its high fatality rate, the incidence and mortality rates are almost equal. The incident cases of HCC diagnosed in Sweden are fewer than 400 per year [31]. HCC is irregularly distributed worldwide, following the geographical distribution of its recognised risk factors, mainly Hepatitis B virus (HBV) and Hepatitis C virus (HCV). For example, the incidence is very high in sub-

Saharan Africa, eastern and southeastern Asia. Other well established environmental risk factors for HCC, in addition to chronic infection with HBV or HCV, are dietary intake of aflatoxin B₁ or excessive alcohol consumption. Tobacco, endogenous and exogenous hormones and schistosomiasis are other factors considered to be carcinogenic [11]. Global patterns of HCC are changing [32, 33]. In some of the high risk HCC populations the incidence is decreasing while in some low risk populations the rates are increasing. In Sweden, the incidence decreased 1978-1992 and has been low and stable during recent years [34].

Migration of individuals between countries with different incidence of HBV infections and the clinical course of HCV infected individuals will probably influence the incidence markedly in the future. In Sweden, with a low incidence of HCC and a relatively high immigration rate, an increase in HBV-related HCC in the future is likely. In the United States the incidence of HCC is increasing [35]. The temporal changes in risk factors among the HCC patients in the United States remain unclear, but HCV infections acquired 2-4 decades ago explain at least half of the observed increase of HCC. Thus, an increase in HCV-related HCC is possible also in Sweden.

The demographics of patients with HCC varies globally [36]. Typically though, HCC is rarely diagnosed in patients younger than 40 years of age. The incidence increases thereafter progressively with age and peaks at approximately 80 years of age. In areas with a high incidence of HCC, the patients tend to be one to two decades younger when diagnosed [37]. An explanation for this is probably a HBV infection early in life. In areas where the incidence of HCC is low, HCV virus infections and alcoholic cirrhosis occur later in life and the HCC is diagnosed later. In general, men are affected two to four times more often than women. This ratio is

higher in areas with a high HCC incidence [30].

Chronic liver diseases are closely connected to HCC and more than 80% of the patients with HCC have cirrhosis. Chronic liver disease, regardless of aetiology, is characterised by varying degrees of inflammation and fibrosis, with cirrhosis being the most advanced stage of fibrosis. Approximately 5% of the world's population is chronically infected with HBV and this infection leading to cirrhosis remains the most important precancerous aetiological risk factor for HCC [38]. In a prospective cohort study including persons chronically infected with HBV, the relative risk (RR) for HCC mortality was 18.8 among men and 33.5 among women, respectively [39]. There is also considerable evidence for a causal link between chronic HCV infection and HCC [40]. For instance, in some high incidence HCC areas as many as 75% of the HCC patients have antibodies for HCV.

Clinical features of HCC are a right upper quadrant mass, a deterioration of the general health in a patient with cirrhosis. The disease is often asymptomatic and is first detected as a coincidental finding in conjunction with a radiological examination. HCC is thought to progress from adenomatous hyperplasia through atypical hyperplasia to early carcinoma [41]. Symptoms such as pain, pressure, fever, fatigue and loss of weight usually appear late in the course of tumour growth [42, 43]. The symptoms are usually not present until the tumour is 10 cm. Late symptoms are more severe pain and jaundice which could develop if the tumour is located close to the liver hilus. Paraneoplastic syndromes (hypoglycaemia, polycytemia, hypercalcaemia, hypercholesterolaemia) can occur with HCC [44]. The spread of HCC is primarily through the blood vessels. Metastases are usually found in local lymph nodes, the abdominal cavity and the lungs. Overgrowth to other organs may occur. The tumour grows typically in a form with central necrosis. Sometimes

the tumour is multifocal. Tumour thromboses are common in the portal vein, indicating a worse prognosis. An unusual complication is spontaneous rupture of the tumours with acute bleeding into the abdominal cavity [45].

HBV and HCV only exist in man and these infections are accessible for primary prevention. Studies from Taiwan, where HBV vaccination of newborns was introduced in 1984, have shown a 50% reduction in the incidence of HCC among adolescents [46]. Currently there is no vaccine for the prevention of HCV infections. This highlights the importance of screening of blood donors and efforts to reduce transmission among intravenous drug addicts.

Since HCC tends to occur more often in population with chronic hepatitis or cirrhosis, it is tempting to initiate screening programs to be able to detect small tumours and initiate therapy. Suggested diagnostic methods are periodic examination with ultrasound, computerised tomography and measurements of tumour related proteins such as α -fetoprotein. The effect on mortality and cost-effectiveness of such programs is currently not established.

Cholangiocellular cancer

Except for some very uncommon types of tumours, cholangiocellular cancer (CCC) accounts for almost all diagnosed primary liver cancer other than HCC, approximately 15% [47]. More than 90% of CCC is adenocarcinoma. Approximately 90% are located at the liver hilus (Klatskin tumours). CCC has a late clinical presentation. The presenting symptoms depend on the tumour location. Location in the bifurcation of the hepatic ducts or in the distal common bile duct usually causes symptoms secondary to biliary obstruction. Tumours arising in the liver tend to cause symptoms such as malaise, weight loss and abdominal pain. The incidence of intrahepatic CCC has increased and that of

extrahepatic CCC has decreased, the past few decades [48]. The number of CCC patients pales in comparison with the number of HCC patients and the aetiological factors for CCC have attracted less research attention. Known risk factors account for only a few cases of CCC, but the risk seems to be associated with chronic inflammation of the biliary epithelium. Primary sclerosing cholangitis is the commonest known factor predisposing for CCC in the western world. Two aetiological factors that are proposed to increase the numbers of patients with CCC and also influence the regional differences are liver fluke infection and intrahepatic gallstones [49, 50].

Metastases

Colorectal liver metastases

The most common metastases to the liver are metastases from colorectal cancer (CRM). The main reason for this is the direct drainage of the colon and upper rectum to the portal vein system. In the world about 800,000 new cases of colorectal cancer are diagnosed and 400,000 persons per year die of colorectal cancer [51]. In the western world it causes approximately 10% of cancer deaths [52]. In Sweden approximately 5500 new cases of colorectal cancer are diagnosed every year [31]. Approximately 50% of all patients with colorectal cancer develop CRM, 25% synchronous and 25% metachronous [6, 53, 54]. Thus, approximately 2750 new cases of CRM to the liver appear every year in Sweden.

In the light of new possibilities for treatment of primary and recurrent CRM, screening may be considered. A wide range of strategies have been suggested in the literature, and there is no consensus concerning follow up [55, 56]. When tumour markers (CEA and CA19-9) are elevated the patients are at high risk for recurrent disease. Abdominal ultrasound and CT scans of the liver to detect

metastases have been reported to have sensitivities of 35-48% and 70-80%, respectively [57, 58]. In Sweden, follow up most commonly includes repeated chest X-ray, measurement of CEA in blood and clinical examinations.

Neuroendocrine liver metastases

Carcinoid tumours account for about two thirds of all neuroendocrine tumour metastases to the liver. Most other tumour metastases are from islet cell neoplasms. Patients with metastases from neuroendocrine tumours are appropriate for palliative cyto-reductive surgery [59]. The rationale for this is the tumours' relatively slow growth, the ineffectiveness of chemotherapy and the need to reduce associated symptoms. For patients with unresectable tumours, hepatic artery embolisation or RFA are effective treatment options for tumour debulking and symptom palliation [60, 61].

Other liver metastases

Surgical resection is the main treatment option for CRM but surgery for other metastases is more questioned. Most patients with non-colorectal and non-neuroendocrine tumours have few treatment options and the amount of experience of liver resection on this indication is limited. Hepatic resection for gastric liver metastases is usually not indicated due to frequent peritoneal carcinosis. Other common liver metastases are from ovarian and gastric cancer. Liver metastases from breast cancer, melanoma and ovarian cancer are usually a sign of disseminated disease and are usually not considered appropriate for resection, although subgroups exist and each case has to be considered individually.

Preoperative radiological workup

Radiological liver workup is highly important and is increasingly utilised not only to detect but also to diagnose the type of malignant lesion in the liver. Also, preoperative staging of patients with liver tumours should help to guide the surgeon in decisions concerning whether or not the tumour can be resected and in planning of the operation. Thus, preoperative staging should focus on the diagnosis, number, size and location of the malignant lesions. Furthermore, detection of potential extrahepatic disease is important.

In order to make a preoperative survey of the liver, various radiological modalities are used [62]. Often several modalities have to be used to optimise the preoperative staging. Liver biopsies have limited place to confirm the diagnosis. Biopsies may lead to malignant seeding and interfere with a later curative resection [63, 64].

Ultrasound is globally the most commonly used imaging technique for liver disease. The development of contrast agents for ultrasound has significantly extended its clinical applications. Real-time evaluation of the vascular phase can be achieved by contrast agents. The agent is injected i.v. and the microbubbles enhance the signals from the vessels, which improves the images. Even small lesions down to 3 mm can be detected. Also, contrast-enhanced ultrasound allows characterization of focal liver lesions, with an accuracy similar to those of dynamic computed tomography and magnetic resonance imaging [65]. Ultrasound is also widely used intraoperatively to detect small lesions and to assist in locating intrahepatic vasculature to guide the resection. The use of contrast media has further improved the feasibility of intraoperative ultrasonography [66, 67]. Dynamic helical computed tomography scan with i.v. contrast is considered the standard radiological examination and is

widely used as the modality of choice in preoperative staging.

Magnetic resonance imaging (MRI) is also widely used for liver imaging. Liver specific i.v. contrasts for MRI are available and have further enhanced tumour detection and characterisation. With advances in magnets and computer software, it is now also possible to image the biliary tree by magnetic resonance cholangiopancreatography (MRCP) [68, 69]. MRI may be used as a single non-invasive tool for tumour characterization and surgical planning.

Positron emission tomography (PET) with ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) is valuable in detection of CRM and extrahepatic growth [70], but is not suitable for detection of HCC [71]. Where extrahepatic growth is concerned, promising results has been reported with ^{18}F -FDG PET [72]. Likewise, promising results have been reported with use of ^{11}C -acetate PET to detect HCC [73].

