LAPAROSCOPY WITH LAPAROSCOPIC ULTRASONOGRAPHY IN THE EVALUATION OF PANCREATIC CANCER

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DECLARATION

I declare that this thesis has been composed by myself. Its content relates to work carried out by myself during my clinical appointments to the Department of Surgery, University of Edinburgh, Royal infirmary, Edinburgh from October 1992. Contributions by other individuals are indicated in the Acknowledgements.

Edinburgh, 6th January 1997

ABSTRACT

This thesis is based on the tenet that careful preoperative patient selection is important before attempting resection with 'curative' intent in patients with pancreatic or periampullary carcinoma. Little consensus has existed as regards the ideal investigative algorithm for evaluating resectability in such patients. The aims of this thesis were to validate staging laparoscopy, laparoscopic ultrasonography (LapUS), and laparoscopic peritoneal cytology (LPC) in the staging of patients presenting with pancreatic or periampullary carcinoma. A series of studies was perfomed over a period of 52 months between 1991 and 1995 to evaluate the efficacy of these techniques.

A systematic method for LapUS examination of the liver, biliary tree and pancreas was devised. In Study 1, the ability of LapUS to image defined anatomical landmarks was evaluated during (i) laparoscopic cholecystectomy, and (ii) staging laparoscopy for pancreatic malignancy. Satisfactory imaging of all anatomical structures considered important was shown to be feasible using LapUS.

In Study 2, staging laparoscopy with LapUS was performed in forty patients with pancreatic or periampullary carcinomas otherwise considered to be potentially resectable on the basis of transabdominal ultrasonography (USS) and / or computerised tomography (CT). Occult metastatic lesions were demonstrated by laparoscopy in 14 patients (35%). Following LapUS, staging information in addition to that obtained from laparoscopy alone was obtained in 20 patients (53%), and changed the decision regarding tumour resectability in 10 patients (25%). Laparoscopy with LapUS was more sensitive and accurate than laparoscopy alone in identifying tumour unresesctability (88% and 89% versus 50% and 65%).

Study 3 comprised a prospective 'blind' comparison of USS, CT, laparoscopy with LapUS and selective visceral angiography (SVA) in the TNM staging of fifty patients with pancreatic or periampullary cancer. The unique role of staging laparoscopy in the detection of intraabdominal metastatic disease was verified by its significantly superior sensitivity and negative predictive value compared with USS and CT. In the evaluation of T stage, laparoscopy with LapUS was significantly less likely to overstage tumour compared with USS or CT. Reliable determination of N stage was not achieved by any investigation. When all these factors were considered, laparoscopy with LapUS was shown to be superior to other

investigations in identifying tumour resectability, and significantly more reliable than CT in determining tumour unresectability.

in Study 4, LPC was performed in 46 of the above patients, and was found to be insensitive in identifying patients with unresectable disease (23%). In seven patients with positive cytology (15%), LPC was highly specific and predictive (100%) for metastatic spread. However, LPC contributed no additional staging information over laparoscopy. The median cumulative survival at three and six months was 17% and 8% for patients with positive LPC compared with 87% and 71% respectively for those with negative LPC.

These studies provide evidence that staging laparoscopy with LapUS is efficacious in the preoperative assessment of patients with pancreatic or periampullary cancer. A rationalised staging algorithm based upon laparoscopy with LapUS is proposed.

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A photocopy of a publication based upon some of the work contained in this thesis apears in the appendix with the permission of the publishers and co-authors.

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ABREVIATIONS

LapUS	Laparoscopic ultrasonography
IOUS	Intraoperative ultrasonography
USS	Transabdominal ultrasonography
EUS	Endoscopic ultrasonography
CT	Computerised tomographic scanning
MRI	Magnetic resonance imaging
SVA	Selective visceral angiography
LPC	Laparoscopic peritoneal cytology
TGJ	Mr Timothy G John
OJG	Mr O James Garden
DCC	Professor Sir David C Carter
SPB	Mr Simon Paterson-Brown
JDG	Mr Donald Greig
MM	Maha Murughia
JW	John Windsor
DNR	Dr Doris Redhead
ARW	Dr Andrew Wright
PLA	Dr Paul Allan
mmHg	millimetres of mercury
CO_2	carbon dioxide gas
FG	French gauge
N/A	Data not available
L / min	litres per minute

Chapter 1 Introduction

"Select better the patients we resect
Select better who does the resection
Resect better those we select"

after Harold Conn[1]

The majority of patients who present with malignant tumours of the pancreas and liver have a poor prognosis, and it is the clinician's duty to try and achieve optimal palliation of symptoms and quality of life. Nevertheless, significant advances in surgical technique in recent years have meant that for some patients, resectional surgery offers the hope of prolonged survival, and perhaps even of "cure" from an otherwise fatal disease. Careful patient selection is, however, fundamental to the success of any attempt at "curative" resection in patients with pancreatic or hepatic malignancy. In this task, the surgeon is reliant upon a variety of investigations to help him in his clinical judgement, a field of practice where substantial improvements have also been achieved in the latter half of this century.

The clinical work which comprises this thesis was performed in the context of a specialist hepatobiliary and pancreatic surgical practice in a university teaching hospital. The advent of the novel technique of laparoscopic ultrasonography in 1991 stimulated renewed interest in its ability to improve the management of patients with pancreatic and liver malignancies. The clinical studies which comprise this thesis will, therefore, be placed in context by a historical review which seeks to outline the natural histories of these diseases, to recount the attempts made by surgeons to ameliorate their courses, and to address the strengths and deficiencies of existing imaging modalities in the assessment of patients presenting with pancreatic and hepatic malignancy.

1.1 Pancreatic and periampullary cancer

Approximately 95% of pancreatic malignancies arise from the ductal system of the exocrine pancreas and are classified histologically as adenocarcinomas[2]. Ductal adenocarcinoma of the exocrine pancreas is one of the most common causes of cancer death in the Western world and its incidence appears to be increasing. There were an estimated 27 000 new cases and 24 500 attributed deaths in the United States in 1988[3] making it the fifth leading cause of death in this category. In recent years, more than 6 500 new cases have been registered annually in the United Kingdom where pancreatic cancer is also ranked as the fifth most common cause of death from malignancy in men, and sixth in women[4].

Effective screening techniques for the detection of presymptomatic disease remain elusive[5-7], and local extrapancreatic tumour invasion and distant metastases are frequently established by the time of presentation resulting in an appalling overall prognosis. Fewer than 20% of affected patients survive the first year, and only 3% of patients survive five years after diagnosis[8]. Over 75% of pancreatic cancers are situated in the head of the gland, with the remainder distributed in the pancreatic body and tail[2, 9]. Most patients are diagnosed as having pancreatic cancer on the basis of their symptoms, the typical presentation being characterised by abdominal pain and / or obstructive jaundice. Weight loss and a profound systemic response marked by cancer cachexia and a rapid decline in wellbeing is commonly observed.

Carcinomas of the proximal pancreas may be considered as part of a larger group of "periampullary" malignancies, which include adenocarcinomas derived from the epithelium of the distal common bile duct, duodenum and papilla of Vater (i.e. malignant neoplasms arising at or within 1 centimetre of the papilla). Periampullary carcinomas show a spectrum of malignant behaviour, and often present at a relatively early stage due to biliary obstruction. They are consequently more often amenable to attempts at curative extirpation than ductal adenocarcinomas of the pancreas, and carry a more favourable prognosis. However, difficulty in distinguishing between true periampullary and pancreatic carcinomas in the clinical setting is well recognised, whether preoperatively, during laparotomy or even following pathological examination of the resected specimen[9, 10]. This dilemma was highlighted by Jones and colleagues who reported a histological diagnosis of periampullary carcinoma in 27% of 118 patients who had undergone resections for presumed pancreatic cancer[11]. Although contemporary staging classifications seek

to differentiate precisely between these pathological entities, continuing debate and clinical uncertainty justify the consideration of pancreatic and periampullary carcinomas together for the purposes of the work performed in this thesis.

1.1.1 Surgery for pancreatic and periampullary cancer

History of surgery for pancreatic malignancy

The first successful local resection of a periampullary carcinoma in continuity with a sleeve of duodenum has been attributed to Halsted in 1898[12]. In the same year, Alessandro Codivilla in Imola, Italy, performed the first pancreaticoduodenectomy to remove a tumour situated in the pancreatic head, the patient surviving 24 days postoperatively[13]. However, it was Walter Kausch in Berlin in 1909 who performed the first truly successful pancreaticoduodenectomy by an *en-bloc* resection of the pancreatic head, distal bile duct and duodenum in two stages in a patient with a periampullary cancer who subsequently survived nine months[14]. Hirschel first reported the performance of a one-stage pancreaticoduodenectomy in 1914[15]. Thereafter, resection of the pancreatic head was refined by a number of surgeons, but it was Allen O. Whipple and his associates in New York who popularised the "Whipple operation". Having first performed a "radical" two-stage resection of the pancreatic head and duodenum in a woman with an ampullary carcinoma in March 1934, Whipple and colleagues reported their experience in three patients[16]. Brunschwig extended the indications for radical pancreaticoduodenectomy to carcinoma of the pancreatic head two years later[17], and Whipple succesfully performed the operation in one-stage in 1939[18], at about the same time as Trimble of Johns Hopkins Hospital, Baltimore[19].

Modifications and refinements of the one-stage operation followed, to include biliary reconstruction by choledochojejunostomy[19, 20], pancreatic stump drainage by pancreaticojejunostomy[20] and distal gastrectomy to avoid a blind duodenal stump[21]. The evolution of the one-stage operation in this way established the operation which is now recognisable as the modern Whipple operation. Numerous technical variations have since described which are beyond the scope of this review. Thus, the concept and feasibility of radical pancreaticoduodenectomy for the attempted cure of pancreatic or periampullary carcinoma was established over fifty years ago, and this has remained the most common indication for pancreatic resection (others include chronic pancreatitis, benign pancreatic neoplasms andtrauma)[22].

However, failure to effect long term survival in all but a minority of patients undergoing pancreaticoduodenectomy for pancreatic cancer, together with a wider recognition of the potential for high postoperative morbidity and mortality, led to increasing skepticism regarding the justification for the Whipple operation for pancreatic cancer. Following the development of alternative methods for the palliation of malignant obstructive jaundice, such as surgical biliary bypass and biliary endoprosthesis insertion, Whipple's original assertation that "the considerable risk of 30% to 35% is justified if they can be made comfortable for a year or two"[23] was increasingly challenged. In 1975, Shapiro reported little benefit for patients undergoing the Whipple operation following retrospective comparison with an apparently comparable group of patients treated by palliative surgical bypass[24], Crile having published similar findings five years earlier[25]. Furthermore, a literature review at that time revealed a post operative mortality rate of 21% and a mean survival of 14 months following the Whipple operation[24]. Gudjonsson's 1987 review of the world literature comprised approximately 37 300 patients with a diagnosis of pancreatic cancer, of whom 4100 (11%) had undergone resection[26]. The average operative mortality in the 145 series reported therein between 1949 and 1986 was 18%. Only 157 five year survivors were identified (of whom 12 had not undergone resection), for an overall five year survival rate 0.4%. He concluded that 50 years of intensive effort at resections for "cure" of pancreatic cancer had yielded dismal results with minimal impact on survival, and urged abandonement of of the notion of "resection for cure" or "curable lesion"[26]. A philosophy of "therapeutic nihilism" thus became prevalent among many surgeons[27].

Nevertheless, new data also emerged showing that a more favourable outcome was possible. In 1968, Howard had reported a series of forty one Whipple operations performed without operative mortality[28]. Then during the 1980's, substantial reductions in post operative morbidity and mortality were increasingly reported from specialist centres, with mortality rates falling below 5% for the Whipple operation[11, 29-41]. Peters and Carey compared the multi institutional results of 2 133 Whipple operations (for all indications) performed during the 1970's, with those performed in 1 474 patients during the 1980's[22]. They reported a reduction in post operative mortality from 18% in the former group to 7% in the latter.

Furthermore, improved survival data following pancreaticoduodenectomy also emerged. A multicentre Japanese study reported pancreatic resection in 753 out of 3 315 patients with pancreatic cancer (23%)[42]. Of the 106 patients with tumours measuring less than 2 cm in diameter (14%), 99% underwent resection for an

operative mortality of 4% and a five year cumulative survival rate of 37%. Trede and colleagues in Mannheim, Germany, reported an actuarial five year survival of 36% among 76 patients who underwent radical curative resection of pancreatic cancer between 1985 and 1989, and an actual survival of 25% for patients with pancreatic cancer who had completed five year follow up[35]. Other reports between 1987 and 1993 documented actuarial five year survival rates of 13 - 24% following resection of pancreatic adenocarcinoma[7, 33, 39, 40, 43]. However, Trede and associates documented that five year survival does not necessarily equate with "cure", as patients alive five years after surgery had later died from recurrent tumour[30, 35]. Nevertheless, the nihilism prevailing at the start of the decade among some commentators gave way to one of "cautious optimism" by the late 1980's[6].

An alternative strategy to the Whipple operation proposed by some surgeons is total pancreatectomy. Theoretical advantages ascribed to total pancreatic resection included elimination of the potentially dangerous pancreatico-enteric anastamosis, eradication of any residual multicentric or pancreatic resection-margin malignancy and the opportunity for a more radical resection of the distal pancreas, spleen and regional lymph nodes[44, 45]. However, no evidence for increased safety or post operative survival has emerged to support total pancreatectomy or radical "regional pancreatectomy" compared with the Whipple operation[29, 30, 45-49]. For these reasons, most surgeons now avoid routine total pancreatectomy in patients with carcinoma of the pancreatic head, although not all[50].

A hundred years after Halsted's seminal report[12], transduodenal local resection, or ampullectomy, remains an alternative operation to pancreaticoduodenectomy for the resection of small periampullary carcinomas. Proponents of transduodenal ampullectomy cite its relative simplicity compared with the Whipple operation, its lesser impact on long-term digestive function and a lower post operative morbidity and mortality[51-53]. As described above, however, the morbidity and mortality associated with pancreaticoduodenectomy is extremely low in the hands of experienced surgeons in specialist centres, while transduodenal ampullectomy has not been reported to be a universally safe operation[10]. Other surgeons prefer the more radical pancreaticoduodenectomy for malignant periampullary lesions[54, 55], although there is little evidence for improved survival. In the absence of a randomised controlled study, the issue of which of these operations should be perfomed for periampullary malignancy remains controversial. Nevertheless, there is good evidence that transduodenal ampullectomy, when performed by experienced

surgeons in selected patients with T_1- T_2 periampullary adenocarcinomas, provides favourable results[10, 56, 57].

Carcinomas of the pancreatic body or tail usually present at an advanced stage and are widely considered to be rarely resectable for cure[50]. However, there have been anecdotal reports of long term survival following aggressive surgery[58], and recent series reported from The Mayo Clinic, Mannheim and Johns Hopkins cite resectability rates of 8-12%, median survivals of 7-13% and actuarial 5 year survivals of 0-11%[59-61]. Improved survival therefore may be possible in selected patients with carcinoma of the distal pancreas.

Indications for pancreatic resection and patient selection

The resectability of pancreatic cancer is a relative concept and no universal consensus exists as to what constitutes a "resectable" lesion. Resectability rates for pancreatic cancer vary widely, and are dependent both on the degree of patient selection prior to referral to a specialist practice, and the philosophy of the surgeon. Resectability rates varied between 5 - 25% in selected series during the 1949 - 1980 period[47], while Gudjonsson estimated a mean overall resectability rate of approximately 10% in his comprehensive review of surgical practice for pancreatic cancer between 1949 and 1986[26]. Increasing resectability rates in more recent years have been attributed to earlier diagnosis and selected patterns of referral. In their review of this subject, Watanapa and Williamson documented a statistically significant rise in resectability from 10% (436 out of 4 157 patients) during the 1971 - 1980 period, to 15% (859 out of 5 650 patients) during the 1981 - 1990 period[62]. The impact of specialist referral practice on resectability rates for pancreatic carcinoma was illustrated by Trede at Klinikum Mannheim, who reported a four-fold increase in resectability rates from 5.1% to 21.3% between 1973-1975 and 1979-1982, while the resectability rate for patients with periampullary carcinoma remained at a constant 73%[30].

Stratification of the results of many studies has identified several factors which appear to herald a poorer prognosis, although the evidence from different centres has not always concurred. Neverthless, it is the pathological tumour stage which ultimately determines resectability, and is influenced by factors which include tumour size, local extrapancreatic invasion and lymph node metastases. Distant metastases preclude any prospect of prolonged survival and represent a universally recognised absolute contraindication to pancreatic resection.