Treatment

Non surgical treatment

Chemotherapy

Neo-adjuvant or adjuvant systemic treatments do not presently have a role in the treatment of resectable HCC. Adjuvant intra-arterial ^{131}I -labelled lipiodol for resectable tumour has been tried with promising results. In a study from Hong Kong, the 3-year overall survival in the treatment and control groups was 86% and 46% respectively [74]. For patients with unresectable tumours, several treatment modalities has been tried but the results are difficult to implement as general guidelines in the clinical setting [75]. One treatment option, however, is chemoembolisation. This local tumour treatment improved survival in selected patients with unresectable tumours [76]. In some patients, downstaging with intraarterial

chemotherapy and interferon, in order to shrink the tumour, is a viable option [77]. In situations of non-resectable CRM, special techniques have evolved to increase the resectability. Encouraging progress has been obtained through new treatment strategies. They involve new chemotherapeutic regimens, interventional radiology and repeated resections or delayed resections after liver regeneration. Systemic chemotherapy can only marginally prolong life expectancy [78], but can convert non-resectable CRM to resectable [79, 80]. 5-Fluorouracil (5-FU), modulated by leucovorin or folinic acid has been most commonly used. However, disease regression has been observed in only 20% of cases with these regimens and there has been no observable impact on survival [81]. Progress has been made by adding new drugs such as oxilipatin and iridotecan in combination with the traditional drugs. Effectiveness is increased by delivering the drugs with chronomodulation [82]. With this technique the administration of the drugs is timed with circadian rhythms, offering better tolerance of the drugs and also permitting higher doses. Progress in downstaging was achieved in 1996 when Bismuth et al. reported a 40% 5-year survival in non-resectable patients treated with 5-FU, folinic acid and oxilipatin followed by a liver resection [83]. In later reports from the same group with patients receiving the same regimen, the 5-year survival rate was 35% [84]. Furthermore, in some institutions regional chemotherapy, hepatic arterial infusion, is used to make non-resectable metastases resectable.

In recent years, agents specifically blocking some functions of neoplastic cells have been developed for the treatment of tumours. Molecules such as cetuximab, an antibody to the epidermal growth factor receptor, and bevacizumab, an antibody to the vascular endothelial growth factor, have been proposed for the treatment of colorectal cancer. These substances are now being evaluated and they are

considered to be an important treatment option for metastatic colorectal cancer [85, 86].

Other non surgical treatments

These treatment options are used for different indications. Interventions with percutaneous ethanol injection (PEI) or Radio-Frequency Ablation (RFA) and other local ablative methods are feasible in selected patients. Of these local ablative techniques, RFA is considered the best treatment option and will be discussed later. Hepatic artery embolisation is mainly used for treatment of neuroendocrine metastases.

Surgical treatment

Resection

The only potentially curative treatment of HCC is a liver resection or liver transplantation. Liver resection is still considered the first alternative. Tumours are resected if the remaining liver function will be sufficient. To prevent postoperative hepatic insufficiency, the hepatic capacity can be assessed with Child-Pugh class or Indocyanine dye retention rate at 15 minutes (ICG 15) [87]. In general, patients with Child-Pugh class A or B and well preserved ICG 15 clearance are candidates for liver resection. The best candidates for resection are patients without ascites, with no extrahepatic metastases, with no vascular invasion or only unilateral vascular involvement and with tumour confined to an area of the liver that may be resected with an adequate remnant.

The five-year survival after a hepatic resection for HCC is reported to be up to 50% [4, 88-92] and even higher in patients with tumours smaller than 5 cm. The overall morbidity is reported to be around 25%. In one recent study, the perioperative morbidity was found to be 56% when more than four segments were resected [7]. The perioperative mortality in cirrhotic patients is reported to be around 10% [92, 93] and

less than 4% in non cirrhotic patients [88, 94].

Liver transplantation is another treatment option. In general, patients with sufficient hepatic reserve or with very large tumours are resected, whereas those with small tumours and/or poor liver function receive transplants. In most centres the criteria for liver transplantation are those proposed by Mazzaferro [95]. They include patients with a solitary tumour of five cm or less in diameter or patients with no more than three tumour nodules, each three cm or less in diameter, no invasion of major blood vessels or lymph nodes or extrahepatic growth. The survival rates for liver transplanted patients, especially cirrhotic patients, are comparable or better compared to liver resected patients [96-98]. To overcome the shortage of donor organs living donor liver transplantation is an option. This method is, however, afflicted by donor morbidity and mortality [99, 100].

Surgical resection is the only treatment that can offer prolonged survival for patients with CCC. Unfortunately only few patients are suitable for surgery. A three-year survival rate of 60% and a 5-year survival rate of 31% following surgery has been reported [101, 102]. Distal CCC are managed by pancreato-duodenectomy (Whipple's procedure). For extrahepatic CCC, affecting the common bile duct, the biliary tree is resected. For most patients where the confluence of the bile ducts is affected a partial hepatectomy is needed to resect the tumour with a margin.

In the absence of treatment of CRM, the median survival is less than one year [103]. The dismal prognosis is also indicated in retrospective studies, with no five-year survival [104, 105]. The resectability rate of CRM is considered to be around 25% [106, 107]. Recent strategies for tumour downstaging have improved this rate, as describer later.

Considering the sometimes challenging surgical technique, it is not surprising that liver surgery for CRM is associated with a

relatively high complication rate. Most series report morbidity rates ranging from 20% to 50% [1, 9, 108], and 30-day mortality rates around 5% [8, 109, 110].

The early reports of CRM resection were met with disbelief [111]. Five-year survival rates following surgery of CRM are now ranging between 25% and 50% [8, 110, 112]. Ten-year survival rates over 20% have been documented [1, 8, 110].

Surgical contraindications of resection of CRM include an insufficient liver remnant or metastases located close to important vascular structures. An oncologic contraindication is non resectable extra-hepatic metastases. In some patients though, with resectable extrahepatic metastases, long-term survival can be obtained [113, 114]. Finally, tumour progression of multiple metastases during chemotherapy treatment, even if the metastases seem resectable, is considered a contraindication for surgery [80].

Special techniques in surgical treatment

Resection can be impossible if the remaining liver parenchyma is too small to provide a sufficient postoperative liver function. It has been empirically estimated that at least 20% of the total liver volume of a healthy liver should be preserved following surgical resection to prevent postoperative liver failure [115, 116]. An even larger volume has to be preserved in patients with chronic liver disease or those whose liver is compromised by high-dose chemotherapy. Volumetric measurements made preoperatively with CT scan correlate well with measured liver being resected [115, 117]. Different methods are in use to evaluate the liver function. Child-Pugh score and ICG 15 measurement are parameters commonly used to estimate the remnant liver function. If function is deemed likely to be insufficient, pre-operative portal vein embolisation (PVE) has been proposed to induce ipsilateral atrophy and contralateral compensatory hypertrophy of the remnant liver, thus

preventing postoperative liver failure [118]. This atrophy-hypertrophy sequence after occlusion of the portal vein was first observed in experimental studies in animals. Maximum regeneration occurs in the first week after a hepatic resection and 70%-80% of the total regeneration has occurred after one month [119]. The time for the liver to regenerate sufficiently to make a liver resection possible with an adequate liver regeneration is estimated to 4-5 weeks. PVE is usually performed percutaneously under local anaesthetic using fluoroscopy or ultrasound guidance. Tumour progression may occur during PVE [120]. It is therefore suggested to treat the patient with a short course of chemotherapy. PVE shows promising results. In two studies, the 5-year survival after PVE and liver resection was 29% and 40%, respectively [121, 122].

Surgery is contraindicated if extensive metastatic disease is present, or with metastases present in both liver lobes, making it impossible to resect in one single procedure. In this situation a two stage hepatectomy can be performed, as reported by Adam et al. [123]. PVE should be used if there is a tumour-free part of the liver that is likely to respond with hypertrophy. The rationale is to minimise the risk of liver failure by performing a second and complete resection of the metastases once the regeneration has occurred. Nevertheless, if the remnant liver does not reach adequate volume even after PVE, a second hepatectomy can be performed. First a resection in one lobe is performed, leaving the tumour in the contralateral lobe to be removed in a second resection. After the first resection the patient is treated with systemic chemotherapy to limit the growth and spread of the remaining metastases. The second hepatectomy is performed only if it can be potentially curative, after re-staging of the metastatic disease has excluded significant tumour progression and when adequate parenchymal regeneration has occurred. The three-year survival rate in the series reported by

Adam et al. is 35%. The five-year survival in larger series of patients has not been established. A relatively high perioperative mortality was reported, 15%. This is not necessarily a consequence of the two-stage technique, as studies in patients undergoing repeat hepatectomies for recurrent disease reveals similar peri-operative morbidity [124-126].

Recurrences following liver resection are frequent after a first and a second resection, despite attempts at curative surgery [127, 128]. A second hepatectomy is technically challenging. However, the morbidity, mortality and long term survival are reported to be similar to that of a first time resection. A third hepatectomy is also suggested to be safe and provides an additional benefit of in terms of survival similar to a first or a second resection [129].

Liver resections for most CRM are possible with traditional liver surgical methods, including inflow or total vascular control [130, 131]. In some situations major vascular resections and reconstructions of the venous outflow are required. These situations could demand total vascular control lasting more than one hour. This long period of time for vascular occlusion is not considered appropriate and could lead to ischemic damage to the liver and induce liver insufficiency. In these cases of complex liver surgery, in situ hypothermic perfusion of the liver is an option. With this technique the hepatic inflow and outflow is clamped and the liver is perfused with hypothermic (4°C) University of Wisconsin solution and the liver suffers from less ischemic injury [132]. It is possible to obtain a sufficient period of time to perform a safe operation and to avoid liver injury. In situ hypothermic perfusion has been evaluated and is shown to increase the liver tolerance to ischemia and provides better post-operative liver and renal function and results in lower morbidity compared to only total vascular control [133].

Ablative techniques

In HCC a liver resection is sometimes not possible due to impaired liver function or unresectability. Non resectable CRM are also a challenge. Other treatment techniques than a liver resection have been developed. Among these are local ablative methods when the tumour is destroyed without necessitating the removal of the tumour and liver parenchyma. The goal is to prolong survival or achieve cure for the patients. The tumours can be destroyed (ablated) by toxic agents, irradiation, cold or heat introduced into the tumours. Examples of these techniques include percutaneous ethanol injection, external ionizing irradiation, cryotherapy, interstitial laser thermotherapy, microwave coagulation, high intensity focused ultrasound and Radio Frequency Ablation (RFA). Of these techniques RFA, interstitial laser thermotherapy, percutaneous ethanol injection and cryotherapy have been most extensively used. RFA is probably the technique that is currently expanding most. Microwave ablation, the most recently developed technique in the field of tumour ablation, is emerging as a promising method. The technique has theoretical advantages: it is possible to ablate larger tumour volumes, to achieve higher intratumoural temperatures, and causes less procedural pain [134].