The concept of improved resectability for patients with "small" cancers was highlighted by the results of a multi-centre Japanese study reporting 753 pancreatic resections in 3 315 patients with pancreatic cancer (23% resectability rate)[42]. Resectability in a sub group of 106 patients (14%) with "small" tumours measuring 2 cm in diameter or less was 99%, and their cumulative five year survival was 37%. Nevertheless, only 44% of these patients had tumour confined to the pancreas, indicating that small cancer is not necessarily "early" cancer. Geer and Brennan reported significantly improved survival for patients with tumours ≤ 2.5 cm in diameter, and tumour size was confirmed by multivariate analysis as a significant predictor of poor survival[39]. Other workers have also confirmed the importance of tumour size in this context[33, 43, 63, 64]. Warshaw and Swanson referred to an arbitrary cut-off size of 3 cm to distinguish between curable and non-curable tumours[65], while others have emphasised a tumour diameter of 4 cm as indicating unresectability[66, 67].

Extension of pancreatic cancer outwith the pancreatic pseudocapsule, which may in turn reflect tumour size, invariably results in invasion of adjacent structures including the hollow viscera, the tissues of the hepatoduodenal ligament, the retroperitoneal tissues and mesenteric root, and the major peripancreatic blood vessels. In particular, the close relationship between the superior mesenteric vessels and the pancreatic head is responsible for early vascular invasion in some patients with pancreatic head malignancy, resulting in anatomical and technical limitations to resection, positive resection margins and locoregional tumour recurrence after pancreaticoduodenectomy[7, 30, 40, 68]. In this way, unsuspected tumour invasion of the superior mesenteric and portal vein is recognised as one of the most commonly encountered criteria for tumour unresectability, and was recognised as early as 1951[69]. The negative prognostic value of peripancreatic vascular invasion has since been documented by several groups[39, 70, 71].

However, not all surgeons have regarded vascular invasion as an absolute contraindication to attempted curative resection of pancreatic or periampullary cancer. Fortner advocated the concept of the "regional pancreatectomy"[72], an aggressive operation combining pancreatectomy with *en-bloc* resection of the peripancreatic soft tissues, regional lymphadenectomy and resection / reconstruction of the major peripancreatic arteries and veins. Prohibitive post operative mortality rates, especially following arterial reconstruction[72], reinforced vascular invasion as a factor contraindicating pancreatic resection, and led to recommendations for the abandonement of this technique[11, 48]. Nevertheless, some surgeons remain prepared

to perform tangential or segmental resection of the portal vein when localised tumour invasion is discovered during pancreaticoduodenectomy, and have demonstrated the feasibility of this manoeuvre with low morbidity[30, 35, 73-76]. Whether limited portal vein invasion can be shown to be a function of tumour site rather than aggressive tumour biology, and therefore benefiting from segmental resection in selected patients, remains a controversial issue.

Regional lymph node metastases have been discovered in the resection specimens of 44-88% of patients undergoing curative pancreaticoduodenectomy, and numerous studies have confirmed this as a poor prognostic factor[7, 33, 39, 40, 42, 43, 47, 65-67, 75, 77-79], although not universally[29, 47]. This issue was also addressed by Fortner in his advocacy of the regional pancreatectomy[72], and some surgeons have demonstrated improved survival following pancreatic resection with extended lymphadenectomy [35, 78, 79]. However, other studies have demonstrated no survival benefit for radical resections compared with standard pancreaticoduodenectomy[39, 80]. As with vascular resection, it remains to be seen whether the results reported by (mainly Japanese) surgeons who perform aggressive retroperitoneal dissections can be extrapolated more widely within the surgical community without incurring the substantial morbidity and mortality which diminishes the worth of the Whipple operation as a curative or palliative procedure.

1.1.2 Rationale for preoperative assessment of resectability in patients with pancreatic and periampullary cancer

The aim of preoperative investigation in patients with suspected pancreatic and periampullary carcinoma is to identify patients with potentially resectable tumours who would benefit from curative resection. Conversely, the detection of those with factors indicative of a poor prognosis allows an alternative treatment strategy to be employed. The rationale for such preoperative patient selection is dependent on several assumptions:

That injudicious tumour resection should be avoided.

As already discussed, identifiable criteria which predict for early tumour recurrence and reduced post-operative survival in patients with pancreatic and periampullary cancer include distant metastases, regional lymph node metastases and extrapancreatic invasion of the retropancreatic soft tissues, major peripancreatic vessels and viscera. Despite the readiness of some surgeons to perform aggressive radical resections, and notwithstanding the philosophy of some which supports

palliative resections in the knowledge of early tumour recurrence, the majority of the surgical community prefer to avoid resectional surgery in the face of advanced pancreatic malignancy. Thus, resectability rates for pancreatic carcinoma have remained in the range of 10 - 20% despite increasing specialisation and regionalisation of services[62].

That diagnostic laparotomy is an unacceptable primary method for evaluating patients with pancreatic and periampullary cancer.

Unnecessary laparotomy may be the source of significant physical and psychological morbidity, and is not a cost effective method of evaluating patients with suspected pancreatic or periampullary malignancy. The review of recent practice by Watanapa and Williamson indicates that laparotomy alone was performed in no fewer than 28% of patients during 1979 - 1980, for an operative mortality of 36% and a mean survival of 2.6 months[62]. This clearly represented poor palliative treatment in this group of patients. The corresponding statistics had improved during the following decade (1981 - 1990) such that 22% of patients were recorded as having undergone laparotomy alone, for an operative mortality of 18% and a mean survival of 3.1 months[62]. Similarly, de Rooij and colleagues reported the experience of the Memorial Sloane-Kettering Cancer Center, New York during 1983 - 1989[81]. Exploratory laparotomy as a single procedure was performed in 117 out of 297 patients with unresectable pancreatic cancer (39%), although a previous surgical bypass had already been fashioned in nearly a third of such patients prior to referral. The median survival in this group was 193 days[81]. In Gudjonsson's review, the "laparotomy with or without biopsy" rate was 33%[26].

Much of this apparent deficiency in the management of patients presenting with pancreatic and periampullary cancer can be attributed to limitations in the reliability of the available preoperative investigative methods. In particular, failure to detect small volume, disseminated intraabdominal carcinomatosis until the time of laparotomy has characterised the management of this disease[82-87].

That there are viable alternatives to surgical palliation.

Laparotomy has always been justified in a proportion of patients with unresectable pancreatic and periampullary carcinoma because of the opportunity to perform palliative biliary and / or gastric bypass surgery. Established or impending malignant biliary obstruction could be relieved by biliary-enteric diversion, and gastroenterostomy could be performed either as a therapeutic procedure or prophylactically in an attempt to relieve malignant gastric outlet obstruction.

Watanapa and Williamson estimated that 49% of 5 650 reported patients treated for pancreatic ductal carcinoma during 1981 - 1990 underwent surgical bypass operations, a significant increase from the 45% managed in this way during the preceding decade[62]. However, the mean operative mortality in this series was 17% (range 4 - 33%), although improved results have again been reported recently from specialist centres. In the Johns Hopkins Hospital, Baltimore, Lillemoe and colleagues reported an operative mortality rate of 2.5% in 118 patients undergoing surgical palliation of unresectable pancreatic and periampullary cancer, 75% of whom had undergone biliary bypass combined with gastroenterostomy[88].

However, alternative non-operative methods of palliating malignant biliary obstruction had been developed. Soehendra and Reynders-Frederix first describe the feasibility of biliary stent insertion during ERCP[89], and this was soon adopted as a rapid and effective method for the relief of obstructive jaundice[90]. Percutaneous transhepatic biliary stent insertion had also been established in this role by the late 1970's[91, 92]. Problems encountered with biliary stents included their tendency to become occluded causing recurrent jaundice and / or cholangitis[93], and requiring readmission to hospital for stent replacement. Also, technical problems prevent stent insertion in a proportion of patients, especially by the endoscopic technique when duodenal diverticulae, angulation of the duct and / or proximal duct strictures are encountered. A randomised trial comparing endoscopic and percutaneous methods of stent insertion in patients with malignant obstructive jaundice considered unfit for surgery demonstrated the endoscopic method to have a significantly superior success in the relief of jaundice, and significantly better 30-day mortality[94]. A combined percutaneous and endoscopic approach has been shown to be succesfull in circumstances where endoscopic stenting is difficult[95, 96].

The role of such non-operative techniques compared with surgical methods of palliation of obstructive jaundice has been addressed in several studies. Watanapa and Williamson compared the collective results of patients with pancreatic cancer who had undergone surgical bypass (1 807 patients), endoscopic stent insertion (689 patients) and percutaneous stent insertion (490 patients)[62]. They discovered similar mean success rates (90 - 93%) and 30-day mortality rates (9 - 14%). However, the mean hospital stay and early complication rate was greater following surgical bypass (17 days and 31%) compared with endoscopic stenting (7 days and 21%)[62]. Of course, biases due to patient selection are unavoidable in this type of meta-analysis.

Bornmann and co-workers reported a randomised comparison of percutaneous transhepatic stenting with bypass surgery in 53 patients with incurable pancreatic cancer[97]. Similar morbidity and mortality was observed, with a significantly shorter post procedural hospital stay in the stent group. An increased incidence of recurrent jaundice requiring readmission in patients with stents offset this early advantage[97]. The first two prospective randomised studies comparing endoscopic biliary stenting with surgical biliary bypass also demonstrated no significant differences regarding relief of jaundice or long-term survival[98, 99]. However, these studies have been criticised for their small numbers, limited follow-up, usage of small bore stents and / or bias towards the stenting arm. Also, the operative mortality of 15 - 24% associated with surgical bypass in these studies is at variance with the results currently achieved in specialist centres[88]. Nevertheless, a recent survey of palliative operations performed for pancreatic cancer in 1 180 patients in U.S. Department of Veterans Affairs hospitals between 1987 and 1991 reported a 13% post operative mortality following biliary bypass[100].

Smith and colleagues at the Middlesex Hospital, London, have since completed a prospective study randomising 201 patients with low malignant biliary obstruction to surgical biliary bypass or endoscopic stent insertion[101]. They reported that in stented patients, there was a significantly lower prodeure-related mortality (3% versus 14%), major complication rate (11% versus 29%) and median total hospital stay (20 versus 26 days). However, recurrent jaundice and gastric outlet obstruction were also problematical requiring readmissions in the stented group, and there was no significant difference in overall survival between stented and operated patients (median 21 weeks versus 26 weeks respectively)[101]. Once more, the results must be considered in the context of a relatively high operative mortality (14%). Indeed, many of the operations were performed at the referring hospital, and not necessarily by a consultant surgeon. It is also pertinent to note that cholecystjejunostomy or choledochoduodenostomy was the method of surgical biliary bypass most frequently employed in these studies, although many surgeons would regard choledocho- / hepatico-jejunostomy as a better operation[102].

A retrospective Dutch study of 148 patients with advanced pancreatic cancer treated between 1980 and 1990 broadly confirmed the findings of these comparative trials[103]. It also sought to clarify the respective roles of endoscopic stent insertion and surgical biliary bypass by stratifying patients into those with long survival (> 6 months) and short survival (< 6 months). They demonstrated that in short-term survivors, the higher late morbidity associated with delayed stent occlusions was

offset by the higher early morbidity and prolonged hospital stay associated with surgical palliation. Conversely, in long-term survivors, there was no difference in initial hospital stay between the two groups, but the late morbidity was significantly higher in the endoprosthesis group of patients. They therefore concluded that biliary stent insertion is the optimal method for palliating patients expected to survive less than 6 months, while surgical biliary bypass should be reserved for patients with longer life expectancy. However, prospective implementation of such a policy requires prognostic criteria. The same authors identified male gender, advanced age, liver metastases and large tumour size as unfavourable prognostic factors[103].

Proponents of a surgical approach to management also cite the role of (i) therapeutic or prophylactic gastroenterostomy for malignant gastric outlet obstruction[102], and (ii) the desire for a histological diagnosis which may be obtained reliably by operative tumour biopsy and will exclude non-ductal pancreatic tumour which have a better prognosis(e.g. neuroendocrine tumour, cystadenoma, cystadenocarcinoma, sarcoma or lymphoma)[104].

The addition of prophylactic gastroenterostomy to surgical biliary bypass does not appear to increase operative mortality, and a late reoperation rate for gastric outlet obstruction of 12-17% has been reported following biliary bypass[62, 100]. Conversely, the reported experience of the Memorial Sloane-Kettering Cancer Center, New York, indicated that a prophylactic bypass added to a therapeutic bypass increased morbidity without prolonging survival[81]. Furthermore, Dutch workers have investigated specifically the role of prophylactic gastroenterostomy at the time of surgical biliary bypass[105]. Citing higher complication rates following gastroenterostomy, and having demonstrated no significant difference in the interval to the occurrence of a symptomatic obstruction following gastroenterostomy in asymptomatic patients, they presented a strong case against routine prophylactic gastroenterostomy. It should also be appreciated that the impact of late gastric outlet obstruction on morbidity and survival was accounted for in the aforementioned randomised studies comparing stent insertion with surgical bypass[97, 101, 103].

Secondly, advances in a wide range of both non-invasive and invasive imaging techniques have significantly improved the yield in obtaining a histological or cytological diagnosis of pancreatic malignancy. Accepting that false negative results are inevitable in a proportion of patients, most now recognise that diagnostic laparotomy is rarely necessary[106].

The available evidence therefore suggests that endoscopic stent insertion is feasible in the majority of patients with unresectable pancreatic cancer, and that in the short-term, it is as least as effective and probably safer than surgical biliary bypass in relieving jaundice. On these grounds at least, laparotomy can no longer be considered mandatory in the management of patients with pancreatic cancer, especially in the elderly or unfit patient without symptoms of gastric outlet obstruction.

There may also be health economic reasons for judicious patient selection for surgical intervention. More efficient utilisation of available hospital resources is facilitated by reliable planning of major resectional surgery, and avoidance of unnecessary operations.

1.2 Methods of preoperative assessment of patients with pancreatic and periampullary cancer

The pancreas is a small and complex organ situated within the retroperitoneal tissues of the abdomen and concealed by overlying vicera. Intimately related to major splanchnic blood vessels, the head of the pancreas marks the point of intersection of all areas of the body and has accordingly been described as the "topographical centre of man"[9]. Thus, the pancreas has always been recognised as a difficult organ to image, and has been called the "hidden organ" [107]. During the last two decades, the development of a variety of sophisticated radiological techniques has allowed direct visualisation of primary abnormalities of the pancreatic parenchyma, ductal system and vasculature, as well as changes in surrounding tissues.

The type of information required of the imaging examination in patients with suspected pancreatic malignancy may be divided broadly into two types; (i) *diagnostic* information, where an abnormal pancreatic lesion is suspected and confirmation of the diagnosis is required, and (ii) *staging* information, where the anatomical extent of established tumour is determined. This reflects the priorities encountered in the management of patients who present with malignant obstructive jaundice or suspected pancreatic cancer. Pancreatic cancer implies a grave prognosis, and it is important to first establish the diagnosis so that the patient may be properly informed and advised. Secondly, if one accepts the rationale for accurate tumour staging (see Section 1.1.2), it is desirable both to identify patients with localised tumours who may benefit from resectional surgery, and to

demonstrate those with more advanced disease in whom efforts should be directed at palliative measures.

Appraisal of the results of published studies of imaging investigations is often confounded by variations in study design, methods of data analysis and the definition and validation of endpoints. Furthermore, differences in equipment and technique, and variations in the level of local expertise may introduce biases. Most published studies of radiological imaging in patients with pancreatic and periampullary cancer are "pilot studies", or "studies of diagnostic accuracy" as discussed in Section 2.1.2. In the latter study design, results are expressed as "summary measures of diagnostic accuracy", and the use of standard definitions for such parameters is important to avoid confusion of terminology. For the purposes of this thesis, the following standard definitions were adopted in the diagnosis / staging of pancreatic or periampullary cancer:

Sensitivity: "the proportion of patients with tumour / unresectable tumour who are reported to be positive".
Specificity: "the proportion of patients with no tumour / resectable tumour who are reported negative".
Positive predictive value: "the proportion of patients reported positive who have tumour / unresectable tumour ".
Negative predictive value: "the proportion of patients reported negative with no tumour / resectable tumour".

To facilitate comparisons of the results of published studies, the nomenclature used in this review, and in Tables 1.1 - 1.8, has been adjusted to conform to the above format.

1.2.1 Conventional radiography and contrast studies

Until the development of ultrasound scanning in the 1960's, radiological assessment of pancreatic disease was restricted to various techniques of enhancement of plain abdominal radiographs[108]. Such methods were limited in their ability to confirm a diagnosis of pancreatic cancer, and relied upon the presence of a soft tissue mass in the upper abdomen, or upon indirect signs such as a distended 'Courvoisier' gall bladder, splenomegaly secondary to splenic vein thrombosis, malignant ascites or the discovery of sclerotic bone metastases. The majority of investigations in this

category are of historical interest, and now contribute little to the preoperative assessment of patients with pancreatic disease.

Upper gastrointestinal contrast studies

Upper gastrointestinal contrast studies were used to demonstrate secondary pathological effects of primary pancreatic malignancies in the surrounding structures. In this way, a barium meal could be used to diagnose pancreatic cancer by demonstration of deformity within the retrogastric space, malignant infiltration of the posterior wall of the stomach (the "pad sign")[109], and disfigurement of the medial outline of the duodenum with shrinkage and traction giving the "inverted 3 sign"[110]. Insufflation of the stomach with air was described as a further manoeuvre which could provide information missed by a barium meal[108]. However, the fallibility of such methods was illustrated by Hodes and colleagues who failed to identify pancreaticoduodenal tumours in a half of patients studied in this way[111].