RFA

With this technique the tumour is destroyed by heat coagulation. The rationale for this is that malignant cells have been shown to be more sensitive to hyperthermic injury than normal cells [135]. An alternating electrical current is introduced into the tumour via an electrode using ultrasound guided technique. The procedure should preferably be performed by a radiologist and a surgeon in co-operation. A high-frequency generator, 500 kHz, is used. The current causes ionic vibration as the ions attempt to follow the change in the direction of the rapidly alternating current and heat is generated.

The heat is further conducted to adjacent tissues. At temperatures above 42°C the intracellular proteins are denatured. Thermal coagulation and desiccation occurs at approximately 70°C and 100°C, respectively.

There are different generators and probes on the market. The generators are heat or impedance controlled. The size and shape of tissue necrosis are determined largely by the size and configuration of the probe, the temperature of the treated tissue and the duration of energy application [136]. Some probes consist of a single straight needle tip and some are constructed as a movable hub with several retractable curved electrodes [137].

The procedure can be performed percutaneously, using laparoscopic guidance or during an open surgical operation. The percutaneous and laparoscopic approaches both have the advantages of minimally invasive surgery. However, 20% to 40% of the patients will have additional lesions not seen in the pre-operative work up [138]. Per-operative contrast-enhanced ultrasound is therefore recommended and this limits the applicability of thermal coagulation in patients being treated percutaneously.

RFA is considered a safe method. The mortality rate is reported to be less than 1% and complication rate less than 10% [139, 140]. However, complications are recognised. They include abdominal bleeding, infections and visceral damage. In the liver, vascular and biliary tract damage is reported and this influences the selection of patients suitable for RFA treatment: patients with tumours close to major vascular structures are considered less suitable for treatment. Also, treatment of tumours adjacent to major vessels may lead to residual viable tumour against the vessel wall due to the cooling effect of the bloodstream (heat sink effect) [141]. A complication limiting the use of RFA is heat injury to the bile ducts, especially when tumours close to the liver hilus are treated. This may result in bile leaks, ductal strictures and fistulas and such heat

injury occurs in approximately 1% of the treated patients [140]. A suggested technique for protection of the bile ducts is intraductal cooling (IDC). With this technique the bile ducts are infused with cooled liquid. Currently the technique is not properly evaluated in experimental or clinical studies but has been tried with promising results [142, 143]. This technique has the potential to be an important tool to treat more patients with greater safety and is evaluated in Paper II. The benefit of RFA has been addressed in several studies. There has been little systematic analysis of outcomes. It is difficult to evaluate earlier studies and compare RFA to other local ablative techniques or liver resections in terms of their influence on survival. Different patients, technical variables, different neo-adjuvant treatments and different types of tumours make it difficult to estimate the benefit in relation to other techniques. However, promising long-term survivals after RFA are reported. In one study including patients with Child-Pugh A or B and with small HCC tumours, ≤ 3 cm in diameter, the five-year survival was 33% [144]. In a recent study with patients with the same Child-Pugh score and with one tumour ≤ 5 cm in diameter or up to 3 tumours ≤ 3 cm in diameter, a 41% five-year survival was reported [145]. Selected patients excluded from surgery are reported with a three-year survival rate ranging between 34% and 52% [146]. Local recurrences after RFA have to be considered. In a recent meta-analysis, significantly fewer recurrences occurred after treatment of small tumours, neuro-endocrine metastases, tumours in non-subcapsular locations and locations away from large vessels [147]. Other factors that favoured lower recurrence were open treatment approach, vascular occlusion, general anaesthesia, a 1-cm intentional margin and a more experienced surgeon. RFA is accepted as a promising technique for use on unresectable tumours, on inoperable patients or as a complement to a

liver resection. It is widely used and there are reasons to believe a further expansion in the field.

Laparoscopic liver surgery

The term laparoscopy refers to the visual examination of the abdominal cavity by the means of an endoscope (Greek: laparo: the flank, skopein; to examine), usually with carbon dioxide insufflated in the abdominal cavity. More than 100 years ago the first cholecystectomy was performed by Langenbuch [148]. Laparoscopy had a major breakthrough in 1985 when a laparoscopic cholecystectomy was performed by Mühe [149]. The media quickly portrayed and popularised the technique under different names: “minimally invasive surgery” or “Nintendo surgery”. In the last two decades, the introduction of laparoscopic techniques has revolutionised general surgery. Laparoscopic surgery, which often yields a reduction in postoperative pain and disability, has proven successful in decreasing length of hospital stays and reducing patient recovery time [150, 151].

Laparoscopy, the technique of examining the abdominal cavity and its content by creating pneumoperitoneum, was first described by Kelling in 1901 [152]. Veress described a needle for creation of pneumoperitoneum in 1938 [153]. Open laparoscopy was described by Hasson in 1974 [154]. In 1987 Mouret performed the first laparoscopic cholecystectomy with the establishment of pneumoperitoneum [155]. Currently, virtually all procedures that can be surgically performed can be performed by laparoscopy, which is considered the standard procedure for many indications. Laparoscopic appendectomy was first described by Semm in 1983 [156]. It is now a common procedure and often favoured in women and obese patients. Laparoscopic fundoplication was first described in 1991 simultaneously by Geagea and Dallemagne [157, 158] and is now considered the standard procedure for oesophageal reflux disease. Also, a rapid development in

laparoscopic solid organ surgery was done in the first years following the introduction of laparoscopic cholecystectomy. Laparoscopic splenectomy, adrenalectomy, and pancreatic surgery are examples of this development [159-161].

Laparoscopic liver surgery (LLS) was first developed by surgeons experienced in both laparoscopic procedures and liver surgery. The first laparoscopic liver resection, a non-anatomic wedge biopsy, was reported by Lefor in 1994 [162]. The still limited development of laparoscopic liver surgery is probably due to several factors. The technique is challenging and basic manoeuvres, i.e. manual palpation, organ mobilization, vascular control and parenchymal transection, are more difficult during laparoscopic surgery than during an open procedure.

Potential specific risk factors during laparoscopic liver surgery are recognised. The two most important are addressed in this thesis, namely CO₂ embolisation to the cardio-pulmonary circulation and bleeding in the liver parenchyma during the transection. These complications are factors that could limit the development of LLS.

In Paper III and IV, CO₂ embolisation during LLS is addressed. During LLS and CO₂ pneumoperitoneum, embolisation occurs. Animal studies have showed a high risk [163]. In patients during laparoscopic cholecystectomy 11/16 patients were noted to have emboli [164]. The clinical impact of this is unclear and during LLS few occasions have been reported, and they have had but little clinical relevance [165]. However, we consider emboli during dissection and transection in the highly vasculated liver parenchyma likely to occur. The topic is still the subject of controversy and further studies are encouraged concerning emboli and the possible negative influence on morbidity after LLS.

Bleeding during the parenchymal dissection is a challenge during the dissection in this highly vasculated organ. The ability

to secure liver parenchymal blood vessels and at the same time avoid CO₂ embolisation is crucial. This issue is also addressed in paper IV.

In 1992, Gagner et al. reported the first complex laparoscopic liver resection [165]. Today liver resections for benign tumours [166], malignant tumours [167] and living donor operations [168] are performed with a safety record that is comparable to that of open surgery. The technique is expanding and reported to be safe and offer short term benefits to the patients [169-171]. CO₂ embolisation is not commented on as a problem in these series, but the monitoring for such events is scarcely described. A further expansion of LLS is likely to occur but long-term survival data for malignant disease need to be confirmed.

Aims of the studies

Paper I

What was the incidence and what were the results of liver operations, and the characteristics of patients operated in Sweden for liver disease, before the introduction of RFA and LLS?

Paper II

How well does IDC perform in an experimental animal model examining: whether IDC impairs the RFA-induced heat necrosis in the liver tissue, when RFA is performed at a distance from the IDC treated bile duct, and whether IDC prevents immediate bile duct damage caused by heat during RFA?

Paper III

How are pulmonary and cardiovascular variables influenced by CO₂ embolisation in an animal model?

Paper IV

Is there a risk of CO₂ embolisation during laparoscopic liver parenchymal transection? Is the risk influenced by different surgical techniques such as: 1) ultrasonic

dissector, 2) ultrasonic shears and 3) vessel sealing system? Do the different techniques differ in operating time and bleeding?

Methods

Ethical approval for the animal studies (II, III, IV) was obtained from the local ethics committees in Stockholm (II, IV) and Uppsala (III).

Paper I

All patients 15 years of age and older, who were admitted for liver operations in Sweden between the years 1987 and 1999, were selected from the Inpatient Registry using procedure codes. For each person admitted for liver surgery, additional data were linked from the Swedish Cancer Registry and the Cause of Death Registry. Medical data include the primary diagnosis, secondary diagnoses, procedure codes, tumour site, histological type, date of diagnosis, causes of death and dates of death. Administrative data include the name of the hospital, department and county, dates of admission and discharge and length of stay.

The Centre of Epidemiology at the National Board of Health and Welfare maintains these national registries [172].

Indications for surgery were categorised as malignant or non-malignant diseases.

This was performed by analysing whether the primary diagnosis, any secondary diagnoses or Cancer Registry data indicated a malignant tumour. For these diseases, four major categories were formed; primary liver cancer, other cancers, metastases from colorectal cancer and metastases from other tumours. If no malignancy was detected, the indication was categorised as non-malignant disease. These indications were categorised in two groups; benign tumours and all other indications.

The operations were categorised as major or minor. Resection of one segment or less,

enucleation, excisions and other local operations, including ablative methods were regarded as minor operations. All other operations were considered as major operations.

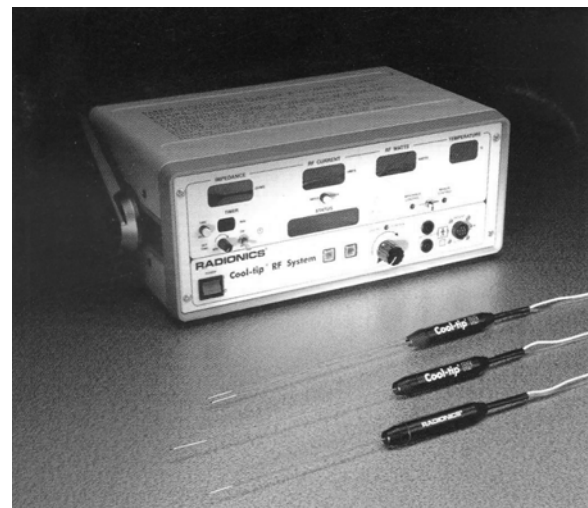
Statistical method

Univariate survival functions for the different diagnostic groups were estimated using the product-limit (Kaplan-Meier) method. Survival analyses with multiple covariates were performed using Cox's proportional hazards models, separately for patients diagnosed with malignancies at the time of surgery and for patients with non-malignant diseases.