Pneumoperitoneum and pneumostratigraphy

Insufflation of the peritoneal cavity with gas was performed in an attempt to outline the body and tail of the pancreas by demonstrating radiographically the tissue - gas interface of the retroperitoneal structures. In 'pneumostratigraphy', the simultaneous insufflation of the stomach and retroperitoneum was combined with lateral and axial tomograms[108]. Thus, the pancreas was defined anteriorly by stomach gas, and posteriorly by retroperitoneal gas. Local irregularities due to a pancreatic tumour could be defined, and it was claimed that the technique was sufficiently sensitive to detect retropancreatic lymphadenopathy[108]. The presence of adhesions was an obvious limiting factor in the performance of this technique.

Hypotonic duodenography

Air insufflation following the ingestion of oral barium was used to produce a double-contrast duodenogram, while hypotonia of the duodenal loop was achieved through the administration of a spasmolytic agent. This revealed fine detail of the duodenal mucosa in the vicinity of the papilla and pancreatic head sufficient to demonstrate even small tumours[108].

During the last twenty years, these techniques have largely been superseded by upper gastrointestinal endoscopy as the investigation of choice for suspected direct

involvement of the upper gastrointestinal tract by tumours of the pancreas and periampullary region.

1.2.2 Cholangiography and pancreatography

Percutaneous transhepatic cholangiography (PTC)

Percutaneous transhepatic cholangiography became a routine method for routine biliary opacification after Okuda developed the "Chiba" needle in 1974[112, 113]. Its accuracy in establishing the diagnosis of malignant biliary obstruction was demonstrated by Freeny and Ball who described its use in 112 patients[114]. Successful opacification of the biliary tree was achieved in 100 patients (89%), and pancreatic cancer was diagnosed with a sensitivity of 100% and specificity of 96%. However, its diagnostic role in patients with suspected pancreatic malignancy was rapidly superseded by ERCP, and indications for its use became restricted to instances where diagnostic or therapeutic ERCP was not possible.

Endoscopic retrograde cholangiopancreatography (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) was first described by McCune and colleagues in 1968[115], enabling direct, non-surgical imaging of the biliary and pancreatic ducts for the first time. Combined with the opportunity for endoscopic observation and biopsy of locally invasive tumour, and later therapeutic intervention to achievebiliary decompression[89], ERCP rapidly became established as a primary modality in the management of patients with malignant biliary obstruction in the 1980's. In Freeny and Ball's study[114], ERCP was performed in 376 patients with suspected pancreatic disease between 1975 and 1979, yielding a sensitivity of 94% and a specificity of 97% in the diagnosis of pancreatic cancer. Obstruction ("blunt, tapering, irregular or meniscus" stenoses) of the main pancreatic duct and / or comon bile duct were the most commonly observed criteria for the diagnosis of pancreatic cancer, and the "double duct" sign was present in 27% of patients with pancreatic cancer[114].

Nevertheless, such abnormalities of the bile and pancreatic ducts were not exclusive to pancreatic cancer, and the limitations of ERCP (in common with all available investigations) in differentiating malignancy from chronic pancreatitis were recognised[116, 117]. Furthermore, the continued development of abdominal CT scanning led some authors to challenge the role of ERCP within increasingly complex diagnostic algorithms for suspected pancreatic cancer, in which ERCP

contributed little in addition to less invasive investigations such as CT, particularly with regard to tumour staging[118]. Silverstein and colleagues employed the technique of decision analysis to model and analyse diagnostic strategies in the diagnosis of suspected pancreatic cancer in terms of diagnostic accuracy, cost and invasiveness[119]. Assuming a sensitivity of 90% and a specificity of 95% from previously published studies, it was estimated that ERCP would be indicated in just 8-11% of patients if transabdominal USS was used as the first investigative method, but that abandonement of ERCP altogether would substantially increase the subsequent requirement for diagnostic laparotomy. In a cost-benefit analysis of the diagnostic algorithm for pancreatic cancer employed at University College Los Angles, Alvarez and colleagues have reported that the results of ERCP rarely altered the management of patients in whom a pancreatic mass had been demonstrated on CT[120]. Like Freeny and Ball a decade before[114], they recommended its restriction to use when CT was "normal or atypical". However, these findings should be considered in the context of a practice where the therapeutic role of ERCP made little contribution, endoscopic palliation of malignant obstructive jaundice usually being deferred in favour of surgical palliation.

1.2.3 Transabdominal ultrasonography (USS)

Real-time B-mode transabdominal USS was developed in the 1960's, and was the first cross-sectional imaging technique that permitted direct imaging of the pancreas[121, 122]. The principles of B-mode USS imaging are discussed in Section 1.2.8. Its safety, repeatability and relative inexpense made USS a popular primary method in the investigation of patients with suspected pancreatic cancer. In particular, USS was shown to be a reliable method for demonstrating biliary dilatation and establishing the diagnosis of obstructive jaundice[123]. However, disadvantages of USS include its operator dependency and its vulnerability to image degradation caused by factors such as body wall tissues and bowel gas. This was reflected in the widely varying results obtained using USS in the investigation of obstructive jaundice. Whereas some workers reported being able to use USS to both define the level of biliary obstruction and diagnose the underlying lesion in 94-95% and 68-81% of cases respectively[124, 125], others were unable to reproduce these good results[126, 127].

In the hands of enthusiasts, technical refinements and improvements in USS scanning techniques yielded consistently better results in the investigation of patients with obstructive jaundice during the 1980's. Laing and co-workers were able to

define the level of biliary obstruction in 92% of patients, and establish the underlying diagnosis in 72%[128]. For Gibson and colleagues in the Hammersmith Hospital, London, the corresponding figures were 95% and 80% respectively, which in their experience compared favourably with CT[129]. Lindsell reported a sensitivity of 84% and specificity of 95% for USS in defining abnormalities of the pancreas and bilary tract, and recommended USS as a prelude to ERCP in the management of patients with suspected malignant biliary obstruction[130].

The reported performance of diagnostic USS in identifying focal pancreatic tumours also varied widely. Gudjonsson reviewed the results of 23 studies reported between 1977 and 1986, in which USS was used in the diagnosis of pancreatic cancer[26]. There were marked variations in the design of these studies, in patient selection, in the exclusion of technically inadequate examinations and in the requirement for histological proof of the diagnosis, and comparison of results was therefore difficult. The reported sensitivities for USS in diagnosing pancreatic cancer ranged from 23% to 95%[26].

The results of other studies evaluating the diagnostic sensitivity of USS in this role and published since 1982 are summarised in Table 1.1. Again, a variety of methodologies and a wide range of results are apparent. Single-centre, single-modality studies of USS performed by enthusiasts yielded sensitivities of 98%[131] and 83%[132]. In particular, the retrospective study reported by Maringhini and colleagues comprised a population of 1 020 patients with suspected pancreatic disease, of whom 80 (8%) were shown to have pancreatic cancer[132]. Despite the unusually low prevalence of pancreatic cancer for a study such as this, the utility of USS in their hands was illustrated by a negative predictive value of 95% and sensitivity of 83%. Conversely, poorer results were reported from prospective studies where comparison with other newer modalities was performed(sensitivities 51% - 65%)[126, 133-138]. Nevertheless, USS was shown to be more sensitive than CT in the diagnosis of pancreatic cancer in two small comparative studies[139, 140].

Few studies have evaluated the role of transabdominal USS in the staging of pancreatic cancer (Table 1.2). The only study which has supported a primary role for transabdominal USS in the assessment of resectability of pancreatic cancer was reported by Campbell and Wilson[131]. They evaluated retrospectively 54 patients presenting with pancreatic neoplasms in Toronto General Hospital during 11 months in 1986. Malignant lymhadenopathy was correctly identified in 16 patients (30%), but missed in five. Liver metastases were detected in 16 patients (30%), and

overlooked in three. Vascular invasion was identified in 12 patients (22%), seven of which were validated as such at operation, with four false negative examinations identified. In terms of overall staging, no false positive examinations were reported (i.e. 100% specificity), and 31 out of 38 patients (82%) were identified as having unresectable tumours. However, not all these findings had been validated surgically.

A retrospective Dutch study compared the results of USS and CT in the staging of pancreatic cancer in 24 patients over ten years[135]. Despite repeating USS in some patients, neither technique was able to satisfactorily predict tumour resectability. Four prospective, comparative studies have also reported USS to have been insensitive in detecting criteria which contraindicated curative resection (sensitivities 8-16%), and poorly predictive of tumour resectability (predictive values of negative results 29-68%)[136-138, 140]. One study reported USS to have consistently overstaged the disease with respect to vascular invasion, citing the predictive value of a positive result as 11%[136]. However, this has not been the experience of others[131, 135, 137, 138].

1.2.4 Computerised tomography (CT)

Computerised tomographic scanning was introduced into clinical practice in 1975, and initial reports documented its ability to generate cross-sectional images of the abdominal organs including the pancreas, and diagnose pancreatic cancer through the demonstration of focal pancreatic masses or contour abnormalities[141-145]. Refinements in CT technology subsequently improved the quality of pancreatic imaging. The speed of data collation was increased such that the original "18-27 second scanners" were replaced in the early 1980's by those requiring only 5-10 second scanning times[146, 147]. Image resolution was improved by the use of thinner (5-10 mm) 'slices', and dynamic intravenous bolus contrast -enhanced CT protocols were developed[148]. These techniques maximised the density differences of normal and pathological tissues, achieving bright enhancement of the abdominal viscera with brilliant opacification of abdominal vessels. Thus, radiologists were able not only to diagnose pancreatic neoplasms, but also to evaluate their relation with surrounding tissues. In their description of the technique in 100 patients with proven pancreatic cancer, Ward and colleagues identified a pancreatic mass in 95%, a lucent area within the mass in 75%, coeliac or SMA involvement in 60%, pancreatic duct dilatation in 50%, biliary dilatation in 38% and hepatic metastases[149].

Table 1.1 - Summary of published studies (1982-1993) evaluating USS in the diagnosis of primary peripancreatic malignancy

Author and year	Study design *	Results
Baron et al [126] 1982	Prospective vs. CT n = 12 (103)	Sensitivity = 67%
Hessel et al [133] 1982	Prospective vs. CT n = 52 (279)	Sensitivity = 56%
Campbell et al [131] 1988	Retrospective USS only n = 51	Sensitivity = 98%
Päivänsalo et al [139] 1988	Retrospective vs. CT n = 36	Sensitivity = 86%
Yasuda et al [134] 1988	Prospective vs. CT / EUS n = 42 (187)	Sensitivity = 72%
de Roos et al [135] 1990	Retrospective vs. CT n = 41	Sensitivity = 51%
Bakkevold et al [137] 1992	Prospective Multicentre vs. CT / SVA n = 310	Sensitivity = 52%
Rösch et al [136] 1992	Prospective vs. CT / EUS / SVA n = 60	Sensitivity = 78%
Yasuda et al [140] 1993	Prospective vs. CT / EUS n = 29	Sensitivity = 86%
Palazzo et al [138] 1993	Prospective vs. CT / EUS n = 49 (64)	Sensitivity = 65% Specificity = 60% PPV = 84% NPV = 35%
Maringhini et al [132] 1993	Retrospective USS only n = 80 (1020)	Sensitivity = 83% Specificity = 99% PPV = 86% NPV = 95%

* figure in parentheses indicates total number of all USS examinations performed, including those with a diagnosis other than pancreatic cancer.

Table 1.2 - Summary of published studies (1988-1993) evaluating USS in the staging of peripancreatic malignancy

Author and year of publication	Study design	Type of information	Results
Campbell et al [131] 1988	Retrospective USS only n = 51	Overall resectability	Sensitivity = 82% Specificity = 100%
de Roos et al [135] 1990	Retrospective vs. CT n = 24	Overall resectability	Sensitivity = 18% Specificity = 100% PPV = 100% NPV = 18%
Bakkevold et al [137] 1992	Prospective Multicentre vs. CT / SVA n = 160	Overall resectability	Sensitivity = 16% Specificity = 98% PPV = 95% NPV = 29%
Rösch et al [136] 1992	Prospective vs. CT / EUS / SVA n = 40	PV invasion	Sensitivity = 9% Specificity = 72% PPV = 11% NPV = 68%
		Node metastases	Sensitivity = 12% Specificity = 80%
Palazzo et al [138] 1993	Prospective vs. CT / EUS n = 38	PV invasion	Sensitivity = 17% Specificity = 100% PPV = 100% NPV = 41%
		Node metastases	Sensitivity = 8% Specificity = 100% PPV = 100% NPV = 33%
Yasuda et al [140] 1993	Prospective vs. CT / EUS n = 29	Vascular invasion	Accuracy = 55%

Megibow illustrated the evolution of the technique of CT scanning for pancreatic cancer in a study which compared CT findings in 104 patients studied during 1979 - 1982, with 107 examinations during 1984 - 1987[148]. Pancreatic masses were identified more frequently in the second group both for lesions situated in the head of the gland (94% vs. 76%), and for lesions situated in the body and tail (96% vs. 89%). Thus, the development during the 1980's of rapid CT scanning techniques with 'dynamic incremental' table movements and high volume, high concentration bolus pump infusion of intravenous contrast enabled the detection of subtle, intraparenchymal lesions, pancreatic and bile duct dilatation as well as hepatic and

nodal metastases. Oral contrast was also administered prior to scanning to opacify adjacent bowel loops. However, limitations associated with CT scanning were observed in patients with a history of allergy to contrast material, in uncooperative patients where respiratory movements or body motion prevents adequate scanning and in those with marked weight loss where the absence of retroperitoneal fat hindered the definition of tissue planes[107, 147, 150].

Gudjonsson reviewed the results of 21 studies evaluating CT in the diagnosis of pancreatic cancer which had been reported between 1977 and 1986[26]. As before (see Section 1.2.3), methodological flaws and variations in CT technique and in the study designs confound valid comparison. This collective experience showed the proportion of positive CT examinations to vary from 63 to 100%[26]. It was noteworthy that, despite improvements in CT technique over a decade, the studies performed later in the period did not necessarily show better results. Furthermore, Gudjonsson concluded that despite USS and CT having heralded a new era in diagnostic imaging, no changes in the duration of symptoms up to the time of diagnosis or in survival were apparent[26].

The results of 13 other studies evaluating the "accuracy" of CT in the diagnosis of pancreatic cancer and published since 1982 are summarised in Table 1.3. Diagnostic sensitivities in the range 69-99% are not at variance with the earlier experience reported by Gudjonsson[26]. Reasons for the relatively poor performance of CT in a recent study includes the use of unenhanced CT techniques, perhaps reflecting a lack of specialist interest in pancreatic imaging[135]. Neverthless, the 70% sensitivity reported by a prospective multi-centre Norwegian study may well be representative of wider practice outwith specialist centres[137]. However, this does not apply to several prospective comparative studies reporting diagnostic sensitivities of 69-85%, which may reflect their higher proportion of patients with small pancreatic cancers and periampullary tumours[134, 136, 138, 140]. That CT imaging alone is ultimately unable to differentiate reliably between pancreatic cancer and other focal lesions such as chronic pancreatitis is illustrated by the occurrence false positive examinations, giving specificities of 53-69%, and positive predictive values of 83-92%[150-152].

Although CT has become the principal imaging modality used in the assessment of resectability in patients with pancreatic cancer during the last decade, the reported experience with staging CT has not been uniformly reliable. The results of abdominal CT in the staging of pancreatic and periampullary cancer in studies

Table 1.3 - Summary of published studies (1982-1993) evaluating CT in the diagnosis of pancreatic cancer

Author and year	Study design *	Results
Baron et al [126] 1982	Prospective vs. USS n = 12 (103)	Sensitivity = 83%
Hessel et al [133] 1982	Prospective vs. USS n = 52 (279)	Sensitivity = 84%
Freeny et al [150] 1988	Retrospective CT only n = 161 (174)	Sensitivity = 99% PPV = 91%
Yasuda et al [134] 1988	Prospective vs. ERCP / USS / EUS / SVA n = 42 (187)	Sensitivity = 78%
Päivansalo et al [139] 1988	Retrospective vs. USS n = 36	Sensitivity = 69%
de Roos et al [135] 1990	Retrospective vs. USS n = 26	Sensitivity = 77%
Bakkevold et al [137] 1992	Prospective Multicentre vs. USS / SVA n = 209	Sensitivity = 70%
Rösch et al [136] 1992	Prospective vs. USS / EUS / SVA n = 60	Sensitivity = 85%
Megibow [148] 1992	Prospective CT only n = 107	Sensitivity = 94%
Freeny et al [154] 1993	Retrospective CT only n = 213	Sensitivity = 97%
Yasuda et al [140] 1993	Prospective vs. USS / EUS n = 29	Sensitivity = 72%
Bryde Andersen et al [152] 1993	Retrospective CT only n = 52 (77)	Sensitivity = 92% Specificity = 69% PPV = 92% NPV = 69%
Palazzo et al [138] 1993	Prospective vs. USS / EUS n = 49 (64)	Sensitivity = 69% Specificity = 53% PPV = 83% NPV = 35%

* figures in parentheses indicates total number of CT examinations performed

reported since 1984 are summarised in Table 1.4. Jafri and colleagues provided the first evidence to support CT as a reliable non-operative method of assessing the resectability of pancreatic cancer in a retrospective comparison with SVA[153]. Both techniques performed comparably, correctly identifying 20 out of 22 patients withunresectable tumours with no reported false positive results. However, no independent validation of such findings was available in eight of these patients, the authors instead citing "unequivocal findings on preoperative radiography".

However, it is Freeny and co-workers in Seattle who were mainly responsible for the popularisation of dynamic CT in the staging of pancreatic cancer with their papers of 1988[150] and 1993[154]. In their initial study, 161 patients with pancreatic cancer were studied prospectively over 6 years, with histological confirmation of the diagnosis in 72%[150]. Local tumour extension was reported in 68% of patients, contiguous organ invasion in 42%, liver metastases in 36%, lymph node metastases in 28%, and / or vascular invasion of the major peripancreatic arteries or veins in 84%. Validation of these findings was performed at laparotomy in 51 patients (32%), nine of whom were thought to have had potentially resectable tumours, and 25 of whom had also been evaluated with SVA. There were no proven instances where CT or SVA examinations had overstaged the tumour, although palliative pancreatic resections were performed in four cases. Seven out of nine patients were amenable to "curative" pancreatic resection (albeit with nodal micrometastases in five patients). The findings of SVA and CT were approximately comparable, and the abandonement of SVA in favour of CT was recommended by the authors.

The same group subsequently reported their updated experience over ten years[154]. They performed CT in 213 patients with pancreatic cancer, and SVA in 60 patients, correlating the findings with those obtained at surgery in 71 patients (33%). The incidence of CT criteria indicating tumour unresectability were essentially the same as the previous study. As before, there were no false positive results pertaining to tumour resectability, and SVA again failed to contribute additional staging information over CT. Of the 18 patients considered to have potentially resectable tumours on CT in whom laparotomy was performed, six were found to be unresectable (i.e. negative predictive value 33%). Also, only three out of 11 resected tumours were histologically free of local or regional tumour spread.

While these studies seemingly provide reassurement that CT does not overstage pancreatic cancer, thereby denying patients with potentially resectable tumour a

Table 1.4 - Summary of published studies (1984-1993) evaluating CT in the staging of peripancreatic cancer

Author and year	Study Design	Type of Information	Results
Jafri et al [153] 1984	Retrospective vs. SVA n = 27	Overall staging	Sensitivity = 91% Specificity = 100% PPV = 100% NPV = 71%
Freeny et al [150] 1988	Retrospective vs. SVA n = 51	Overall staging	Sensitivity = 95% Specificity = 100% PPV = 100% NPV = 78%
Ross et al [155] 1988	Retrospective CT only n = 66	Overall staging	Sensitivity = 72% Specificity = 75% PPV = 93% NPV = 38%
		Local invasion	Sensitivity = 56% Specificity = 82% PPV = 90% NPV = 38%
de Roos et al [135] 1990	Retrospective vs. USS n = 26	Overall staging	Sensitivity = 50% Specificity = 50% PPV = 85% NPV = 15%
Warshaw et al [86] 1990	Prospective vs. MRI / Lap / SVA n = 55	Overall staging	Sensitivity = 56% Specificity = 88% PPV = 92% NPV = 45%
Bakkevold et al [137] 1992	Prospective Multicentre vs. USS / SVA n = 209	Overall staging	Sensitivity = 27% Specificity = 98% PPV = 97% NPV = 35%
Gulliver et al [156] 1992	Retrospective CT only n = 67	Overall staging	Sensitivity = 91% Specificity = 76% PPV = 89% NPV = 80%
Rösch et al [136] 1992	Prospective vs. USS / EUS / SVA n=60	PV Invasion	Sensitivity = 36% Specificity = 85% PPV = 50% NPV = 78%
		Node metastases	Sensitivity = 36% Specificity = 80%
Freeny et al [154] 1993	Prospective vs. SVA n = 71	Overall staging	Sensitivity = 90% Specificity = 100% PPV = 100% NPV = 33%

Table 1.4 (continued) - Summary of published studies (1984-1993) evaluating CT in the staging of peripancreatic cancer

Author and year	Study Design	Type of Information	Results
Bryde Andersen et al [152] 1993	Retrospective CT only n = 52	Overall staging	Sensitivity = 68% Specificity = 67% PPV = 70% NPV = 64%
		Vascular invasion n = 38	Sensitivity = 90% Specificity = 39% PPV = 62% NPV = 78%
Palazzo et al [138] 1993	Prospective vs. USS / EUS n = 38	PV invasion	Sensitivity = 71% Specificity = 86% PPV = 89% NPV = 63%
		Node metastases	Sensitivity = 19% Specificity = 92% PPV = 83% NPV = 34%

curative resection, it should be noted that surgical validation of positive findings was obtained in no more than one third of all patients. Also, the prevalence of resectable pancreatic cancer in this study (6%) was so low, that the apparent CT detection of tumour unresectability was skewed to provide a stated sensitivity of 97%[154]. Thesefindings may not be representative of specialist surgical practices where higher rates of tumour resectability are encountered, and unsurprisingly, several other studies have failed to reproduce similar data (Table 1.4).

Other published studies evaluating CT as a staging method in patients with pancreatic and periampullary cancer all reported false positive findings and identified a variable tendency to overstage tumour. In the context of overall tumour staging, this was reflected by specificities of 50-98%, while the predictive value of a CT result indicating tumour unresectability varied from 70-97%[86, 135, 137, 152, 155, 156]. More specifically, the specificity of CT in demonstrating vascular invasion has been reported as 39-86%, and the positive predictive value 50-89%[136, 138, 152]. Some authors therefore maintain that CT alone is not an adequate basis on which to determine the operability of patients with pancreatic or periampullary cancer[86, 152, 155].

Despite a comonly held belief that CT is highly sensitive in identifying liver metastases[107, 148], several workers have recorded the failure of CT to detect small

metastatic lesions of the liver and peritoneal surfaces[135, 152, 155-158]. Moreover, in their study of 88 consecutive patients with pancreatic or periampullary cancer, Warshaw and co-workers reported CT to have missed such "occult" metastases in 25 out of 27 patients, and have recommended routine preoperative laparoscopy to address this deficiency[86]. This issue is considered more fully in Section 1.2.7. However, not all surgeons accept these findings as representative of their practice[159]. In a study of 90 patients evaluated by CT and SVA at the Johns Hopkins Hospital, Baltimore, there were only six instances where unsuspected peritoneal metastases were reportedly discovered at laparotomy[160].

In an attempt to improve the sensitivity of CT in the detection of peritoneal metastases in the context of gynaecological malignancy, Halvorsen and colleagues performed intraperitoneal contrast enhanced CT[161]. They reported an increased sensitivity of 100% (16 / 16) compared with 64% (11 / 16) for unenhanced CT. However, a comparative study of intraperitoneal contrast enhanced CT versus standard CT in patients with a variety of abdominal malignancies by Nelson and co-workers failed to show any advantage[162]. Such techniques have never been employed routinely in the evaluation of patients with pancreatic cancer, in whom intra-peritoneal tumour dissemination is typically of minimal volume.

A significant recent advance in CT technology was the development of spiral (or helical) CT[163, 164]. This technique enables faster acquisition of truly volumetric CT data, and was made possible because of technical refinements such as the slip-ring gantry, improved detector efficiency and greater tube cooling efficiency[164]. A pilot study of spiral CT of the pancreas has reported far superior vascular opacification with reduced respiratory artifact compared with conventional CT, while the capability for rapid imaging permits the acquisition of thin ($\leq$ 5 mm) sections with correspondingly increased resolution[163]. Also, retrospective reconstruction of overlapping slices has enabled three-dimensional images of the portal venous sytem to be created[165]. The implications of these technological advances for the staging of patients with pancreatic cancer remain to be defined, and studies investigating the efficacy of spiral CT in the assessment of tumour resectability are awaited.

1.2.5 Magnetic Resonance Imaging (MRI)

The role of MRI in the diagnosis and staging of patients with pancreatic and periampullary carcinoma is unclear. Several comparative studies have reported no discernible advantage for MRI over CT in identifying tumour unresectability due to

extrapancreatic tumour spread[86, 166, 167]. The results of an American multi-centre study comparing CT and MRI in the staging of pancreatic cancer are awaited[148].

1.2.6 Selective visceral angiography (SVA)

The rationale for performing SVA in patients with suspected pancreatic malignancy is threefold; (i) to establish the diagnosis of pancreatic cancer, (ii) to assess tumour resectability and (iii) to define the arterial anatomy of peripancreatic region.

The feasibility of angiographic examination of the abdominal vasculature was first reported by Farinas in 1941[168]. Seldinger subsequently refined the technique of transfemoral visceral angiography with the introduction of flexible arterial catheters which could be used to cannulate selectively the coeliac and superior mesenteric arteries[169]. However, the first reported angiographic diagnosis of pancreatic cancer through identification of an abnormal tumour circulation was achieved by translumbar aortography[170]. The ability of the interventional radiologist to demonstrate abnormalities of the pancreas markedly improved with continued refinements in the technique of SVA[171], and the procedure was established as an important diagnostic tool during the 1960's and 1970's.

Tylén and Arnesjö documented the correct diagnosis of pancreatic cancer in 79 out of 116 patients (68%)[172], and Freeny and colleagues also reported SVA to have been "valuable for diagnosis" in 68% of cases[173]. The diagnostic sensitivity of SVA was reported to be 72% in a prospective study by Mackie and colleagues[174], and more recently 54% in the experience of Appleton and co-workers[175]. The results of a multi-centre survey of Norwegian hospital practice, where SVA was associated with a 33% diagnostic sensitivity for pancreatic cancer, may be more representative of non-specialist practice[137]. Clearly, subsequent experience has not supported Bookstein's original observation that a normal angiogram "nearly excluded" pancreatic cancer[176]. No angiographic criteria have been identified which are specific enough to differentiate between pancreatic cancer and chronic pancreatitis[116, 177].

The advent in the 1970's of less invasive imaging techniques such as USS, CT and ERCP gradually replaced SVA as a diagnostic modality in patients with suspected pancreatic pathology, with recommendations that it should be reserved for investigation of rare vascular neoplasms, for instances where the results of other

investigations were equivocal and for the preoperative assessment of tumour resectability[177].

The use of SVA in the preoperative staging and assessment of resectability of pancreatic and periampullary cancer is controversial. Although it was originally shown to be possible to demonstrate hepatic metastases using SVA[178], other studies have discounted its utility in this role, reporting sensitivities of 33 - 46%, and frequent false positive findings[116, 179, 180]. Rather, SVA has been used primarily to assess local tumour invasion, Bookstein and colleagues having recognised in 1969 that vascular invasion could be diagnosed by the signs of major artery occlusion and irregular encasement[176]. Other workers also confirmed that angiographic evidence of arterial invovement determined operability and survival[172, 181].

It has since become clear that portal-superior mesenteric venous invasion is inevitably present in patients with involvement of the coeliac and / or mesenteric arteries due to cancer of the pancreatic head[86]. Indeed, Buranasiri and Baum had emphasised the importance of the portal venous phase of SVA in identifying portal vein invasion in their report of 1972[182], and portal venous occlusion, stenosis, encasement or displacement during the portal venous phase of SVA became established as criteria indicating tumour unresectability. Other workers attempted to improve portal vein contrast enhancement by direct cannulation of the superior mesenteric vein in percutaneous transhepatic portography[171, 183], or by direct puncture of the spleen in splenoportography[184]. Reichardt and Ihse also demonstrated that portal venography could identify local tumour invasion where none had been evident on arteriography[183]. However, the invasiveness of these techniques, together with continued refinements in portal phase venography during SVA and the overall diminishing role of SVA with the advent of less invasive modalities in the 1980's led to their abandonement as routine procedures.

The results of studies evaluating the ability of SVA to predict tumour resectability, and validating the findings by surgical exploration, vary and are summarised in Table 1.5. It is clear that SVA commonly understages pancreatic cancer, inasmuch as its sensitivity in demonstrating tumour unresectability ranged from 41-91%, and the predictive value of negative findings ranged from 44-83%[86, 136, 137, 153, 160, 175, 180]. Therefore, the absence of angiographic abnormalities neither excludes the diagnosis of pancreatic cancer, nor the presence of malignant vascular invasion.

Table 1.5 - Summary of published studies (1984-1993) of SVA in the evaluation of pancreatic cancer

Author and year	Study design	Type of information	Diagnostic accuracy
Jafri et al [153] 1984	Retrospective vs. CT n = 27	Overall staging	Sensitivity = 91% Specificity = 100% PPV = 100% NPV = 71%
Appleton et al [175] 1989	Retrospective SVA alone n = 43	Overall staging	Sensitivity = 58% Specificity = 88% PPV = 88% NPV = 58%
Warshaw et al [86] 1990	Prospective vs. CT / MRI / Lap n = 54	Overall staging	Sensitivity = 66% Specificity = 94% PPV = 95% NPV = 54%
Dooley et al [160] 1990	SVA alone n = 90	Overall staging	PPV = 79% NPV = 77%
Bakkevold et al [137] 1992	Prospective Multicentre vs. USS / CT n = 72	Overall staging	Sensitivity = 44% Specificity = 88% PPV = 88% NPV = 44%
Rösch et al [136] 1992	Prospective vs. CT / EUS / SVA n = 40	PV invasion	Sensitivity = 45% Specificity = 100% PPV = 100% NPV = 83%
Murughia et al [180] 1993	Prospective SVA alone n = 46	Overall staging	Sensitivity = 41% Specificity = 90% PPV = 85% NPV = 52%

Of more concern is the incidence of false positive angiographic findings, where signs of tumour unresectability on preoperative SVA were refuted during surgery. This reality is reflected by reported specificities of 88-94%, while the predictive values of positive results have been cited in the range 79-95%[86, 137, 160, 175, 180]. However, not all studies report tumour overstaging with SVA[136, 153]. Explanations for false positive findings include "notching" in the vicinity of the portal - superior mesenteric venous junction which has been labelled a "normal variant"[160], spasm of the SMA mimicking tumour encasement[160], and coiling of the hepatic artery causing indentation of the portal vein[35].

Table 1.6 - Summary of published studies (1979-1993) of SVA in the evaluation of the peripancreatic arterial anatomy in patients with pancreatic cancer

Author / year No. patients	CHA or RHA from SMA or Aorta (%)	Total arterial anomalies (%)
Mackie et al [174] 1979 n = 103	14	25
Jafri et al [153] 1984 n = 27	15	-
Rong et al [186] 1987 n = 120	27	34
Appleton et al [175] 1989 n = 76	15	25
Biehl et al [188] 1993 n = 64	22	30
Murughia et al [180] 1993 n = 46	26	35

Detractors from SVA cite its unreliability in tumour staging and the availability of effective alternative modalities[35, 174, 177, 180, 185], comparative studies with dynamic CT having shown the latter to be at least as reliable as SVA in predicting tumour unresectability[150, 153]. In other centres, CT and SVA are considered complimentary modalities[86, 160]. Nevertheless, proponents of routine preoperative SVA maintain its empirical contribution to tumour staging, and cite its utility in providing beneficial information regarding the peripancreatic arterial anatomy[160, 175, 186-188].

The rationale for obtaining a preoperative "anatomical roadmap" has been justified by the reported high incidence of anomalies of the peripancreatic arterial anatomy. In particular, the presence of an accessory or replaced common or right hepatic artery arising from the aorta or SMA has been reported with an incidence of 14-27% in angiographic series (Table 1.6)[153, 160, 174, 175, 180, 186, 188]. Such an aberrant hepatic artery may run behind, through or in front of the pancreatic head, and is frequently discovered passing posterolateral to the structures within the hepatoduodenal ligament. It is at particular risk of injury during transection of the retropancreatic fascia in the final stages of resection of the pancreatic head[189].

Injury to such an artery may result in ischaemia of the biliary anastamosis causing dehiscence or stenosis, and / or hepatic ischaemia[189, 190]. Alternatively, routine SVA has been recommended to detect unsuspected coeliac axis compression or stenosis, as division of the gastroduodenal artery during pancreatic resection in such cases may provoke hepatic ischaemia[187].

Nevertheless, it may be possible to identify anomalous hepatic arterial anatomy using other modalities such as dynamic CT[154], or laparoscopic ultrasonography[158], while SVA can itself fail to identify important vascular anomalies[159]. Moreover, the detection and safeguarding of arterial anomalies during surgery for pancreatic cancer can be accomplished by experienced pancreatic surgeons without resort to SVA[35].