All statistical analyses were performed using PROC PHREG and PROC LIFETEST in the Statistical Analysis System package (SAS release 8.02).

Paper II

Twenty pigs were anaesthetised. Two polyethylene catheters were introduced in the common bile duct and secured. For IDC, cooled saline (8°C), was infused in one catheter and extracted from the other. A Radionics Cool-Tip RF system with an internally cooled single RFA needle was used, **picture 5**.



Picture 5. RFA apparatus and needles.

The performance of the RFA apparatus was monitored regarding power, impedance and temperature with Radionics Real Time graph (RRT graph). The needle

was inserted and positioned with an ultrasound-guided technique. In the first set of experiments a safety margin was left between the bile ducts and the lesions. In ten pigs 40 lesions were created, 20 with and 20 without IDC, four in each animal liver, **figure 1**. The RFA needle was positioned at a safety margin of at least 1.5 cm to the bile duct and the gallbladder. To avoid a cooling effect from blood vessels (heat sink effect)

[141], the needle was positioned away from vessels larger than 3 mm in diameter. The baseline temperature (as measured with the needle), the temperature after five minutes of only IDC prior to RFA and the temperature in the RFA lesion immediately after the ablation (end temperature) with and without IDC was measured. Finally we assessed the size and shape of the RFA lesions created with and without IDC. Four lesions were created in each liver, two with

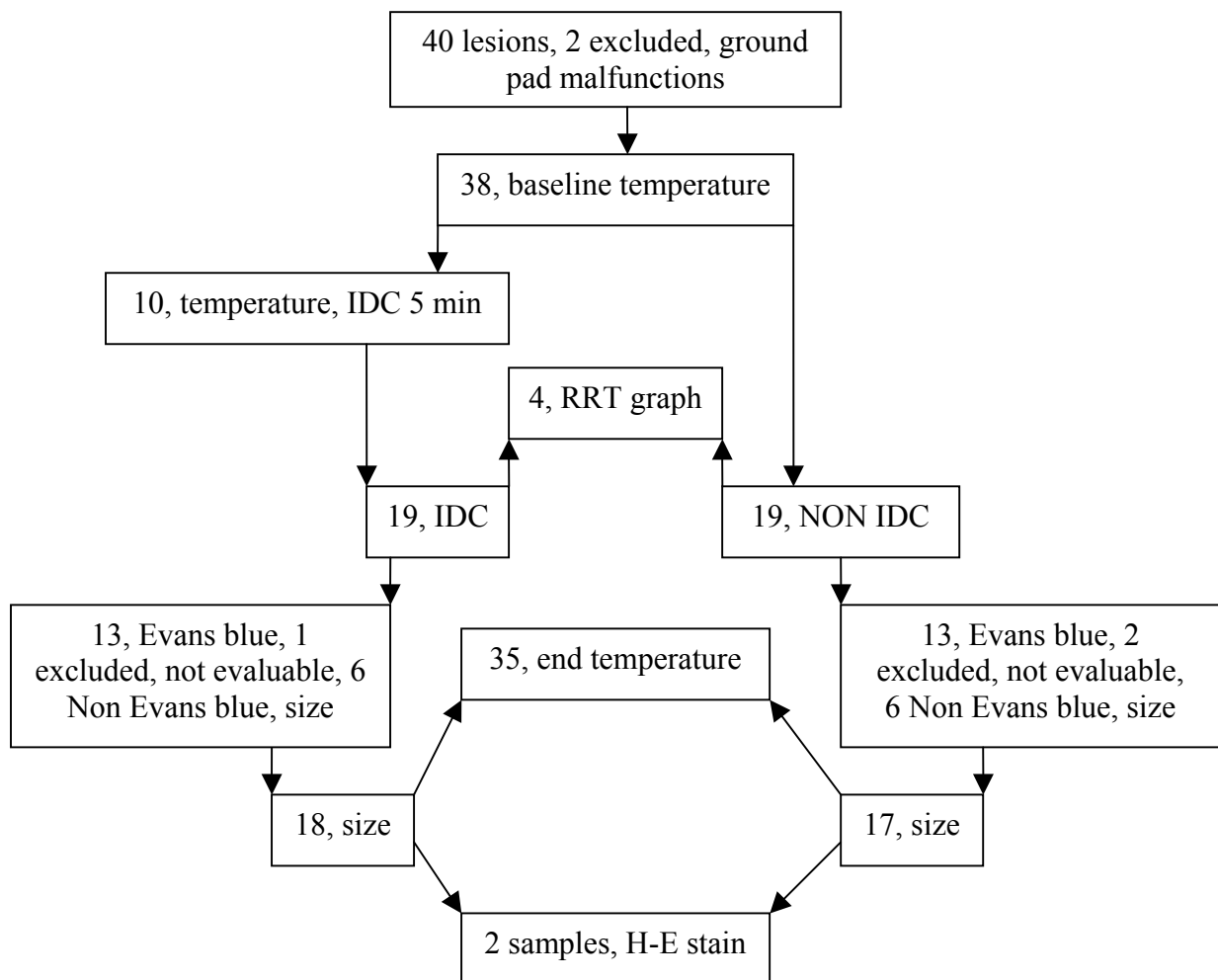


Figure 1. Experimental procedure. Safety Margin. IDC, intraductal cooling; H-E, hematoxylin-eosin; RRT, Radionic Real Time Graphics.

IDC and two without IDC alternately, one lesion in each of the four liver lobes. Two IDC and two non IDC lesions were monitored during the creation by RRT graph. The formation of the lesions and signs of flow in the bile ducts during IDC were monitored with ultrasonography during the entire procedure. Once the ablation cycle was completed, the end temperature was recorded in all lesions. Finally, 15 minutes before sacrifice, Evans Blue dye was administered i.v. to seven randomly selected animals. The liver was then harvested, the lesions identified and excised. The lesions were then sliced for macroscopic evaluation.

The slicing was performed in skew planes for macroscopic measuring of maximal extension [173]. Two randomly selected samples were taken for validation of the limit for standard microscopic defined necrosis after H-E stain with the limit for macroscopic defined necrosis as obtained by the Evans Blue stain.

In another set of experiments the lesions were created with no safety margin to the bile ducts. Ten pigs were used and 20 lesions were created, **figure 2**.

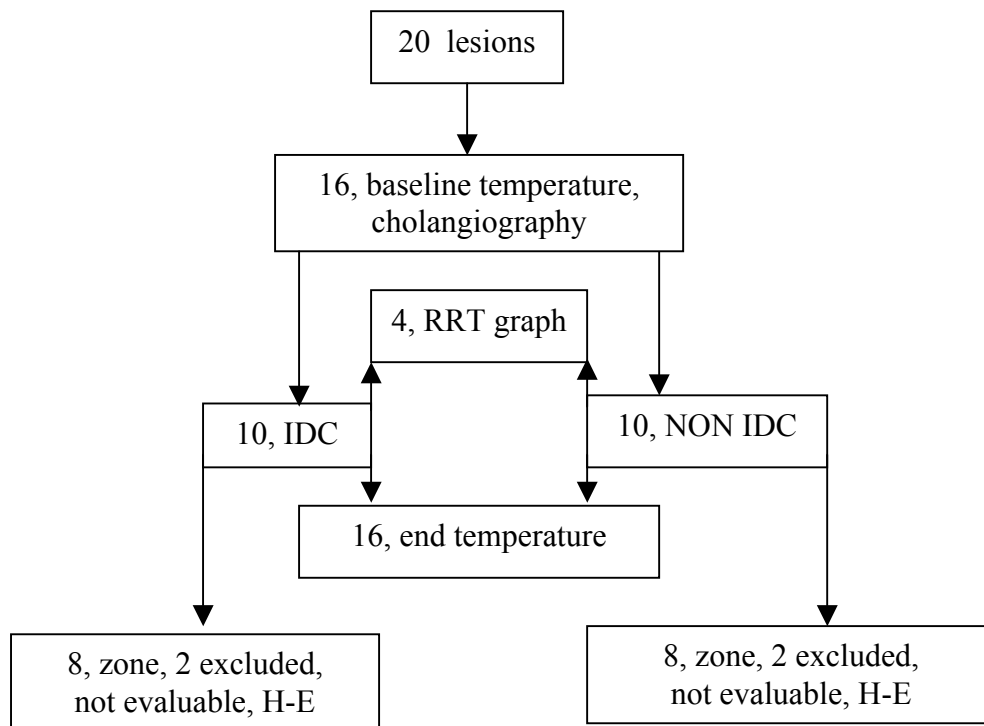


Figure 2. *Experimental procedure. No safety Margin. IDC, intra ductal cooling; H-E, hematoxylin-eosin; RRT, Radionic Real Time Graphics.*

One lesion with IDC and one lesion without IDC were created alternately close to the same bile duct in one selected lobe. Baseline temperature and end temperatures in each lesion were recorded. Two randomly selected IDC and two non IDC lesions were created, monitored by RRT graph. The RFA needle was positioned perpendicular to the bile ducts. IDC flow was evaluated with ultrasound and Doppler as in the first set of experiments. Cholangiography with a non-ionic contrast agent injected in the IDC catheter was performed after creation of all the lesions to evaluate any immediate effect on the bile duct. All lesions were freshly cut out in 4 cm cubes, each cube including one complete lesion surrounded by normal liver tissue. The cubes were fixed in 4% buffered formalin, sliced and microscopically evaluated after standard H-E staining. Microscopic evaluations of the severity of heat-induced necrosis in the lesions were performed in a blinded fashion using a method described by McGahan [174]. The paired IDC and non IDC lesions were compared.

Statistical method

In comparisons between IDC and non IDC lesions the t-test for dependent samples and the Wilcoxon Matched Pairs test were used to analyse continuous data. The Wilcoxon Signed Rank Test was used to analyse variables measured on a nominal scale (zones according to McGahan).

Paper III

Eleven anaesthetised piglets were used. A pulmonary artery catheter was inserted for pressure monitoring and an artery catheter was inserted into the aortic arch for pressure monitoring and blood sampling. A central venous catheter was inserted into the right external jugular vein, and an artery catheter was inserted into the left iliac artery for insertions of the Paratrend[®] sensor.