1.2.7 Laparoscopy

History

Kelling is widely regarded as being the first person to introduce the concept of laparoscopy in 1901, having inspected the abdominal cavities of dogs using air insufflation and a cystoscope[191]. Nevertheless, Ott, a Russian gynaecologist, is also reported to have performed laparoscopy in 1901 in a patient with oesophageal cancer[192]. In his description of 'laparoskopie' in 1911, Jacobeus was one of the first to find a clinical use for laparoscopy in human patients in diagnosing ascites, liver cirrhosis, metastatic liver tumours and tuberculous peritonitis[193]. Meanwhile, at the Johns Hopkins University Medical School, Baltimore, Bernheim reported the first "organoscopy" in the United States, in a patient of Halsted's with pancreatic cancer[194]. Prophetically, he speculated that the technique"...may reveal general metastases or a secondary nodule in the liver, thus rendering further procedures unnecessary and saving the patient a rather prolonged convalescence"[194]. The concept of diagnostic laparoscopy having been established, its continued evolution was facilitated by technical advances. Kalk was responsible for improved instrumentation and the use of a second access port [195]. In 1933, Fervers, who used laparoscopy to treat adhesions, described the use of carbon dioxide or oxygen instead of room air for creation of a pneumoperitoneum[196]. Veress invented the spring loaded insufflation needle in 1938[197], which until recently remained the instrument of choice for achieving a pneumoperitoneum. Using forward-viewing optics, the utility of the laparoscope in the evaluation of liver disease, ascites, and gastric, colorectal and gynaecologic malignancy was further established in the Johns Hopkins Medical School[198, 199]. Further development of the Hopkins rod-lens

optical system and the fibreoptic bundle finally allowed enhanced light transmission[200, 201], leading to the development of contemporary videolaparoscopy systems providing high resolution laparoscopic images for multiple observers.

Despite these advances, diagnostic laparoscopy failed to find widespread popularity amongst general surgeons, and it was gynaecological specialists who were responsible for most of the major developments in laparoscopy before the late 1980's[202, 203]. Nevertheless, a role for diagnostic laparoscopy in the setting of emergency general surgery was recognised by Paterson-Brown and his colleagues at St Mary's Hospital, London, who demonstrated its efficacy in clinical decision making in the management of patients presenting with an "acute abdomen"[204]. Since the late 1980's, laparoscopic techniques have attracted massive attention within the general surgical community with the development of therapeutic laparoscopic and "minimal access" procedures. An account of the developments of laparoscopy in this context is outwith the scope of this thesis.

The techniques by which a pneumoperitoneum, and laparoscopic trocar and port insertion, may be achieved are worthy of further consideration. Until the 1980's, most laparoscopies worldwide were performed by gynecologists, using the spring-loaded Veress needle[197] to enter and insufflate the peritoneal cavity so permitting 'blind' insertion of a trocar / port assembly into the cushion of abdominal gas. The safety of laparoscopy performed by this technique was documented by the confidential enquiry of the Royal College of Obstetricians and Gynecologists into gynecological laparoscopy in 1978 which consisted 50 247 procedures[205]. There were 1 818 complications (3.6%), including four deaths (gas embolism (n=1), bowel perforation (n=1), cardiac arrest (n=2)) for a mortality rate of 8 per 100 000. However, whereas the 'minor' complications of laparoscopy were usually related to the insertion of the Veress needle, more serious complications such as intestinal insufflation, gas embolism or blood vessel injury have been documented with this technique[206]. In an attempt to diminish the incidence of such occurrences, the alternative technique of 'open laparoscopy' by direct cutdown to the peritoneal cavity, as initially advocated by Kelling[191], has been recommended by gynecologists[207] and surgeons alike[208]. Furthermore, Byron and colleagues performed a randomised trial comparing Veress needle and direct trocar insertion in the context of gynecological laparoscopy[209]. They reported a significant reduction in the incidence of 'minor complications' (preperitoneal insufflation, failed entry or more than three attempts to access the peritoneal cavity), and a significant saving in

operating time for the direct insertion technique. For details of these techniques see Section 2.3.1.

Laparoscopy in the assessment of pancreatic cancer

Modern laparoscopic optics and light sources provide a highly resolved and magnified view of the peritoneal cavity. Laparoscopic examination is a sensitive technique in the detection of intraperitoneal tumours, small quantities of malignant ascites and tiny metastatic lesions involving the serosal surfaces of the peritoneal cavity, omentum and liver. Between 1973 and 1989, this was illustrated by a series of diverse reports which documented the utility of laparoscopy in the assessment of patients with a variety of intra and extrabdominal primary tumours without resort to laparotomy. Thus, the utility of diagnostic and staging laparoscopy was demonstrated in patients with bronchogenic carcinoma[210], ovarian tumours[211], gastroesophageal carcinoma[212-215], gall bladder carcinoma[216], breast carcinoma[217], malignant melanoma[218] and lymphoma[219, 220] in whom the laparoscopic findings directly influenced patient management.

However, attempts to evaluate the pancreas using laparoscopy were hindered by its retroperitoneal location. The diagnosis of pancreatic malignancy was usually inferred from the observation or 'palpation' of a retrogastric mass, and secondary signs such as the features of obstructive jaundice, ascites or metastases, and portal hypertension or splenomegaly in the presence of portal vein invasion. Nevertheless, some workers described the feasibility of direct laparoscopic inspection of the pancreas by 'supragastric pancreoscopy', where the pancreas was visualised through the gastrohepatic omentum[221], 'supragastric bursoscopy' where the lesser sac was entered having incised the lesser omentum[222-224], and 'infragastric bursoscopy' where the lesser sac was entered having incised the gastrocolic omentum or mesocolon[83, 225]. These techniques could also be used to facilitate laparoscopic biopsy of pancreatic masses under direct vision[223].

However, the success of supragastric pancreoscopy was dependant upon the quantity of fat in the lesser omentum, Meyer-Berg and colleagues reporting a success rate of only 60% using this approach[226]. Furthermore, obliteration of the lesser sac with adhesions, inadequate access to the the pancreatic head, and little available information regarding local tumour invasion of retroperitoneal structures were probable reasons for the failure of this approach to attain widespread acceptance as a viable method of evaluating pancreatic disease at a time when newer radiological

imaging techniques were gaining in popularity. Similarly, attempts to improve the diagnostic yield of laparoscopy in patients with suspected obstructive jaundice by laparoscopic cholecystcholangiography, where contrast radiography was performed following transhepatic needle puncture of the gall bladder, were rapidly superceded by more refined techniques such as PTC and ERCP[227, 228].

Conversely, laparoscopy was reported to be highly efficacious in the detection of metastatic disease in patients with pancreatic malignancy, as originally described in Bernheim's seminal report of 1911[194]. Ishida and colleagues in Tokyo performed laparoscopy in 71 patients with pancreatic cancer between 1976 and 1981, detecting intraabdominal metastatic disease in 43% of examinations[229]. They identified liver metastases in 11% and 50% of patients with tumours of the pancreatic head and body respectively, and peritoneal dissemination in 24% and 64%. Meanwhile, Cuschieri's group in Dundee had performed laparoscopy immediately prior to a proposed laparotomy in 73 patients with pancreatic cancer[83, 85]. Large omental deposits (n=8), peritoneal seedlings (n=39) and / or hepatic metastases (n=55) were identified laparoscopically. Furthermore, direct tumour invasion of adjacent organs (colon, mesocolon, duodenum and / or stomach) was detected in 12 patients, and an overall histological / cytological diagnosis of pancreatic malignancy was achieved in 61 / 65 patients (92%). However, it is not possible to assess the impact of laparoscopy in relation to alternative imaging techniques in the Tokyo study, while in Cuschieri's series, preoperative imaging tests had already indicated liver metastases in 49 out of 55 patients, and the laparoscopic findings did not affect the decision to operate in 51 out of 73 patients (70%). Nevertheless, preoperative investigations had failed to detect peritoneal carcinomatosis in any of the laparoscopically detected cases, although CT scanning had only been available in six[83, 85].

Warshaw's team in Boston performed staging laparoscopy to assess tumour resectability in 86 patients between 1982 and 1989[84, 86, 230]. Laparoscopy detected intraabdominal metastases in a total of 35 patients (41%). The sensitivity of laparoscopy in detecting such lesions was 96% (22 / 23), whereas intravenous contrast enhanced CT failed to detect these in all but two cases. Stepwise discriminant analysis confirmed the unique role played by staging laparoscopy in this context[86].

Preliminary work in the University Department of Surgery, The Royal Infirmary, Edinburgh has reproduced these findings[158], demonstrating unsuspected hepatic

metastases, peritoneal seedlings and / or malignant ascites in four out of twelve patients following laparoscopy.

1.2.8 Laparoscopic Ultrasonography (LapUS)

The principles of high-resolution contact ultrasonography

In general terms, B-mode real-time ultrasound imaging involves the generation of "live" cross-sectional grey-scale images of the tissues underlying the ultrasound transducer. The transducer, which is mounted on a probe, is connected by cable to a dedicated digital electronic system or scanner. The critical element of the transducer is the piezoelectric crystal, which has unique physical and electrical properties. The elements used most commonly in contemporary ultrasound transducers are composed of lead circonite titanite crystals. Application of an electrical current to the crystal causes it to vibrate and generate sound waves. Conversely, if mechanical force (such as a sound wave) is applied to the crystal, an electrical potential is generated. Thus, the crystals within a transducer serve as emitters and receivers of ultrasound. The emitted ultrasonic pulses are partially reflected to varying degrees from the structures being scanned. The returning echoes cause the transducer to generate electrical signals which are transmitted to the scanner, amplified and displayed on a high definition monitor as a pattern of pixels. The resultant two-dimensional (B-mode) grey-scale image varies in brightness in proportion to the intensity of the reflected ultrasound, which is determined by the properties of the tissues being scanned.

The quality, detail and sharpness of the ultrasound image are dependent on both the axial and lateral resolutions of the transducer, which represent the ability of the scanner to discriminate two reflective points in line with, and perpendicular to, the ultrasound beam respectively. Greater axial resolution is achieved by the use of higher wavelength frequencies, while increased lateral resolution is dependent on a narrower ultrasound beam width and focus.

Laparoscopic intraoperative ultrasonography utilises the principles of intraoperative contact ultrasonography (IOUS) during laparoscopy. The fundamental advantage of IOUS compared with conventional transabdominal USS derives from the placement of the ultrasound transducer in direct apposition with the intraabdominal tissues. This manoeuvre permits the use of relatively high frequency transducers (7.5 - 10 MHz) which achieve correspondingly high image resolution, while avoiding the

image degradation experienced when scanning from outside the body wall during transabdominal USS. This "acoustic attenuation" is widely attributed to interposed body wall tissues, overlying viscera and bowel gas. The increased tissue penetration of these structures required of the ultrasound beam during transabdominal USS dictates the use of a lower resolution transducer, with correspondingly poorer resolution.

Other factors which are important in determining image quality include the purity of sound produced by a crystal, and the sophistication of the electronic signal processing systems software used in the scanner. A variety of artifacts and image degradations which are instrument related and which may cause interpretative errors have been defined[231]. However, these factors may be recognised and discounted with experience, and have been minimised with modern ultrasound systems.

Of greater significance is the global degradation in image quality arising from corruption of the beam forming process, with aberrations of the acoustic wavefronts due to non-uniform acoustic velocities which reduce spatial and contrast resolution[232]. These instrument-independent artifacts and image degradations are attributed to an ultrasound-tissue interaction, and it has been suggested that this is due to a simple anatomical "monolayer" such as subcutaneous fat[233]. In their recent study attempting to elucidate and quantify the factors which affect image quality during transabdominal USS, Shmulewitz and colleagues scanned 140 predominantly elderly patients[231]. Satisfactory USS imaging of the intraabdominal organs was attempted, including the liver, hepatoduodenal ligament and pancreas. While visualisation of the major organs was possible in 98% of cases, an improvement in image quality was said to be desirable in 78%. Obesity and immobility were found to be associated with poor image quality, and poor "acoustic windows", where the acoustic path to the organ of interest was obscured by ribs or gas containing intestine.

In a separate experiment in an animal model, transabdominal USS was performed sequentially following the dissection and removal of the anatomical layers of the abdominal wall[231]. Image quality was reported to gradually improve from the epidermis inwards, until optimal image quality was achieved with the transducer placed against the liver surface. Thus, aberrations could not be attributed to any single anatomical layer, but rather the aggregated effect of the various abdominal wall structures. These studies offer an explanantion for the improved resolution and

image quality which have stimulated the development of intraoperative and laparoscopic contact ultrasonography.

Assessment of pancreatic disease by intraoperative ultrasonography

Intraoperative ultrasonography has been shown to aid the operative decision making process during operations for both benign and malignant pancreatic disease, localising and characterising impalpable abnormalities and providing information which would otherwise require extensive dissection. In particular, IOUS may help establish the diagnosis of pancreatic carcinoma, and define the local resectability of the lesion with regards to its involvement of the adjacent peripancreatic blood vessels. In this way, IOUS was reported to have been 'very or moderately helpful' in 11 of 22 operations undertaken by Plainfosse and colleagues[234]. Serio and co-workers found IOUS helpful in 21 out of 24 operations where pancreatic resection for carcinoma had been attempted[235], the information obtained indicating tumour resectability in 12 cases, and unresectability in nine. The largest experience with IOUS during 177 pancreatic operations reported by Machi and colleagues confirms the utility of IOUS in this role[236], where beneficial additional information was derived from IOUS in 73% of cases. Compared with preoperative radiological investigations (presumably CT), IOUS was reported to have been significantly more specific and accurate in the determination of tumour unresectability due to portal vein invasion[236]. Nevertheless, many pancreatic surgeons have preferred to undertake a trial dissection or mobilisation of the pancreas at open operation, and the adoption of IOUS in this role has remained confined to a relatively small number of enthusiasts.

History of laparoscopic ultrasonography

Laparoscopic ultrasonography is now possible using commercially available ultracompact, sterilisable probes with similar imaging specifications as contemporary high resolution IOUS systems, and which may be introduced through standard 10 / 11 mm diameter laparoscopic ports. However, the concept of LapUS was first reported in the 1950's Japanese literature[237], and later repeated by German investigators in the early 1970's[238]. These early studies in LapUS utilised prototype A-mode scanners, which were the forerunners of modern B-mode instruments. A-mode scanners generate uni-dimensional spikes which reflect the amplitude strength of the returning echo on the vertical axis, and the distance from the transducer along the horizontal axis. Although inherently more difficult to interpret than the cross-

sectional images of B-mode imaging, Look and co-workers demonstrated the feasibility of these A-mode LapUS devices in diagnosing cholelithiasis and gall bladder cancer[238].

A variety of prototype LapUS instruments were tested by Japanese workers during the early 1980's, all of which employed B-mode transducers incorporated into the shaft of the laparoscope itself and termed "echolaparoscopes". Their findings were presented to the 1982 Congress of the Swedish Society for Medical Sciences. Ota and colleagues at the University of Tokyo compared their 7.5 MHz mechanical radial scanning echolaparoscope with a contemporary transabdominal scanner[239]. They reported "sharp and fine" images of the abdominal viscera, an improved lateral resolution of 1.0-1.3 mm, the demonstration of small intrahepatic tumours below the ribs which could not otherwise be imaged and "an approach to the pancreas could be carried out with available informations". Furukawa and colleagues also used a 5-7.5 MHz 360° radial scanning echolaparoscope in 126 patients[240]. They were able to image liver tumours, liver cysts, gallstones and tumours of the digestive tract (including the panceas) using this device. Success with a similar instrument was also reported by Aramaki and colleagues[241].

In 1984, Okita and colleagues in Yamaguchi University School of Medicine, Ube, Japan, reported their experience with prototype LapUS instruments which utilised a 3.5 - 5 MHz linear array transducer at the flattened end of a 13 mm diameter laparoscope which could be articulated through 180° in two planes[242]. They described the first case of successful LapUS imaging of a pancreatic carcinoma in a patient in whom CT, SVA and laparoscopy alone had produced equivocal results.

With the exception of isolated workers in Europe who continued to investigate the utility of LapUS in the assessment of the liver, LapUS failed to become established as a method for investigation of pancreatic disease during the remainder of the 1980's. However, two developments were probably responsible for stimulating renewed interest in the concept of LapUS in the early 1990's. In addition to its use in pancreatic surgery, IOUS had increasingly been shown to be indispensable in liver surgery, and had become a technique with which many hepatobiliary surgeons were familiar. There were also several studies demonstrating that IOUS could be at least as accurate as intraoperative cholangiography in detecting CBD calculi during cholecystectomy[236, 243-246]. Secondly, the dramatic changes in surgical practice which occurred with the popularisation of laparoscopic surgery, and in particular laparoscopic cholecystectomy, led to increasing interest in LapUS as a method of

examining the CBD as an alternative to intraoperative cholangiography. In 1991, Röthlin and co-workers in Zürich reported their experience with a prototype 5.5 MHz 360° radial sector scanning LapUS probe originally designed for examination of the lower urinary tract[247]. They were able to image the structures of the hepatoduodenal ligament and the entire biliary tract during laparoscopic cholecystectomy, also detecting CBD stones in the process.