For the i.v. CO₂ embolisation a catheter was inserted in the left iliac vein. To

validate the embolisation the right outflow tract in the heart was observed with transoesophageal ultrasound (TEE), **picture 6**.



Picture 6. *Transoesophageal echocardiography.*

Two of the eleven piglets were only catheterised but not infused with CO₂ and used as controls. An embolism was obtained by injecting 0.4 ml/kg CO₂ during 20 seconds. Temperature (T), standard lead ECG, heart rate (HR), arterial blood pressure (MAP) and pulmonary artery pressure (MPAP) were continuously monitored and recorded. Pulmonary capillary wedge pressure (PCWP) was measured and cardiac output (CO) was calculated using the thermodilution technique. Arterial blood gases (PaCO₂, PaO₂, pH) were monitored continuously on line by the Paratrend sensor, **picture 7**.



Picture 7. *Paratrend monitor.*

End-tidal carbon dioxide (ETCO₂), peak inspiratory pressure (PIP) and physiologic dead space (V_d/V_t) were recorded and calculated. Pulmonary vascular resistance was calculated as: Mean pulmonary artery pressure - Pulmonary capillary wedge/ cardiac output.

Statistical method

Trend analyses were performed by procedure Mixed in SAS. The model was set up as a one-way repeated measures design with a first order autoregressive covariance structure.

Paper IV

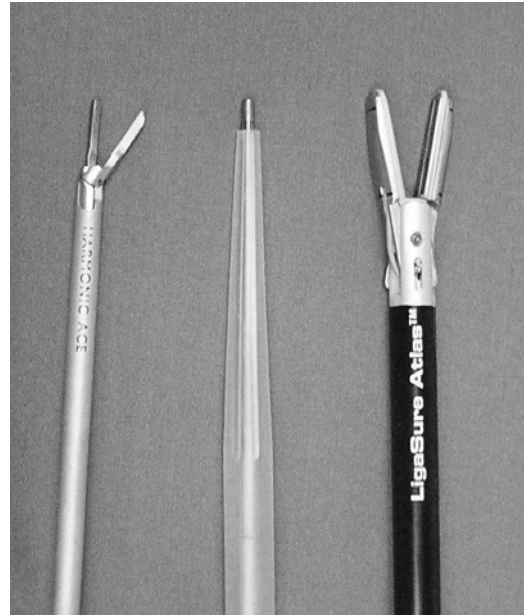
Twelve anaesthetised piglets were used. The experimental setup is shown in **picture 8**.



Picture 8. *Experimental setup.*

Pulmonary artery catheter, artery catheters, and central venous catheter were inserted in the same manner as in study III. The operations were performed by one surgeon. Pneumoperitoneum was obtained with CO₂ insufflation. The laparoscope was introduced and two additional trocars were placed. A device for hand-assisted approach was used. On each pig liver three standardised transections, 6 cm into the liver, were performed with three different devices; ultrasonic dissector (CUSA Exel™), ultrasonic shears (Autosonix™) and vessel sealing system (LigaSure™), **picture 9**.

Each operation was videotaped and bleeding and emboli simultaneously evaluated on the same monitor.



Picture 9. *End blades of ultrasonic shears, end tip of ultrasonic dissector and end blades of vessel sealing system.*

The overall bleeding in each operation was recorded and estimated in arbitrary units: No bleeding = grade 0, slight bleeding = grade 1, profuse bleeding = grade 2. Embolisation in the right outflow tract of the heart was observed with TEE. The most extensive CO₂ embolism during each operation was recorded and estimated in arbitrary units. No gas bubbling = grade 0, slight gas bubbling = grade 1, profuse gas bubbling = grade 2. The total operation time was measured.

The time for visible emboli was recorded. The amount of bleeding, the amount and time of gas emboli was judged from the video tape by two blinded observers. During the operations the arterial blood gases were continuously monitored by a Paratrend sensor. After the operation, the liver was harvested the dissected area was calculated.

Statistical method

In comparison between the three devices, Friedman's ANOVA followed by multiple comparisons between machine types based

on ranks, was performed. $p < 0.05$ is considered statistically significant.

Paper I

A total of 2,405 liver operations among 2,256 admitted patients were recorded. The annual number of operations increased from 17 to 29 per million inhabitants per year during the study period. Of the operations possible to categorise (97%), 44% were major and 53% were minor.

Results

The mean hospital stay fell from 21 to 13 days during the study period. Sixty-three percent of the operations were performed at eight university hospitals.

The most frequent indication for surgery was metastases from colorectal cancer (27%), followed by primary liver cancer (18%), **table 1**.

Indications	n	%	Person		%	Death/100 person
			years at risk	Death n		
Primary liver cancer	408	18	938	273	67	29.1
Other cancers than primary liver cancer	573	25	1196	400	70	33.5
Gastric	83		147	70	84	47.5
Gallbladder	162		248	110	68	44.4
Pancreas	64		129	55	86	42.8
Small intestine	59		208	27	46	13.0
Peritoneal/retroperitoneal	17		29	11	65	38.1
Kidney	37		103	25	68	65.0
Endocrine	17		34	9	53	26.2
Ovarian	18		59	14	78	23.9
Miscellaneous cancers	116		240	79	68	29.5
Metastases from colorectal cancer	600	27	1618	404	67	25.0
Other liver metastases than colorectal	87	4	180	49	56	27.2
Benign liver tumours	204	7	998	35	17	3.5
Other indications, including trauma	384	17	1885	101	26	5.4
Total	2,256		6,815	1,262	55.9	18.5

Table 1. *Indications for surgery, person years at risk and mortality during the study period.*

Within 30 days after the operation, there were only small differences in survival between patient groups, **table 2**. Survival was lowest among those with primary liver cancer and other indications for liver surgery, including trauma. After one year, two thirds of the patients operated on for primary liver cancer were alive. Survival after a first resection for metastases from colorectal cancer was higher and almost

three out of four patients were alive after one year. The mortality of patients operated on for benign liver tumours was low. Patients operated on for non-malignant diseases, notably trauma, had a high early mortality and for the majority trauma was the cause of death.

More than half of the patients died within the follow-up period, **table 3**.

Indication	30 days	(95% CI)	One year	(95% CI)	Five years	(95% CI)
Primary liver cancer	0.90	0.87-0.93	0.68	0.63-0.73	0.27	0.22-0.32
Other cancer	0.95	0.94-0.97	0.57	0.52-0.61	0.24	0.20-0.28
Metastases from colorectal cancer	0.97	0.95-0.99	0.78	0.75-0.81	0.26	0.22-0.30
Other liver metastases	0.94	0.89-0.99	0.72	0.62-0.82	0.24	0.12-0.36
Benign liver tumours	0.97	0.95-1.00	0.91	0.87-0.95	0.81	0.75-0.88
Other indications	0.87	0.84-0.90	0.81	0.76-0.85	0.71	0.67-0.76

Table 2. Proportion surviving 30 days, one year and five years after surgery. Confidence Interval, 95 per cent (CI 95%).

Indication for surgery	Primary liver cancer	Other cancers	Non-malignant diseases	Cardio-vascular diseases	Total
Primary liver cancer	190	52	16	15	273
Other cancers	8	365 ²⁾	12	15	400 ²⁾
Metastases from colorectal cancers	2	375 ¹⁾	11	16	404 ¹⁾
Other liver metastases	2	47	0	0	49
Benign liver tumours	11	10	6	8	35
Totals	216	866	107	73	1,262

¹⁾ 361 (89.4%) of the 404 patients originally operated on for metastases from colorectal cancer had colorectal cancer as underlying cause of death.

²⁾ Most common causes were gallbladder cancer n=102 (25.5%), gastric cancer n=59 (14.8%), and pancreatic cancer n=52 (13.0%).

Table 3. Underlying causes of death in 2,256 patients. Causes of death (n=1,262).

Among the 273 patients operated on for primary liver cancer, 70% died from their tumours. Among patients operated on for colorectal metastases, 89.4% had colorectal cancer as underlying cause of death. In the multivariate analysis, we found that patients with metastases from colorectal cancer had the best prognosis. Women had a better prognosis than men.

Paper II

In the first set of experiments the RRT graph did not reveal any difference in the performance of the RFA apparatus during the creation of the two control IDC/ non IDC lesions. A significant decrease in the liver temperature was observed after five minutes of IDC prior to RFA. There were no significant differences in the end temperature between the IDC and non IDC groups.

All lesions were ellipsoid and uniform in shape and there were no significant differences in size between the IDC and non IDC lesions.

In the other set of experiments the RRT graph did not reveal any difference in the performance of the RFA apparatus during the creation of the two control IDC/ non IDC lesions. No immediate RFA related damage on the bile ducts was seen on cholangiography. There was no significant difference in end temperature between the IDC and non IDC lesions.

Comparisons of the paired IDC and non IDC lesions are shown in **table 4**. When we compared the affected zones the protective effect of IDC did not reach statistical significance.

<i>Animal</i>	<i>IDC/ NON IDC (Lesions in order of creation)</i>	<i>Base line temperature (°C)</i>	<i>End temperature (°C)</i>	<i>Zone (A-E)</i>
1	IDC	38	48	E
	NON IDC	38	49	E
2	NON IDC	38	60	Excluded
	IDC	38	41	Excluded
3	NON IDC	40	50	E
	IDC	40	42	D
4	NON IDC	39	48	D
	IDC	39	40	E
5	NON IDC	39	54	C
	IDC	39	34	E
6	NON IDC	39	49	C
	IDC	39	44	E
7	IDC	38	43	E
	NON IDC	38	50	D
8	IDC	39	57	E
	NON IDC	39	47	C
9	NON IDC	39	47	B
	IDC	39	48	B
10	IDC	39	49	Excluded
	NON IDC	39	49	Excluded

Table 4. Lesions created without safety margin. Temperatures and severity of heat necrosis.

Paper III

All pigs survived during the four hours following the CO₂ injection and no malignant cardiac arrhythmia was observed. In the two control animals no changes were seen in the monitored

variables, except for a decrease in heart rate.

The effects of CO₂ embolisation on the most important variables in the nine experimental animals are illustrated in **figure 3-8**.

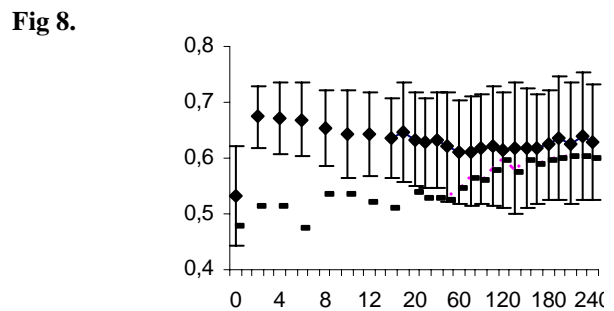
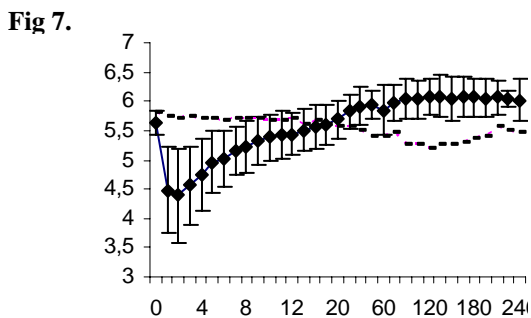
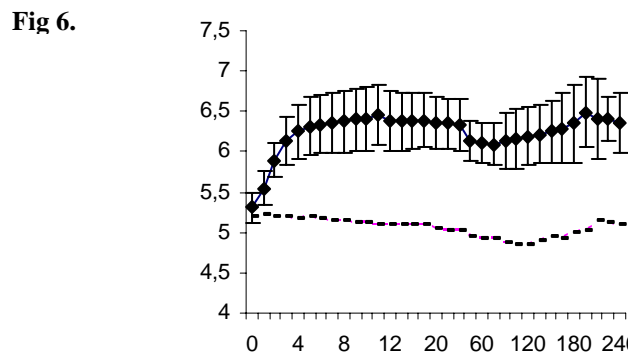
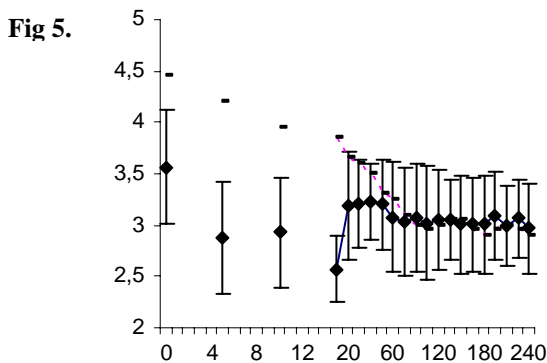
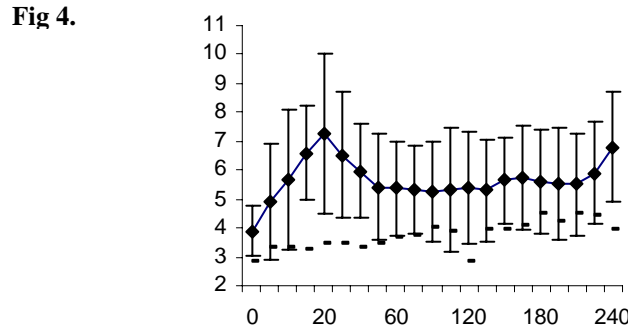
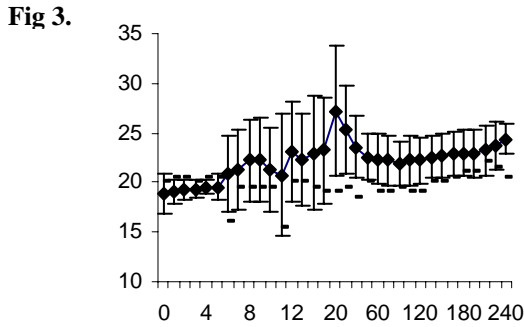


Figure 3-8. Time courses, 240 minutes, for the six most important variables. Dotted lines denotes mean of the two control animals: **Fig 3.** MPAP(mmHg); **Fig 4.** PVR (mmHg x min/l); **Fig 5.** CO (l/min); **Fig 6.** pCO₂(kPa); **Fig 7.** EtCO₂(kPa); **Fig 8.** Vd/Vt

Hemodynamic variables: MPAP, **figure 3**, increased gradually over the entire four-hour study period. Calculated PVR, **figure 4**, increased during the first 20 minutes after which it remained stable. No changes in HR were observed. CO, **figure 5**, decreased during the first 15 minutes to 2.6 l/min and stayed close to this level during the rest of the study period.

Acid–base variables: These variables were monitored continuously. PaCO₂, **figure 6**, increased during the first five minutes from 5.3 to 6.3 kPa after the CO₂ injection.

Respiratory variables: ETCO₂, **figure 7**, decreased from 5.6 kPa at baseline to 4.4 kPa during the first five minutes and then gradually increased, reaching preinjection values after approximately 30 minutes. After this, it remained at the same level. At baseline the V_d/V_t, **figure 8**, was 0.5. Three minutes after the CO₂ injection V_d/V_t had increased to 0.7 and stayed at this level during the study period.

Paper IV

All operated animals survived surgery and no major complications occurred. Two animals were excluded due to instability during the preparation with the catheters before surgery, which meant that no baseline values were obtained. In one piglet we were not able to obtain the correct TEE image. The results from this animal are included in the study except for the embolisation parameters. The results are presented in **table 5 and 6**.

No difference was seen between the transected areas when comparing the three devices. Operation time was longer for CUSA compared to LigaSure and Autosonix. When comparing LigaSure and Autosonix no difference was seen.

During the transection, bleeding was larger for CUSA compared to Autosonix but there was no difference between CUSA and LigaSure or Autosonix and LigaSure.

	Transection areas (cm²) Median (range)		
Autosonix	7.20 (5.00-10.5)		
LigaSure	6.21 (3.42-11,25)		
CUSA	7.46 (4.00-10.92)		
	Operation times (s) Median (range)		
Autosonix	450 (300-690)		
LigaSure	337 (240-420)		
CUSA	1111 (480-1320)		
	Bleeding		
	0	1	2
Autosonix	6	4	0
LigaSure	5	5	0
CUSA	0	8	2

Table 5. Transection areas, operation time and estimated bleeding for ten piglets. Statistically significant differences are indicated: * p≤0.05, ** p≤ 0.01, *** p≤ 0.001. The overall bleeding in arbitrary units: No bleeding = grade 0, slight bleeding = grade 1 and profuse bleeding = grade 2.

	Emboli time/ operation time (%) Median (range)		
Autosonix	0 (0-8)		
LigaSure	16.4 (0.38)		
CUSA	0 (0-20)		
	Emboli grade		
	0	1	2
Autosonix	6	2	1
LigaSure	2	4	3
CUSA	6	2	1

Table 6. Gas emboli time as proportion of total transection time and estimated most extensive grade of embolism for nine piglets. Statistically significant differences are indicated: ** p≤0.01. The most extensive emboli in arbitrary units: No gas bubbling = grade 0, slight gas bubbling = grade 1 and extensive gas bubbling = grade 2.

There was an overall statistical significant difference when comparing grade of emboli bubbling in the right heart between the devices but no difference was proved when the devices was compared in pairs. The total time for emboli seen as part of the total operation time was longer for

LigaSure compared to CUSA and LigaSure compared to Autosonix. No difference was obtained between CUSA and AutoSonix. Five episodes of grade 2 emboli were recorded, three with LigaSure, one with CUSA and one with Autosonix. When two of these events occurred, both during LigaSure transections, an immediate rise in $p\text{CO}_2$, decrease in $p\text{O}_2$ and pH was registered as illustrated in **figure 9**.

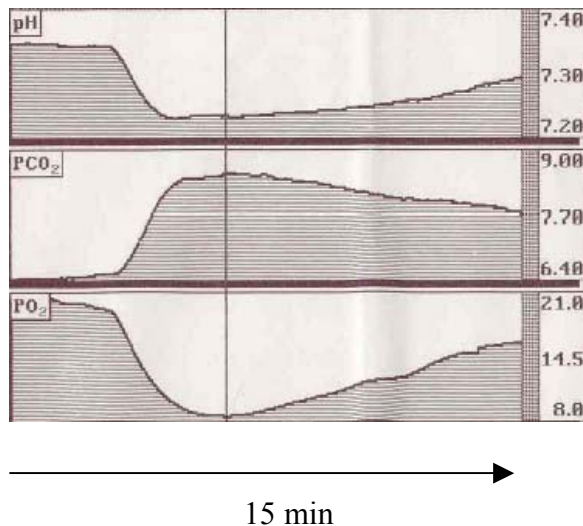


Figure 9. The course for arterial blood gases during fifteen minutes after a CO_2 embolisation during a vessel feeling system transection.

Discussion

Paper I

High quality is crucial for the validity of registries. The amount of data concerning underlying and contributing causes of death missing from the Cause of Death Registry is considered to be low. Also, comparison between hospital discharge records and death certificates shows that the accuracy of data for malignant diseases is high [175]. In a study from 1994 a sample from the Inpatient registry from 1986 was evaluated [176]. In total 11% of the procedure codes and 17% of the primary diagnoses were reported to be incorrectly registered. The annual percentage of unregistered admissions is estimated to be approximately 1% [177].

The most common indication for liver operation was CRM. Also, patients with metastases from colorectal cancer had the best prognosis after an operation for a malignant tumour. If this also reflects a selection of patients or a better overall treatment is unclear. Women had a better prognosis than men. This was more pronounced in patients with non-malignant diseases, probably due to a relatively larger number of male trauma patients and women with benign liver tumours. The risk of dying fell significantly during the last two time periods for all patients with malignant tumours, probably due to better peri-operative treatment of the patients. Considering the current indications for surgery on patients with hepatic malignancies our study may indicate an undertreatment for this indication and a selection of patients.

We consider “full coverage” National quality registries to be highly valuable in research, development of new techniques and most important for patient safety in liver surgery. In Sweden no such national registries presently exist.

Paper II

In this study we created standardised lesions in the liver with RFA. Viewed macroscopically, the lesions were ellipsoid and uniform, which is considered a sign that the RFA system has performed appropriately and given complete ablation. The first set of experiments evaluated whether IDC had any deleterious effect on the shapes and sizes of lesions created with at least 1.5 cm safety margin to the bile duct. No such effect was seen. The temperature in the liver parenchyma was significantly decreased after IDC without RFA. We considered this a sign of a sought effect of the IDC procedure.

The fact that the lesions were not influenced by IDC in terms of size and shape suggests that there is little risk that the RFA effect will be insufficient, when tumours away from the bile ducts are

treated during IDC. It may thus be relevant to use IDC on a more regular basis during RFA procedures to decrease the potential risk of bile duct injuries.