Meanwhile, the team in the Royal Infirmary, Edinburgh, had adapted for use during laparoscopy a sterilisable 16 mm diameter 7.5 MHz linear array ultrasound probe designed for endorectal contact sonography (Aloka US660-7.5). A custom built large port assembly was used to achieve access to the peritoneal cavity and this improvised LapUS system was successfully used to evaluate patients with liver tumours[248]. Laparoscopic ultrasonography was also used to evaluate twelve patients with pancreatic malignancy, all of whom were considered potential candidates for pancreatic resection on the basis of available ultrasound and CT scans[158]. Now using a commercially available 7.5 MHz linear array LapUS probe (Aloka UST 5522-7.5), images of the pancreatic cancer and its relationships with neighbouring ducts and vessels were observed. Findings of intrahepatic metastases (n=4), regional lymphadenopathy (n=4), retroperitoneal invasion (n=2) and / or portal vein invasion or displacement (n=4) were documented in six patients in whom laparotomy was avoided. Thus, LapUS alone defined criteria of unresectability in two patients, in addition to four patients shown to have metastatic spread following laparoscopic inspection. Five out of the six patients deemed to be resectable by LapUS underwent pancreatic resection, one patient being shown to have malignant lymphadenopathy at the time of laparotomy[158].

Dutch workers had contemporaneously evaluated LapUS, also improvising with a 16 mm diameter 7.5 MHz linear array transrectal probe before employing the purpose designed Aloka UST 5522-7.5[249, 250]. In Eindhoven, Jakimowicz successfully employed LapUS in the assessment of a variety of intraabdominal malignancies, but emphasised the role of the technique in the evaluation of the biliary tree during laparoscopic cholecystectomy in a series of 145 patients[250]. In Amsterdam, Cuesta also reported the utility of LapUS in detecting intrahepatic metastases during staging laparoscopy for a variety of neoplasms, although was not successful in satisfactorily imaging pancreatic tumours[251]. In addition, several reports have documented the successful use of LapUS in the routine examination of the biliary tract during laparoscopic cholecystectomy[252-255].

1.2.9 Peritoneal Cytology

Cytopathological examination of peritoneal washings obtained during laparotomy or laparoscopy has been advocated for the identification of exfoliated pancreatic cancer cells within the peritoneal cavity, two studies having reported that positive peritoneal cytology may yield important diagnostic and staging information in patients with pancreatic cancer[256, 257]. In the first study, Martin and Goellner performed peritoneal cytology following laparotomy in 76 patients with a variety of intra-abdominal malignancies, twenty of whom had pancreatic cancers, 18 of which were unresectable[256]. Positive peritoneal cytology was observed in five patients (25%), all of whom had advanced tumours precluding resection. Three of these patients had overt metastatic disease involving the liver, peritoneum or omentum. However, the other two patients were noteworthy inasmuch as negative peritoneal cytology had been obtained at initial laparotomy when local invasion of the superior mesenteric vein had prevented resection. Several days later, repeat peritoneal cytology at reoperation for intraoperative radiotherapy was positive. The authors concluded that positive peritoneal cytology was common in patients with pancreatic cancer, reflecting the propensity of such tumours to disseminate within the abdominal cavity at an early stage[256]. They also hypothesised that pancreatic mobilisation and biopsy may be implicated in the intraperitoneal dissemination of such tumours.

Although peritoneal cytology was recommended as a simple and inexpensive technique in the evaluation of pancreatic cancer during laparotomy, its potential use in the preoperative diagnosis and staging of patients with panceatic cancer was not recognised until Warshaw reported its use during staging laparoscopy[257]. Forty patients with pancreatic cancer considered potentially resectable by CT underwent cytological analysis of peritoneal washings obtained at staging laparoscopy (27 patients) or laparotomy (13 patients). Positive peritoneal cytology was obtained in 12 patients (30%): 33% during laparoscopy versus 23% at laparotomy. Positive peritoneal cytology was associated with a significantly worse resectability rate (10% versus 52%) and a significantly diminished six month survival. Furthermore, a significant association between positive peritoneal cytology and previous percutaneous needle biopsy was reported (75% versus 19%).

Warshaw[257] thus concurred with Martin and Goellner[256] that pancreatic cancer sheds malignant cells into the peritoneal cavity early and commonly, that cytological findings provided an additional index of resectability and established that laparoscopic lavage was an effective means of cytological study. He also concluded

that intraperitoneal spread of cancer cells may be promoted by tumour biopsy, and that peritoneal cytology correlated with survival[257]. No other work reproducing these findings was in evidence at this time.

1.2.10 Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography (EUS) permits high resolution, real-time B-mode scanning of the pancreas and neighbouring tissues from within the lumen of the stomach and duodenum using an echoendoscope. The echoendoscope incorporates a small, high-frequency ultrasound transducer at its distal end, and high resolution images of the adjacent tissues are generated using similar principles of contact ultrasonography as those exploited during IOUS and LapUS (as discussed in Section 1.2.8). The technique was originally developed in the early 1980's, and although marked technical refinements have since occurred, pioneers of EUS demonstrated the feasibility of the technique in diagnosing small pancreatic tumours, and in demonstrating evidence of local tumour invasion[258-262].

Studies evaluating EUS in the diagnosis of pancreatic and periampullary cancer have reported excellent results, with EUS demonstrating superior sensitivities (85-100%) compared with ERCP, USS, CT and / or SVA, as summarised in Table 1.7[134, 136, 138, 140, 263]. However, there is substantial overlap in the sonographic appearances of malignant and benign lesions, and no reliable criteria have been defined which allow accurate differentiation between focal pancreatic lesions due to neoplasia and those due to chronic pancreatitis[264].

In the staging of pancreatic and periampullary cancer, and in the hands of experts, EUS has been shown reproducibly to be highly accurate in determining resectability according to the T stage (see Table 1.8)[134, 136, 138, 140, 263, 265]. Furthermore, prospective comparison with USS, CT and / or SVA in this context has shown EUS to be superior in determining malignant vascular invsion[134, 136, 138, 140].

However, EUS has been recognised as less accurate in the diagnosis of regional malignant lymphadenopathy[264, 266]. Having adopted an arbitrary node size of ≥ 5 mm in diameter to represent malignant involvement, reported positive and negative predictive values vary from 47-100% and from 55-71% respectively[136, 138, 265]. Although significantly better than corresponding diagnostic accuracies yielded by USS and CT (see Tables 2 and 4), the incidence of false positives due to reactive hyperplasia, and false negatives due to nodal micrometastases has limited the clinical

Table 1.7 - Summary of published studies (1988-1993) of EUS in the diagnosis of peripancreatic malignancy

Author and year	Study design *	Results
Yasuda et al [134] 1988	Prospective vs. USS / CT / SVA n = 42	Sensitivity = 100%
Rösch et al [136] 1992	Prospective vs. USS / CT / SVA n = 60	Sensitivity = 98%
Snady et al [263] 1992	Prospective vs. CT / ERCP n = 42 (60)	Sensitivity = 85% Specificity = 80% PPV = 89% NPV = 73%
Palazzo et al [138] 1993	Prospective vs. USS / CT n = 49 (64)	Sensitivity = 96% Specificity = 73%
Yasuda et al [140] 1993	Prospective vs. USS / CT n = 29	Sensitivity = 100%

* figure in parentheses indicates total number of EUS examinations

utility of EUS in lymph node staging[264].

The procedure is also technically difficult, requiring ultrasound and endoscopic expertise, and has been slow to gain widespread acceptance. Several other limitations have emerged in the use of EUS. These include difficulties in intubating the pylorus and duodenum with large calibre echoendoscopes, especially in patients with locally invading tumours of the pancreatic head or periampullary region. Imaging of the distal pancreas from within the stomach may also be impeded by interposed bowel gas, and these factors have accounted for technical failure rates of 5-14%[264]. The optimal focal range of the transducer is usually 2-4 cm, which restricts imaging of the majority of the right hemiliver, and of the peripancreatic vasculature when tumours larger than 4 cm are encountered. For this reason, EUS is insensitive in detecting distant metastases during tumour staging in patients with pancreatic and periampullary cancer.

Table 1.8 - Summary of published studies (1988-1993) of EUS in the staging of peripancreatic malignancy

Author and year	Study design	Type of information	Results
Yasuda et al [134] 1988	Prospective vs. USS / CT / SVA n = 42	PV invasion	Sensitivity = 93% Specificity = 88% PPV = 100% NPV = 89%
Tio et al [265] 1990	Prospective EUS alone n = 67	Ca head of pancreas (n = 45)	
		Overall T stage	Accuracy = 92%
		Node metastases	Sensitivity = 91% Specificity = 42% PPV = 75% NPV = 71%
		Periampullary Ca (n=24)	
		Overall T stage	Accuracy = 87%
		Node metastases	Sensitivity = 80% Specificity = 36% PPV = 47% NPV = 71%
Rösch et al [136] 1992	Prospective vs. USS / CT / SVA n = 60	PV invasion n = 40	Sensitivity = 91% Specificity = 97% PPV = 91% NPV = 97%
		Node metastases	Sensitivity = 72% Specificity = 73%
Snady et al [263] 1992	Prospective vs. CT / ERCP n = 42	Overall resectability n = 24	Sensitivity = 85% Specificity = 80% PPV = 89% NPV = 73%
Palazzo et al [138] 1993	Prospective vs. USS / CT n = 49	PV invasion	Sensitivity = 100% Specificity = 65% PPV = 83% NPV = 100%
		Node metastases	Sensitivity = 62% Specificity = 100% PPV = 100% NPV = 55%
Yasuda et al [140] 1993	Prospective vs. USS / CT n = 29	PV invasion	Sensitivity = 88% Specificity = 78%
		Node metastases	Accuracy = 66%

Summary

A variety of radiological techniques have found popularity in the diagnosis and staging of partients with pancreatic and periampullary cancer, particularly USS, CT and SVA. Other modalities such as MRI, laparoscopy, LapUS and EUS have not achieved widespread usage and continue to be evaluated. The available evidence indicates that no single modality is alone accurate in evaluating such patients. Although investigative algorithms have been devised to optimise their assessment, there remain inadequacies in their preoperative evaluation, particularly in the selection of patients with potentially resectable lesions. There is therefore a need to improve current methods of evaluating patients with pancreatic and periampullary cancer such that patients with resectable lesions are selected reliably, while those with inoperable lesions may be spared unnecessary surgery.

Hypothesis

Laparoscopy, laparoscopic ultrasonography and laparoscopic peritoneal cytology have the potential to influence clinical decision and therefore the management of patients with pancreatic and periampullary cancer.

Aims

To assess the efficacy of laparoscopic ultrasonography in imaging the normal hepatobiliary and pancreatic anatomy.

To assess the role of laparoscopy and laparoscopic ultrasonography in the preoperative diagnosis and staging of patients with pancreatic and periampullary carcinoma.

To further validate the accuracy of laparoscopy and laparoscopic ultrasonography in the preoperative diagnosis and staging of patients with pancreatic and periampullary malignancy by prospective comparison with alternative imaging techniques.

To assess the role of laparoscopic peritoneal cytology in the staging of patients with pancreatic and periampullary carcinoma.

Chapter 2 Patients and Methods

2.1 STUDY ENDPOINTS

2.1.1 Definition of resectability and staging conventions

As discussed in Section 1.1.1, definitions of tumour resectability vary widely, and depend on the philosophy prevailing in individual institutions. Standardised methods of documenting tumour stage are therefore essential to permit meaningful comparison of clinical results in different groups of patients, and the staging of cancer has thus been deemed as "hallowed by tradition" and its justification said to be "unassailable"[267]. The TNM (Tumour, Node, Metastasis) staging system was conceived by Denoix in 1943[268], and adopted by the Union Internationale Contre Le Cancer (UICC) in 1950[267]. Its application in the staging of pancreatic cancer, and its retrospective validation was performed independently in the 1970's by Rainsbury's and Pollard's groups[269, 270]. Further validation by prospective use in the first randomised, multi-centre trials of chemotherapy for patients with pancreatic cancer have confirmed the clinical validity of this concept[63, 271].

In 1987, the 1983 UICC TNM classification of pancreatic cancer and the 1981 AJCC (American Joint Committee on Cancer) system were incorporated to form a revised staging classification[272] (Table 2.1). This system facilitated a "telescopic ramification" mechanism which permitted further classification by grouping into stages I - IV (Table 2.1). Meanwhile, a different and more complex staging system had been adopted by the Japanese Pancreatic Society[273]. However, the 1987 UICC staging classification has been accepted by all National TNM committees to enable international comparisons and is the system most commonly employed in the Western literature.

Table 2.1

Pancreatic cancer staging from the 1992 UICC TNM classification[272]

T category

T_0	No evidence of primary tumour
T_1	Tumour limited to the pancreas
	T_{1a} (≤ 2 cm) T1b (> 2 cm)
T_2	Extends directly to duodenum, bile duct, peripancreatic tissues
T_3	Extends directly to stomach, spleen, colon, adjacent large vessels
T_x	Minimum requirements to assess the primary tumour cannot be met

N category

N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
N_x	Minimum requirements to assess the regional and juxta-regional lymph nodes cannot be met

M category

M_0	No distant metastases
M_1	Distant metastases
M_x	Minimum requirements to assess the presence of distant metastases cannot be met

Stage grouping

Stage I	T1-2, N0, M0
Stage II	T3, N0, M0
Stage III	T1-3, N1, M0
Stage IV	T1-3, N0-1, M1

As discussed in Section 1.1, strict differentiation between cancers of the pancreas and those arising in the periampullary region can be difficult. Although the most recent UICC staging classification strictly distinguishes between these entities[267, 272], tumours which infiltrate both papilla and pancreatic head could be classified pathologically as T_4 periampullary cancers, or alternatively as T_2 pancreatic cancers. For the purposes of the studies performed in this thesis, all carcinomas of the pancreas and periampullary region were considered together and classified according to the UICC TNM classification of pancreatic cancer (Table 2.1). A similar approach has been adopted by others[137], and is justified for the purposes of determining an endpoint of tumour resectability, as opposed to the outcome of treatment.

The measured endpoints of "tumour resectability for cure" which were adopted in studies 2 - 4 are based upon the 1987 UICC staging classification[272] (Table 2.1). The convention adopted for the purposes of these studies defined tumour resectability as:

T_1 Tumour limited to pancreas / periampullary region
T_2 Tumours invading the medial duodenal wall and / or distal bile duct only
N_0 No regional lymph node metastases
M_0 No distant metastases
(i.e. Stages I - II)

Criteria which were taken to represent tumour unresectability were defined as:

T_2 Tumours invading retroperitoneal (retropancreatic) tissues
T_3 Tumours invading stomach, spleen, colon, adjacent large vessels
N_1 Regional lymph node metastases
M_1 Distant metastases
(i.e. Stages II - IV)

2.1.2 Methods of analysis

The need to evaluate and compare the efficacy of the numerous new investigative techniques which have been developed in clinical medicine over the past twenty years has witnessed the development of a range of statistical designs and analyses. In this thesis, several different study designs were employed, and these may be defined according to the criteria stipulated by Freedman in his 1987 review article[274].

Pilot studies

Pilot studies typically evaluate the feasibilty of a new technique and address qualitative issues such as the acceptibility of the method and the quality of the images. Although such studies are descriptive and have negligible statistical content, they are considered a necessary preliminary when a novel technology is first evaluated. Study 1 was a pilot study, where laparoscopic ultrasonography was evaluated with respect to its acceptability in imaging the hepatobiliary and pancreatic anatomy, and where technical aspects of the procedure were assessed.

Diagnostic accuracy

Studies of diagnostic accuracy compare the diagnosis obtained using the study technique with a final, or "gold standard" (or "evidence based") diagnosis. The term "diagnostic accuracy" uses the concept of diagnosis in its broadest sense e.g. in staging investigations where the issue is tumour resectability. This study design is that which is most commonly reported in the literature, and Freedman has made the analogy of diagnostic accuracy studies with phase II clinical trials (e.g. screening for the activity of a drug against a disease)[274].

The results in Studies 2 - 4 were analysed using measures of diagnostic accuracy, and were expressed in the form of summary measures: *sensitivity, specificity, positive predictive value, negative predictive value and accuracy.* The definitions of these measures involve two assumptions: (i) that one particular disease is of interest, and (ii) that the result is reported as either positive or negative for the disease in question. The work in this thesis satisfies these assumptions inasmuch as all patients evaluated in Studies 2 - 4 were selected on the basis that the diagnosis of pancreatic or periampullary carcinoma was ultimately established. Secondly, the results of the study investigations were expressed as "positive" or "negative" corresponding respectively to "tumour present or absent", "tumour unresectable or resectable", "metastases present or absent" etc. Thus, in the context of tumour staging, factors contraindicating tumour resection were regarded as "positive", whereas findings supporting the feasibilty of tumour resection for cure were regarded as "negative".

The method used for formulating summary measures of diagnostic accuracy comprised the 2 x 2 contingency table (Table 2.2), where the reported results are defined as *true positive, true negative, false positive or false negative*[275]. In broad terms, sensitivity is defined as "the proportion of diseased patients who are reported to be positive", i.e. "the proportion of true positives that are correctly identified by

the test". Specificity is defined as "the proportion of patients free of the disease who are reported negative", i.e. "the proportion of true negatives that are correctly identified by the test".

Predictive values reflect the probability that a test will give the correct diagnosis, and provide direct information about how much reliance can be placed on the imaging result. Thus, the positive predictive value (PPV) is "the proportion of patients reported positive who have the disease" or "the proportion of patients with positive test results (i.e. true positives plus false positives) who are correctly diagnosed (true positive)". Conversely, the negative predictive value (NPV) is "the proportion of patients reported negative (true negatives plus false negatives) who do not have the disease (true negative)" or "the proportion of patients with negative test results who are correctly diagnosed"[276]. In the context of Study 3, the PPV reflected the predictive value of the statement "this patient's tumour is unresectable", while the converse was true for the NPV.

Predictive values depend upon sensitivity and specificity, and critically, upon the prevalence of the abnormality in those patients being tested[274, 276]. The prevalence can be interpreted as the probability, before the test is performed, that the patient has the abnormality ("prior probability" of the disease). By incorporating it into the formulae used to calculate positive and negative predictive values, these parameters may be used to compare the utility of the investigation in environments with different disease prevalence (Table 2.2)[274, 276]. In this way, calculations of PPV and NPV in Study 3 were adjusted for the prevalence of tumour unresectability derived from previous experience in Study 2.

Statistical comparisons between summary measures of diagnostic accuracy in Study 3 were performed using the continuity-corrected chi square method, or Fisher's exact test when expected frequencies were less than five. Statistical significance was taken as $P \leq 0.05$.

Table 2.2

Format for calculating parameters of diagnostic accuracy by the 2 x 2 contingency table method

		Result of staging investigation	
		Resectable (-)	Unresectable (+)
Outcome	Resectable (-)	TN	FP
	Unresectable (+)	FN	TP

TN = True Negative; TP = True Positive; FN = False Negative; TP = True Positive

$$\text{Sensitivity} = \frac{TP}{(TP + FN)} \qquad \text{Specificity} = \frac{TN}{(TN + FP)}$$

$$PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$NPV = \frac{\text{specificity} \times (1\text{-prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

PPV = positive predictive value; NPV = negative predictive value

Clinical value

Clinical value studies aim to evaluate the contribution of an imaging technique to real-life clinical management. The impact of the technique on both the diagnostic and therapeutic process is studied by consideration of the clinician's assessment of the patient before and after receiving the findings of the study investigation. This study method was incorporated into Studies 2 and 3, where the efficacy of laparoscopy and LapUS in detecting tumour dissemination was studied in patients previously thought to be free of such disease. The resultant effect of laparoscopy and LapUS in changing patient treatment was documented. Freedman has made the analogy of clinical value studies with phase III clinical trials which attempt to establish the place of a specific therapy in routine practice (e.g. randomised controlled trials in a clinical setting)[274].

Survival analysis

In Study 4, life table analysis was used to calculate actuarial survival from the time of staging laparoscopy, and Kaplan-Meier plots were constructed[277].

2.2 PATIENT SELECTION AND STUDY DESIGN

2.2.1 Study 1

Two groups of patients were studied.

(i) Patients undergoing elective laparoscopic cholecystectomy were studied to quantify the frequency with which defined anatomical landmarks could be imaged using LapUS. The LapUS examinations were performed as part of a prospective study evaluating the role of LapUS and intraoperative cholangiography in the detection of common bile duct stones during laparoscopic cholecystectomy. It was anticipated that the hepatobiliary and pancreatic anatomy would be relatively "normal" in this group of patients in whom there was no evidence of malignancy. The indications for laparoscopic cholecystectomy included chronic gallstone disease, previous episodes of acute gallstone related pancreatitis and gallbladder polyps. Consent to perform LapUS was obtained as an integral part of the laparoscopic cholecystectomy. It was explained that the procedure would be limited to ten minutes, and that no additional ports would be required. The findings regarding the diagnosis of common bile duct stones are beyond the scope of this thesis and will not be presented.

(ii) Patients with suspected pancreatic or periampullary carcinoma undergoing staging LapUS as a definitive procedure were also studied (see also Study 3). In this context, the ability of LapUS to identify defined peripancreatic anatomical landmarks was investigated, using a modification of the technique used in (i). In addition, the ability of LapUS to identify the anomaly of an accessory or replaced right or common hepatic artery was investigated. All patients provided written consent prior to this procedure.

2.2.2 Study 2

All patients had presented with carcinoma of the pancreatic head or periampullary region, having been referred by a surgeon or physician in another department, or by their general practitioner, for further specialist treatment. All patients were considered to be candidates for exploratory laparotomy and tumour resection with curative intent on the basis of preceding USS and CT examinations (i.e no evidence of local tumour invasion, regional lymphadenopathy or distant metastases). In this scenario, all patients were studied with laparoscopy and LapUS to determine: (i)

summary measures of diagnostic accuracy of laparoscopy alone compared with the combined findings of laparoscopy and LapUS in predicting tumour resectability, and (ii) the impact of laparoscopy in changing clinical decision making and avoiding unneccessary laparotomy.

All patients provided written consent prior to the LapUS examination.

2.2.3 Study 3

Patients with carcinoma of the pancreatic head or periampullary region were prospectively evaluated by an investigative algorithm consisting of USS, CT, LapUS and SVA prior to laparotomy. A prospective blind comparison of the diagnostic accuracies of these staging investigations in predicting tumour resectability was performed.

All patients provided written consent prior to the LapUS examination.

2.2.4 Study 4

Patients with carcinoma of the pancreatic head or periampullary region studied in the evaluation of laparoscopic peritoneal cytology (LPC) had all been recruited in Study 3, and were subject to the same methods of validation. Summary measures of diagnostic accuracy of LPC in predicting tumour resectability, and the implications of positive LPC on patient survival were evaluated. However, laparoscopic peritoneal cytology was not performed in all patients in Study 3. The omissions are attributable to breaches of protocol.

While all patients provided written consent for LapUS on these occasions, no specific written consent for LPC was obtained as the instillation and retrieval of peritoneal fluid was performed as an integral part of the routine LapUS examination.

2.3 TECHNIQUE OF LAPAROSCOPY WITH LAPAROSCOPIC ULTRASONOGRAPHY (LapUS)

2.3.1 Laparoscopy - General considerations

Laparoscopy was performed under general anaesthesia with endotracheal intubation, mechanical ventilation and muscle relaxation in all cases. Having prepared and draped a sterile field on the abdominal wall using povidone iodine solution, laparoscopic access to the peritoneal cavity was achieved by one of two methods. (i) The "closed technique", which was utilised during the earlier stages of Studies 1 and 2. A small skin incision was made in the immediate supra- or sub-umbilical region, and a Veress needle inserted at an angle of 45° directed towards the pelvis. Satisfactory insufflation of CO_2 gas through the Veress needle at a flow rate of 1 L / min was ensured and a tense pneumoperitoneum with a pressure of 10-13 mmHg confirmed by the presence of abdominal distension with a tympanitic percussion note over all areas of the abdominal wall. Following removal of the Veress needle, a 10mm diameter disposable laparoscopic trocar and port assembly (Endopath, Ethicon Ltd, Edinburgh, UK) was inserted through the umbilical incision and into the abdominal cavity, again aiming towards the pelvis. Disposable ports were used in preference to re-usable ports to minimise the risk of trauma to the vulnerable laparoscopic ultrasound transducer from the spring-loaded metal trumpet valves which were a feature of the non-disposable instruments. (ii) The "open technique", which was utilised from February 1993 onwards (Figure 1). The umbilicus was everted using toothed grasping forceps and a small vertical skin incision was made from the apex of the umbilicus in a caudal direction. The 'umbilical tube' and its junction with the linea alba identify the close approximation of the parietal peritoneum with the umbilicus. A small stab incision at this site was enlarged by blunt dissection with an artery forceps, permitting direct entry into the peritoneal cavity. A disarmed disposable port (i.e. without the sharp trocar) or blunt Hasson trocar (Endopath, Ethicon Ltd, Edinburgh, UK) was inserted under direct vision, thereby avoiding risk of injury to the viscera. Rapid insufflation of CO2 gas via the inlet of the port was commenced at a flow rate of 4 L / min, and having established a 10-13 mmHg pneumoperitoneum, a second 10 mm disposable laparoscopic trocar and port was inserted away from any adhesions or viscera under direct laparoscopic vision (Figure 2).

A variety of videolaparoscopic camera systems were employed (Olympus OTVSX, KeyMed Ltd, Southend-on-Sea, UK; or Solos GS9635, Sigmacon Ltd, Heriots Wood, UK). In each case, a 30° laparoscopic telescope (Solos, Sigmacon Ltd, Heriots Wood, UK) was used to facilitate side-viewing of certain regions of the abdomen such as the anterior abdominal wall, the diaphragmatic surface of the right hemiliver, the undersurface of the left hepatic lobe and the pelvic viscera. The videolaparoscopic examination was viewed using two high resolution Sony Trinitron PVM-1443-MD monitors which were positioned either side of the head-end of the operating table.

The examination was terminated with evacuation of the pneumoperitoneum and the removal of all ports, taking care to arrest any port site bleeding. The midline fascial defect in the linea alba was repaired with interrupted 1/0 Poly Dioxanone Sulphate sutures (PDS, Ethicon, Edinburgh, UK), and skin edges closed with subcuticular 4/0 PDS sutures. Local anaesthetic infiltration of the wounds was performed using 10 - 20 ml of 0.5% Marcain (Bupivicaine Hydrochloride) (Astra Ltd, Kings Langley, UK).

2.3.2 Laparoscopic ultrasonography - General considerations

Laparoscopic ultrasonography was performed using a variety of commercially available equipment featuring similar specifications (Figures 3 - 5). A 7.5 MHz multi-element linear-array LapUS probe, which consisted of a 9mm diameter rigid wand incorporating a 3.8 - 4 mm transducer 'footprint' at its flattened end, was used in every case (Aloka UST-5521-7.5 or Aloka, UST-5523L-7.5, KeyMed Ltd, Southend-on-Sea, UK; or Tetrad 8A, Englewood, CO, USA). The LapUS probe was connected by a sterile cable to a portable ultrasound machine (or "scanner") which was positioned alongside the operating table (Aloka SSD-500 or Aloka SSD-680, KeyMed Ltd, Southend-on-Sea, UK; or Tetrad 2200 imaging system, Englewood, CO, USA, respectively). Sterilisation of the LapUS probe was achieved by immersion for 20 minutes in 2.2% - 2.5% activated glutaraldehyde solution (Cidex, Johnson & Johnson Ltd, Skipton, U.K.).

The LapUS scanning machines featured several variable image parameters (gain, image direction, magnification, electronic measuring calipers, freeze frame) which were adjusted by an unscrubbed assistant or theatre nurse under the direction of the laparoscopic ultrasonographer (Aloka SSD-500 or Aloka SSD-680), or by the

operator using a remote control handset placed within a sterile plastic sleeve (Tetrad 2200) (Figure 2).

Laparoscopic ultrasound images appeared in real-time on the small monitors which were integral to the scanners. However, simultaneous viewing on the large operating theatre monitors of both the laparoscopic view of the abdominal cavity and the sonographic images was achieved by 'picture-in-picture' video mixing using a Panasonic WJ-AVE5 audio-visual mixing desk (KeyMed Ltd, Southend-on-Sea, UK).

The linear array LapUS transducers used generated real-time B-mode rectilinear sonograms when placed in contact with the underlying abdominal tissues. The first LapUS system used (Aloka UST-5521-7.5 / SSD-500) was tested using an industry standard "phantom" to validate these specifications and to document its lateral and axial image resolution. A full description of the test is shown in Appendix A. In all cases, a standard image direction setting was used such that the distal end of the LapUS transducer was represented on the right side of the sonogram, and the proximal end on the left side.

Images were recorded using a Sony Umatic video cassette recorder, and hard copies were obtained by video frame capture using an Aloka SSZ 700 colour echo copier (KeyMed Ltd., Southend-on-Sea, UK) which utilised a dye transfer thermal sublimation technique.

2.3.3 Diagnostic and staging laparoscopy

The insertion of two laparoscopic ports served two purposes; (i) the LapUS probe and other laparoscopic instruments could be inserted via the second port and used to manipulate the viscera, perform biopsies, aspirate ascitic fluid or peritoneal washings and tamponade bleeding biopsy sites under direct vision; (ii) by alternating the telescope and LapUS probe between two ports, LapUS scanning of the abdominal viscera could be performed about two different planes under laparoscopic guidance (Figure 2).

A systematic examination of the abdominal cavity was performed, examining the serosal surfaces of the anterior abdominal wall, diaphragm, falciform ligament, omentum, pelvic viscera, bowels and their mesenteries. Special attention was paid to the capsular surface of the liver, gall bladder and hilar structures. A probe was

used to displace loops of bowel, and to elevate the left hepatic lobe (Figure 6). The latter manoeuvre was performed to permit inspection of its undersurface and expose the lesser curvature of the stomach and gastrohepatic omentum. The contents of the lesser sac, including the caudate lobe of the liver, the pancreatic body and major branches of the coeliac trunk, could therefore be inspected in patients without excessive intraabdominal fat (Figure 7). The presence of dilated venous collaterals, which might indicate segmental portal hypertension secondary to portal or splenic vein onbstruction, was noted and the disposition of the stomach was inspected for signs of displacement by a retrogastric mass (Figure 8). The probe was used to gently 'palpate' the pancreatic region for a mass (Figure 7A). The porta hepatis, omentum, lesser curve and root of mesentery was inspected for lymph node enlargement. No attempts were made to insufflate or enter the lesser sac, nor was dissection or mobilisation of the pancreatic head or mesenteric root ever performed.

The site and appearance of any abnormalities detected during laparoscopy were documented. Peritoneal tumour seedlings were suspected whenever small white plaques or studs were seen on serosal surfaces (Figure 9). Any free intraperitoneal fluid was aspirated for cytological assessment (see section 2.4).

Liver tumours were suspected whenever a solid focal lesion was visualised at the surface of the organ (Figures 6 and 10). The number, size and site of suspected liver lesions were documented according to the nomenclature of the segmental hepatic anatomy originally described by Couinaud[278, 279]. Liver tumours breaching the hepatic capsule were recognised as pale in colour compared with the surrounding hepatic parenchyma, whereas a discrete alteration in the contour of the liver was regarded as suspicious of an underlying intrahepatic tumour deposit (Figure 6). In the laparoscopic assessment of patients under consideration for resection of liver tumours, particular attention was also paid to the general appearance of the liver, documenting abnormalities such as the diffuse nodularity of cirrhosis, or the yellowish opalescent appearance of diffuse fatty infiltration (steatosis).

Subtle abnormalities affecting the hepatic capsule, whether focal or diffuse, were regarded with caution, especially in the context of established or recently relieved biliary obstruction. It was recognised that serosal tumour seeds and malignant subcapsular liver lesions can appear similar to benign abnormalities such as areas of fibrosis, fatty change, dilated superficial biliary radicles and biliary hamartomas (biliary ectasia / von Meyenberg's complex). Laparoscopic biopsies of such abnormalities were therefore always obtained to verify the diagnosis (Figure 33A).

2.3.4 Technique of laparoscopic ultrasonography

Whenever the stomach and duodenum were seen to be distended, a nasogastric tube was inserted by the anaesthetist and suction applied to evacuate luminal gas and particulate matter which might degrade the LapUS images. The thin film of moisture covering the abdominal organs usually provided excellent acoustic coupling with the LapUS transducer. However, at the discretion of the laparoscopic ultrasonographer, the instillation into the peritoneal cavity of up to 500 ml of normal saline solution at room temperature was used to optimise transducer contact and minimise the temptation to apply down pressure to maintain contact. This instilled fluid also served as peritoneal washings for peritoneal cytological analysis (see section 2.4).

A systematic LapUS examination of the liver, biliary tree and pancreas and surrounding tissues was devised, based upon descriptions contained in standard reference texts of transabdominal[280] and intraoperative ultrasonography[281]. The description of the LapUS examination contined herein has been arbitrarily divided into sections which emphasise imaging of the liver, biliary tree and pancreas. However, it should be appreciated that LapUS of these regions was in reality a continuum between the three anatomical areas, the emphasis of each examination being tailored to the individual circumstances of the patient.

In general, LapUS was performed using a rigid linear array probe which could be moved between an umbilical port and a right flank port (Figure 2). Laparoscopic ultrasonography via the umbilical port produced images orientated about a predominantly sagittal plane. Conversely, scanning was performed about a predominantly transverse plane when the probe was operated from a lateral port. The LapUS probe could be advanced and withdrawn, swept laterally in arc and rotated clockwise or anti-clockwise about its own axis with smooth movements. In reality, scanning occured through a range of oblique and coronal "cuts", enabling the laparoscopic ultrasonographer to appreciate three dimensional anatomical detail from a sequence of two-dimensional real-time images. However, it is convenient to describe the LapUS examination with separate reference to (i) the umbilical port / sagittal scanning plane and (ii) the right lateral port / transverse scanning plane.