In the second series of experiments we created RFA lesions without a safety margin, to evaluate the potential protective effect of IDC on the bile duct wall. The RFA equipment performance was unaffected by the IDC, in agreement with the first set of experiments. Cholangiography did not reveal any immediate RFA-related influence on the bile ducts, such as extravasation of contrast media or interruption of the bile duct. The development of bile duct stenosis cannot be evaluated with certainty in this study design since strictures in the bile ducts usually take weeks to months to develop. In this set of experiments no statistically significant protective effect was achieved by IDC, in contrast to results reported by Raman et al. in a pig study [178]. Promising results have been reported in the clinic [142, 143]. There are several factors in our study design that may have led to the absence of statistical significance of the protective effect of IDC. The IDC performed satisfactorily in this model. However, the bile ducts in pigs vary in size and shape, also between animals of equal weight. This can alter the cooling effect of IDC. Also, we were not able to measure the actual temperatures in the bile ducts, which would have been the most accurate method to determine the cooling effect of IDC. Saline of a lower temperature could improve the IDC effect. We used 8°C saline because it is easy to manage in a normal clinical setting and can be stored in an ordinary refrigerator. Whether saline and Ringer's lactate would differ in their cooling effect is unclear but it seems unlikely. In addition, the method chosen for evaluation of a possible protective effect of IDC could influence the results. We used microscopic evaluation of the liver tissue (according to McGahan) around the bile ducts because this method has been validated in other studies.

Furthermore, we considered evaluation of liver tissue around the bile duct more vigorous, assuming that spared liver tissue around the bile duct strongly indicated that the bile duct would also be unaffected.

We found that IDC did not negatively influence the efficacy of RFA. Other studies have shown that IDC has a protective effect. Despite the absence of a proven protective effect in this paper, we believe IDC has potential to provide protection and the method has to be further evaluated in animal studies in other study designs with a greater number of animals.

Paper III

The main finding in this study was that the effects of CO₂ embolisation on most of the examined variables persisted throughout the four-hour observation time.

The volume of a possible embolisation occurring during LLS is difficult to determine. We suggest 0.4 ml/kg CO₂ and the infusion time, 20 seconds, to be clinically relevant.

An early detection of an embolisation is important. TEE and ETCO₂ have been proposed as monitoring modalities. TEE is suggested to be the most sensitive method to detect minor events of CO₂ embolisation, up to approximately 0.5 ml/kg. In this study we used TEE in four pigs to confirm embolisation to the right heart.

The observed changes in blood gases and ETCO₂ agree with established knowledge concerning the physiological response to pulmonary embolism, e.g., a decreased proportion of tidal volume ventilating dead space and signs of development of shunts. In general, a rapid decrease in ETCO₂ seems to be an early sign of gas embolisation, and it is followed by an increase in pulmonary vascular resistance and pulmonary artery pressure.

After less than 30 minutes, ETCO₂ returned to normal values. It could be anticipated that the CO₂ in the injected bubbles would have dissolved by this time, bringing the situation back to normal. However, as several of the other variables

measured still were affected, the normalisation of ETCO_2 is likely to be the result of an adaptation to the situation with an optimised ventilation-perfusion ratio.

Respiratory function and central circulation are closely linked and pulmonary embolism has an influence on both these systems. The pulmonary circulatory response to experimental microembolism varies, depending on the embolic material, size of emboli, site and amount of embolisation, as well as different experimental protocols.

In this study, as with the respiratory variables and arterial blood gases, we found a fast pulmonary circulatory response to the CO_2 embolisation. The responses rapidly peaked and then declined but did not return to baseline values during the four-hour observation time. Interestingly, the systemic circulatory system did not seem to be involved in this response, as MAP and HR were unchanged. This implies that the embolism evoked no catecholamine stimulant effects and that metabolic needs were being met.

CO , decreased during the study period. Most of the blood is directed to the dependent parts of the lungs, whereas gas embolism preferentially occurs in the upper lung regions. Central venous pressure was scarcely affected, speaking against right heart ventricular failure. The hypercarbia seen was hardly severe enough to exert a cardiodepressant effect. Thus it seems most likely that the increased pulmonary vascular resistance led to the diminished cardiac output.

PVR, increased quickly after the embolisation and declined thereafter. The rise in MPAP followed another time course, as it increased only slowly. An increase in PVR has been observed in patients with embolisation of less than 25% of the vascular bed [179]. Diffuse pulmonary embolism causes increased pulmonary circulatory resistance with resulting increase in MPAP and can sometimes lead to right heart failure [180]. One possible explanation for our results in

the first part of the study is that the CO_2 embolism caused the increase in pulmonary vascular resistance but did not block enough of the capillaries to seriously compromise metabolism, and thus only a slight compensatory increase in MPAP pressure was needed.

We observed statistically significant long term changes in cardiopulmonary physiology after CO_2 embolisation. We believe the long-lasting influence of a clinically relevant CO_2 embolisation, seen in our study, could urge a cautious approach. Laparoscopic liver surgery frequently involves long operations and a patient who suffers a CO_2 embolism could thus be negatively influenced during the peri- and postoperative period, leading to increased morbidity. Our study support extensive monitoring during LLS to evaluate the extent to which alterations in pathophysiological variables influence the patient.

Paper IV

Operation time and excessive bleeding during LLS are associated with a higher rate of complications and shorter long term survival. CO_2 embolisation to the cardiopulmonary circulation is considered a risk factor during LLS with CO_2 pneumoperitoneum.

In this paper three devices for liver parenchymal transection with the endpoints of operation time, bleeding and CO_2 embolism are evaluated in a porcine model. TEE is considered sensitive to detect CO_2 emboli. To improve the monitoring of CO_2 emboli we added continuous monitoring of arterial blood gases.

The main finding in our study was that during two emboli events, an alteration in blood gases occurred which may indicate clinical relevance.

Theoretically, an optimal liver transaction should be performed without necessitating vascular inflow occlusion to minimise the risk for ischemic injury to the liver.

Refinement of the transection technique is therefore important.

CO₂ embolisation during laparoscopic liver parenchymal transection with pneumoperitoneum is a matter of discussion and the clinical relevance is still unclear. Embolic events are reported in animal studies [163, 181]. In two patient series with laparoscopic liver resections no clinically relevant gas embolisation events was observed [165, 182]. No serious clinical embolisation events during LLS have to our knowledge been reported in the literature. However, the risk is considered by surgeons some of whom report that they use abdominal wall lifting devices specifically to avoid the risk of embolism [183]. In order to evaluate the emboli we used TEE but also Paratrend to monitor the impact on arterial blood gases. The Paratrend enables continuous monitoring of arterial blood gases and both rapid as well as persisting changes could be evaluated. A change in blood gases indicates aberration in the gas exchange in the lungs and could imply clinical relevance. In Paper III we found changes in arterial blood gases lasting for four hours of continuous monitoring [184]. These lasting changes occurred despite the fact that ETCO₂ was normalised in less than 30 minutes. An embolisation with possible clinical implications may be seen on TEE only a short time and hard to detect after 10 to 15 minutes. It may therefore be overlooked. In this paper we used TEE to detect emboli and continuous monitoring of blood gases to predict emboli of presumably clinical relevance. The three devices are important to evaluate. They are commonly in use and are considered safe and effective. CUSA is also commonly used in centres performing advanced liver surgery [129]. The ultrasound activated scalpel, of which Autosonix is one, is reported to entail a high risk of severe gas embolism with cardiac arrhythmias in a pig study [163]. LigaSure is relatively new and promising technique for parenchymal transection

[185]. Monopolar technique for heat necrosis in the parenchyma before resection is described [186]. LigaSure device is supposedly a bipolar refinement of this technique, combining heat necrosis of the parenchyma and crush technique. The operation time was longer for CUSA. This can be explained by the more time consuming dissection of the vessels with the CUSA during the transection, with a supplementary diathermia grasp procedure to secure disrupted and bleeding vessels. The procedure can be refined by the use of a monopolar diathermia tip on the CUSA. In this study the bleeding was only significantly larger for CUSA when compared to Autosonix. When using LigaSure and Autosonix a careful but blind insertion of one of the end blades of these devices into the liver tissue is most commonly used during the transection. This could cause bleeding from disrupted vessels. Apparently no such bleeding occurred. The clinical relevance of the minor difference in bleeding between the devices is unclear but probably of minor importance.

In this study a statistically significant difference was obtained between the devices when we put the time for emboli seen with TEE in relation to the total transection time, to the disadvantage of LigaSure. Whether the time during which emboli were seen has implications on the cardiopulmonary circulation is unclear. The size of the emboli could be more important. During two dissections with LigaSure when grade 2 emboli were recorded on TEE, there was a significant change in the arterial blood gases. These recorded grade 2 CO₂ emboli were prominent. This finding implies that there could be difference between the different devices concerning the negative effects of emboli.

Conclusions

Paper I

Liver surgery was performed on a relatively small number of patients in Sweden 1987-1999 compared to expected figures. Most patients were operated on for CRM. These patients also had the best prognosis of patients operated on for malignant liver disease. The outcome in terms of survival was comparable to that reported in other national studies in other western countries. The demand for liver surgery will probably increase in the future.

Paper II

IDC is challenging to evaluate in animal studies. It does not impair the RFA created heat necrosis. A statistically significant protective effect of IDC against immediate RFA induced bile duct injury was not found in this study. We consider further studies with a larger number of animals important. In addition, long term effects need to be studied. IDC could be a promising method for protection of bile ducts from heat damage during RFA.

Paper III

CO₂ embolisation was possible to detect early with TEE. The embolisation was followed by a rapid increase in PaCO₂ and a decrease in PaO₂ and pH. The effects of the CO₂ embolisation on most of the examined cardiopulmonary variables persisted throughout the 4-hour observation time. Of the most important haemodynamic (CO, MPAP, PVR), acid-base (PaCO₂) and respiratory (ETCO₂, V_d/V_t) variables, only ETCO₂ returned to pre embolisation values. The observed long term changes in cardiopulmonary physiology after CO₂ embolisation seen in our study, are of interest when interpreting the results of previous animal studies. The demonstrated pathophysiology of CO₂ embolisation

gives a basis for how to monitor patients during LLS.

Paper IV

CO₂ embolisation, detected with TEE, occurred to some extent with all three techniques: 1) ultrasonic dissector, 2) ultrasonic shears and 3) vessel sealing system. However, embolisation associated with increased pCO₂ occurred only during transection with the vessel sealing system. Operation time was longer with the ultrasonic dissector. Bleeding was larger with the ultrasonic dissector than with the ultrasonic shears.

Future perspectives

Liver surgery has a potential to further develop in different fields. Liver imaging is improving with powerful computers and new, specially designed contrast agents for the different modalities. Screening programs for patients with risk factors for malignant liver disease are being evaluated. It is probably possible to detect early stage disease in more patients, and to treat them to achieve even better survival.

It is also possible that a larger number of patients with advanced tumours could be eligible for treatment. New treatment strategies that combine chemotherapy, advanced liver resections, and local ablative treatment are being evaluated. Minimally invasive surgery, such as laparoscopic liver surgery and ablative techniques, are rapidly expanding. The new techniques are often challenging to properly use and evaluate. Therefore, development of centres for patients with advanced liver disease is often recommended. Sweden will hopefully take part in the development.

It is important to evaluate and refine new techniques, both so they achieve their full potential and to ensure the safety of the patients. In this thesis we have focused on complication risks involved in Radio Frequency Ablation and laparoscopic liver surgery. Alongside microwave ablation,

Radio Frequency Ablation is presently the most promising technique for local ablation of liver malignancies. Probably the therapeutic use of these techniques will increase, further highlighting the importance of assessing patient safety. Concerning bile duct injury from heat during Radio Frequency Ablation, as evaluated in Study II, an animal survival study is suggested. In this study evaluation of the effect of the intraductal cooling on the lesions should be performed after some weeks. Also, a larger number of animals should be used. Later, the technique may be introduced on patients and prospectively evaluated.

Laparoscopic liver surgery is rapidly expanding with a larger number of operations performed and new indications introduced. To improve patient safety, animal experiments are a valuable tool. The optimal technique for safe operations is not yet established. Several variables ought to be evaluated. The possible cause underlying the effect on respiratory function, an activated coagulation system or a pulmonary reaction, should be further evaluated in animal studies. Further studies concerning CO₂ embolisation and cardio-pulmonary physiology are also suggested. Other devices used in laparoscopic liver surgery, also during more advanced liver surgical procedures, could be compared. Moreover, studies with different pneumoperitoneum pressures to evaluate the possible impact of different pressures on the amount and size of emboli could be valuable. To further improve patient safety, potential CO₂ embolisation could be assessed and evaluated in patients during laparoscopic liver surgery by use of extensive monitoring including transoesophageal echocardiography and continuous monitoring of arterial blood gases.

In conclusion, the new techniques have great potential to help us treat more patients with malignant liver disease. Hopefully, more patients will benefit from these treatment options. An encouraging

indication of this is that the number of liver operations and ablative treatments in Sweden are increasing, according to the database of the National Board of Health and Welfare, **diagram 1 and 2.**

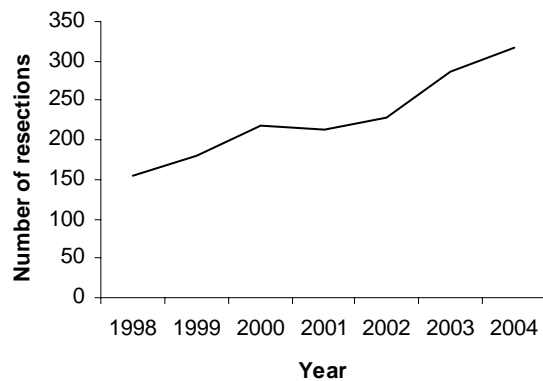


Diagram 1. *Liver resections/year 1998-2004.*

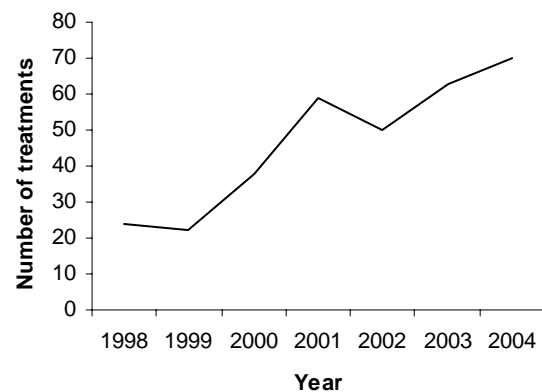


Diagram 2. *Ablative treatments/year 1998-2004.*

However, we must always bear in mind that patient safety has the highest priority.

Summary in Swedish

Leverkirurgi är den enda behandling som kan erbjuda förlängd överlevnad eller bot för patienter med malign leversjukdom. Verksamheten är högt specialiserad, kunskapsintensiv och tekniskt avancerad. Inom många områden genomgår den en snabb och genomgripande utveckling innefattande kirurgisk teknik, teknisk utrustning och behandlingsmetoder. Radiologisk utredning och intervention, onkologisk behandling samt perioperativ vård är viktiga områden som utvecklas och bidrar. Detta innebär en säkrare leverkirurgisk verksamhet och att fler patienter kan erbjudas kirurgisk vård vid malign leversjukdom. Stora krav ställs på samarbete mellan olika specialiteter och också på sjukvården generellt för att möta de ökande kraven. Deltagande i forskning, utvecklingsarbete och kvalitets uppföljning är också av yttersta vikt för att erbjuda kvalificerad, säker och meningsfull sjukvård av patienter med denna allvarliga diagnos.

Med ökad medvetenhet om goda behandlingsresultat av primär och metastatisk levercancer kan en ökad efterfrågan förväntas. En skattning av de patienter som erbjuds kirurgisk vård av levercancer pekar på att en underbehandling sker i Sverige.

Nya behandlingsmetoder av levercancer utvecklas och introduceras. Två metoder som har fått en ökande användning är Radio Frekvens Abladering samt laparoskopisk leverkirurgi ("titthålskirurgi"). Radio Frekvens Abladering innebär att cancer tumörer i levern destrueras genom att föra in en elektrod i tumören med ultraljudsguidning. Via elektroden leds högfrekvent växelström in i tumören som destrueras utan att en resektion görs. Detta kan i vissa fall utföras med perkutan teknik utan att öppna bukhålan. Att operera patienter med andra sjukdomar såsom hjärt- kärl- eller lungsjukdomar kan vara riskfyllt. Patienter med leversjukdomar kan riskera leversvikt

och vara olämpliga att operera. Dessa patienter kan erbjudas percutan RFA behandling som ett alternativ till operation. Laparoskopisk kirurgi innebär fördelar för patienterna med snabbare läkning, mindre smärta efter operationen och snabbare mobilisering. Laparoskopisk lever kirurgi får därför ökad användning vid förutom leverresektioner även vid ingrepp som lever transplantationer med levande donatorer. Detta ställer höga krav på säkerhet.

Det är välbekant att nya lovande kirurgiska tekniker ofta får en snabb spridning där utvärderingen kan komma att bli eftersatt. Radio Frekvens Abladering och laparoskopisk leverkirurgi är behäftade med komplikationsrisker vilka är viktiga att evaluera för att optimera patientsäkerheten. Nationella kvalitetsregister kan bidra till detta. I nuläget finns inga sådana register inrättade för leverkirurgiska patienter.

I denna studie ingår en registerstudie för att ge en översikt av den leverkirurgiska verksamheten i Sverige före introduktionen av Radio Frekvens Abladering och laparoskopisk leverkirurgi. Vidare ingår tre djurexperimentella studier för att evaluera komplikationer vid Radio Frekvens Abladering, värmeskada av gallgångar i levern, samt vid laparoskopisk leverkirurgi, koldioxidembolier (gasbubblor) till hjärt lung-cirkulationen.

Syftet med denna studie är att evaluera dessa två komplikationer.

Delarbete I

Detta presenterar patientuppgifter, indikationer, dödlighet efter lever-operationer samt dödsorsaker. Alla lever-kirurgiskt behandlade patienter i Sverige 1987- 99 inkluderades från det nationella patientregistret, tidigare kallat slutenvårdsregistret. Kompletterande uppgifter inhämtades ur cancerregistret och dödsorsaksregistret.

Delarbete II

Detta är en experimentell studie på sövda grisar där en teknik för att skydda gallgångarna i levern mot värmeskada under RFA-behandling studeras. Denna komplikation sker hos cirka 1 % av de patienter som behandlas med RFA. Vissa patienter med gallgångsnära tumörer kan inte behandlas på grund av risken för gallgångsskada. Metoden har prövats på patienter med lovande resultat och innebär att kyld koksaltsvätska insprutas i gallgångarna under RFA behandling. I en djurmodell utvärderade vi den eventuella skyddande effekten av den kylda vätskan. En skyddande effekt kunde inte statistiskt säkerställt påvisas i detta delarbete men metoden är lovande. Ytterligare studier bör utföras i en annan studiedesign. Studien visade dock att ingen negativ effekt avseende radiofrekvens apparaturens behandlingseffekt sker.

Delarbete III

Vid laparoskopisk leverkirurgi insprutas koldioxid i bukhålan för att åstadkomma ett arbetsutrymme. Vid dissektion i och delning av den rikligt blodförsörjda levervävnaden kan gasembolier tränga in i blodkärlen och föras vidare till hjärtat och lungorna. Detta kan ge upphov till negativ påverkan på lungfunktionen och i förlängningen negativt påverka patienterna med komplikationer under och efter det leverkirurgiska ingreppet. I denna studie kunde vi visa att på sövda grisar sker denna negativa påverkan och kvarstår under timmar efter en experimentell embolisering. Detta är inte tidigare beskrivet i den vetenskapliga litteraturen. Gasembolisering i detta delarbete är av en storlek som teoretiskt kan inträffa vid laparoskopiska leveroperationer på patienter.

Delarbete IV

Under delningen av levervävnaden vid laparoskopisk leverkirurgi finns det risk för blödning och att gasembolier tränger in i blodkärlen i levern. Blödning och embolier

påverkar operationsförloppet negativt och kan även ge upphov till komplikationer hos patienterna efter operationerna. I denna studie på sövda grisar jämförde vi tre olika metoder för att dela levervävnad, ultraljudsdissektor (CUSA), ultraljudssax (Ultrasonix) och ”vessel sealing system” (Liga Sure) med avseende på operationstid, blödnings-mängd och mängd och storlek av eventuella embolier. Vi kunde påvisa att det var små skillnader i operationstid och blödningsmängd som sannolikt inte har någon praktisk klinisk betydelse. Dock sågs vid två operationer med Liga Sure embolier som påverkade gasutbytet i lungorna och som kan innebära komplikationer i samband med laparoskopisk lever-kirurgi.

Acknowledgements

I want to thank all those who in various ways have provided help and encouragement and made it possible for me to complete this thesis. In particular I would like to mention:

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