2.3.5 Laparoscopic ultrasonography of the liver

Whenever a "reference" hepatic lesion was identified either by laparoscopic inspection of the liver, or by preceding radiological investigations, characterisation of its LapUS appearance was performed initially to facilitate recognition of any other intrahepatic lesions, and for comparison with any other abnormalities. Thereafter, a systematic anatomical survey of the liver was undertaken so that the precise pattern of liver involvement could be documented, and no "blind areas" of parenchyma were neglected. The anatomical survey relied on the recognition of intrahepatic vascular landmarks given the paucity of surface markings on the liver capsule (Figure 11). Sonographically, the normal liver parenchyma has a fine homogenous texture of medium echogenicity. Portal tracts were characterised by their hyperechoic fascial sheaths and diverging course away from the hilum. Laminar blood flow could be observed within the prominent portal vein branches, but the intrahepatic arterial and biliary radicles were normally not easily seen. The hepatic veins were always seen converging in a posterosuperior direction towards the inferior vana cava, and were characterised by the observation of central venous pulse fluctuations transmitted from the inferior vena cava and right atrium of the heart.

An appreciation of the hepatic segmental anatomy[278, 279] was fundamental to the anatomical survey and the documentation of liver lesions. The eight hepatic segments are divided into those constituting the right hemiliver (V-VIII), the left hemiliver (II-IV) and caudate lobe (segment I). The right and left hemilivers are divided by the plane of the principal fissure which passes between the gallbladder fossa and the inferior vena cava. This plane has no external markings, but is defined by the course of the middle hepatic vein which was identified at the outset of the anatomical survey with the LapUS probe placed on the diaphragmatic surface of the liver (Figure 11). Advancement of the LapUS probe in a posterior direction traced the course of the middle hepatic vein to the confluence of the hepatic veins with the inferior vena cava. Anteriorly, the structures of the hepatoduodenal ligament were identified traversing the liver hilum. This plane represented an important anatomical landmark from which a systematic survey of the right and left hemilivers was performed (Figure 11).

The left hemiliver comprises hepatic segment IV (the quadrate lobe), and the left hepatic lobe (segments II and III). These entities are separated by the insertion of the falciform ligament and ligamentum teres. Scanning through hepatic segment IV

identified the left hepatic pedicle giving branches to segments I-IV near the ligamentum teres insertion. The boundary between segments II and III was recognised by the course within the left lobe of the left hepatic vein, which converges with the middle hepatic vein to form a common trunk before entering the inferior vena cava. The fascia of the hepatic insertion of the lesser omentum (gastrohepatic ligament) was identifiable as a well defined hyperechoic plane demarcating the caudate lobe, the inferior vena cava and the paraaortic region from hepatic segment II posteriorly.

The right hemiliver is divided by the transverse course of the right hepatic vein into anterior (segments V and VIII) and posterior (segments VI and VII) sectors (Figure 11). This plane has no surface markings, and was best appreciated with the LapUS probe inserted through the right flank port along the right paracolic gutter and right lateral subphrenic space. Scanning in the predominantly coronal plane of the right hepatic vein was achieved from this position. The anterior and posterior sectoral divisions of the right portal pedicle were identified bifurcating perpendicular to the plane of the right hepatic vein, and their respective segmental branches defined.

Focal hepatic abnormalities were characterised as isoechoic, hyperechoic or hypoechoic compared with the background parenchyma (Figure 12). A variety of benign lesions were also encountered, and characterised by their typical sonographic appearances. These included simple hepatic cysts, areas of fatty infiltration, fibronodular hyperplasia and haemangiomas. Simple cysts were anechoic, lacked a defined wall and cause posterior acoustic enhancement. Focal fatty infiltration was commonly observed adjacent to the ligamentum teres insertion and gall bladder fossa in segments IV and V, and appeared as a circumscribed but irregular hyperechoic area. Haemangiomas were identified as round, circumscribed hyperechoic lesions which never caused posterior attenuation of the ultrasound beam ("shadowing"), although frequently were associated with posterior acoustic enhancement. Any hyperechoic intrahepatic lesion causing posterior acoustic *attenuation* was regarded as being highly suspicious of a metastasis of gastrointestinal origin. Diffuse abnormalities of the liver parenchyma were also interpreted with caution. A coarse and predominantly hyperechoic texture throughout the liver was recognised as confirming steatosis or cirrhosis, especially when suspected from the appearances of preoperative radiological investigations or laparoscopic inspection. However, caution was excercised when there was the possibility of diffuse malignant infiltration, and a tissue diagnosis was sought in these circumstances.

In patients with suspected focal hepatic malignancy, a careful and systematic search for malignant focal lesions was performed, with reference to the sonographic appearance of the reference lesion where possible. The presence of an anechoic halo immediately surrounding the lesion was regarded as being pathognomonic for metastases, hence the term "bullseye" or "target" lesions[282-284] (Figure 12). The number, size, site and spatial relationships of the tumour with important vascular structures was documented so that where appropriate, anatomical liver resections could be planned. The hilar and paraaortic regions were examined for malignant regional lymphadenopathy, which was inferred from the finding of discrete lymph nodes measuring more than 10 mm in diameter.

2.3.6 Laparoscopic ultrasonography of the biliary tree

Laparoscopic ultrasonography of the biliary tree was always preceded by examination of the liver to identify intrahepatic duct dilatation or other incidental intrahepatic pathology. Examination of the proximal biliary tree and gallbladder was performed with the LapUS transducer positioned on the diaphragmatic surface of hepatic segments IV and V, using the intervening liver as an acoustic window (Figure 13). The gallbladder wall is normally thin (≤ 3 mm) and exhibits three distinct echo-layers (Figure 14). It was examined for mural thickening, distension, mucosal polyps or distortion by tumour infiltration. The number and size of any contained gallstones, or the presence of echogenic debris or crystals and biliary sludge was documented.

Examination of the extrahepatic biliary tree with the LapUS probe inserted through the umbilical port provided laparoscopic sonograms in the longitudinal axis of the hepatoduodenal ligament (Figure 13). The common bile duct, hepatic artery and portal vein were identified as parallel tubular structures, which were separated posteriorly from the inferior vena cava in the cephalad direction by the wedge shaped caudate lobe of liver. These structures traversing the hepatoduodenal ligament were distinguished by their (i) relative positions, (ii) vessel wall characteristics and (iii) the nature of luminal blood flow. The course of the portal vein, which is normally the largest structure within the hepatoduodenal ligament, was defined by its posterior position, thin wall, lack of pulsatility and visible laminar blood flow. The common hepatic artery was identified by its anteromedial position, thicker wall and visible arterial pulsation. It could be traced inferomedially to its origin from the coeliac axis at the superior pancreatic border, while superiorly its usually traversed the portal vein and common hepatic duct to enter the liver hilum.

The common duct was identified by its anterolateral position relative to the hepatic artery and portal vein, its thicker fibrous wall, and the absence of any luminal flow. Its confluence with the cystic duct was often apparent, and when dilated above normal limits (i.e. ≥ 8 mm in maximum diameter) a sediment of biliary sludge was often apparent. Withdrawal of the LapUS probe from the umbilical port with slight clockwise rotation of the transducer allowed the intra- / retro-pancreatic course of the distal common bile duct to be traced through its divergent path away from the portal vein and anterior to the inferior vena cava to the papilla of Vater. Common duct stones were strongly suspected when a crescentic hyperechoic signal and / or a dense posterior acoustic shadow were observed (Figure 14).

Examination of the extrahepatic biliary system in a predominantly transverse direction with the LapUS probe operated from a right flank port was performed by sweeping the transducer over the length of the hepatoduodenal ligament, gastric antrum and proximal duodenum. Cross-sectional images of the portal vein (posterior), hepatic artery (anteromedial) and common duct (anterolateral) were obtained in this way (Figure 15).

2.3.7 Laparoscopic ultrasonography of the pancreas

Sonographically, the normal pancreatic parenchyma appears homogenous and of similar or slightly increased echogenicity relative to that of the liver, and is intimately related to several major blood vessels and ductal structures. An anatomical survey of the pancreas and peripancreatic structures was performed with reference to standard anatomical landmarks with the LapUS probe operated via umbilical and right flank ports to achieve scanning in two planes.

Laparoscopic ultrasonography of the pancreas via the umbilical port

With the LapUS probe operated in a predominantly sagittal plane via the umbilical port, and having examined the structures of the hepatoduodenal ligament (Section 2.3.6), the portal vein and common duct were followed inferiorly through their mutually divergent courses (Figure 16). The course of the portal vein and superior mesenteric vein posterior to the pancreatic neck was identified as the probe was withdrawn inferiorly over the gastric antrum and first part of duodenum. The pancreatic neck was recognised as a relatively thin structure measuring ≤ 15 mm in the antero-posterior direction, and conveying the main pancreatic duct, which was

identified in transverse section and measured ≤ 3 mm in diameter when normal (Figures 17 and 18).

From this key position of reference for the LapUS examination of the pancreas, slight rotation or lateral displacement of the transducer to the right demonstrated the head of the pancreas and the duodenum. The five echo-layers of the duodenal wall, in which peristaltic movement was usually visible, demarcated the lateral extent of the pancreatic head. The convergent courses of the pancreatic duct and common bile duct anterior to the inferior vena cava were traced until their termination at the papilla of Vater, which could be identified protruding into the duodenal lumen when sufficient intraluminal fluid was present. The uncinate process was recognised as the inferior extension of the pancreatic head which extended medially to "wrap behind" the superior mesenteric vein over a variable distance (Figure 16).

Examination of the body and tail of the pancreas was achieved by rotation or lateral displacement of the LapUS probe to the left from the reference position over the pancreatic neck, using the course of the pancreatic duct as a guide. It was sometimes helpful to position the LapUS transducer on the left hepatic lobe as a "standoff", thus facilitating imaging of the para-aortic region (Figure 19). The superior mesenteric artery was identified passing posterior to pancreatic neck and entering the mesenteric root immediately to the left of the superior mesenteric vein. The origin of the coeliac axis from the abdominal aorta was identified immediately above that of the SMA, and its main branches identified by slight rotatory movements of the probe (Figure 19). The presence of an anomalous (accessory or replaced) right hepatic artery arising from the SMA or aorta was diagnosed by the demonstration of a significant arterial branch arising at this level, and coursing superiorly into the hepatoduodenal ligament while passing posterior to the pancreatic head, portal vein and / or common duct (Figure 20).

Laparoscopic ultrasonography of the pancreas via the right lateral port

Examination in a predominantly transverse direction with the LapUS probe operated from a right flank port required identification of the splenoportal mesenteric venous junction, superior mesenteric artery, aorta and inferior vena cava which were the key vascular landmarks delineating the posterior limits of the pancreas (Figure 21). The walls of the stomach and duodenum beneath the transducer demarcated the anterior limits of the gland. As the transducer was swept superiorly, the emergence of the portal vein at the superior pancreatic border to enter the hepatoduodenal ligament

was identified. At this level, the common hepatic artery was identified arching over the portal vein, with the gastroduodenal and superior pancreaticoduodenal arteries emerging to pass superficially between pancreatic head and duodenum. The full length of the pancreatic duct, and the tortuous course of the splenic artery at the superior pancreatic border could be appreciated from this position. Again, the presence of an accessory right hepatic artery was identified passing posterior to the pancreatic head, portal vein and / or common duct (Figure 20 B).

Laparoscopic ultrasonography for pancreatic and periampullary cancer

Carcinoma of the pancreatic head or periampullary region often caused secondary changes which were apparent during the anatomical survey, such as dilatation of the common bile duct (> 8 mm), cystic duct and gall bladder (Figure 22). When previous decompression of a patient's obstructive jaundice by endoscopic or percutaneous insertion of a biliary stent had caused collapse of the duct, its course was identified by detection of the hyperechoic stent artefact. Dilatation of the pancreatic duct (> 3 mm diameter) was typically accompanied by atrophy of the surrounding pancreatic parenchyma in the pancreatic neck, body and tail.

Ductal carcinoma of the pancreas was diagnosed as a predominantly hypoechoic mass with irregular margins, although often heterogeneous with patchy areas of mixed echogenicity. However, it was also recognised that pancreatic carcinoma less frequently appeared as a diffusely infiltrating and ill-defined tumour which was isoechoic and could be difficult to diagnose (Figures 23 and 24).

Periampullary carcinoma was diagnosed by the appearance of a mass at the site of the papilla of Vater, as indicated by the termination of the common bile duct and pancreatic duct within the duodenal wall. Such lesions were recognised as poorly defined isoechoic lesions prolapsing into the duodenal lumen as a sessile mass, infiltrating the pancreatic head, and / or occluding the lumens of dilated pancreatic and / or distal common bile duct (Figures 25 and 26).

Having characterised the primary pancreatic lesion, its local resectability was assessed. Tumour invasion of the portal vein was the main consideration in determining local resectability of pancreatic or periampullary cancer, with particular attention to the right lateral aspect of the splenoportal venous junction. The following criteria were adopted to indicate vascular invasion: (i) obliteration or thrombosis of the vein, as evidenced by failure of the laparoscopic ultrasonographer to demonstrate a patent vessel in the expected anatomical location, with or without

venous collateralisation; (ii) a fixed stenosis of the vessel wall; (iii) loss of the hyperechoic vessel / tumour interface with encroachment of hypoechoic tumour to the vessel margin; (iv) vessel encasement as evidenced by tumour encirclement and 'rigidity'; (v) the presence of invading tumour within the vessel lumen (Figures 27 - 31). Care was taken to avoid creating artefactually the impression of portal vein compression by excessive probe pressure.

Other evidence for local unresectability was sought by examining for tumour extension into adjacent soft tissue planes, such as the mesenteric root, hepatoduodenal ligament or retropancreatic fascia.

Regional lymph node enlargement (≥ 10 mm maximum node diameter) was arbitrarily regarded as being suspicious of malignant involvement (Figure 32).

2.3.8 Laparoscopic biopsy

Standard straight-blade laparoscopic scissors and toothed forceps were used for excisional biopsy of peritoneal or superficial liver lesions (Figures 9B and 33A). Needle biopsies of deeper seated tumours within the liver or pancreas were performed using a Tru-Cut needle (Baxter, Deerfield, IL, USA). This biopsy needle is available in a range of sizes and incorporates a 20 mm specimen notch within a sliding guillotine sheath. The tip of the biopsy needle was lightly abraded with a scalpel blade to enhance its sonographic signal prior to LapUS guided biopsy. Laparoscopic and LapUS guided needle biopsies were performed by a two puncture "free hand" technique. The site of needle puncture on the abdominal wall was chosen to facilitate access to the target area, anticipating the angle with which the needle would be introduced into the sonographic field. The passage of the needle was identified as a bright point source when the needle was perpendicular to the sonographic 'cut', or as an hyperechoic linear 'artifact' when the needle was in the same plane as the ultrasound beam. Slight rotatory or side-to-side movements of the LapUS probe helped to maintain the three-dimensional orientation of the ultrasonographer during the biopsy procedure.

Laparoscopic and LapUS guided fine needle aspiration cytology was performed for sampling enlarged regional lymph nodes using a 22G needle attached to a 5 ml syringe.

2.3.9 Laparoscopic ultrasonographers

The majority of LapUS examinations reported in this thesis were performed by a Consultant Surgeon with several years experience with intraoperative and LapUS (OJG), or by the author (TGJ) who was a surgical trainee at registrar level, and who trained in the technique from October 1992. In study 1 (imaging of the normal hepatobiliary and pancreatic anatomy), all LapUS examinations performed during laparoscopic cholecystectomy were performed by the author. In addition, all staging LapUS examinations in patients with pancreatic or periampullary cancer in Study 1 were performed by the author or OJG.

All LapUS examinations in Studies 3 and 4, and the majority of those in Study 2, were performed by OJG or TGJ. Several LapUS examinations in Study 2 were performed by surgical trainees at Senior Registrar level (JDG, MM and / or JW) under the supervision of OJG. A standardised proforma (Appendix B) was completed by TGJ or OJG upon completion of the LapUS examination.

2.4 LAPAROSCOPIC PERITONEAL CYTOLOGY

At the outset of laparoscopy, 300-500 ml of normal saline at room temperature was instilled into the subhepatic space. Biopsy of suspicious serosal or liver lesions, or of the pancreas, was always deferred until after the aspiration of lavage fluid to minimise its contamination with tumour cells or blood. Following completion of laparoscopic ultrasonography, an 80 ml sample of lavage fluid was aspirated using a 16 FG nasogastric tube (Vygon, 95440 Ecouen, France) inserted via a 5 mm reducing sleeve and attached to a 30 ml catheter tipped-syringe (Figure 33B). The specimen was transported to the Department of Pathology in 4 x 20 ml sterile universal containers.

Peritoneal lavage specimens were centrifuged at 2 000 rpm for 10 minutes and the supernatant discarded. The sediment was re-suspended in Glasgow's medium containing 0.25% heparin, and cytospin preparations were made using 200 ml aliquots of the suspension spun at 500 rpm for four minutes. The cytospin preparations were fixed immediately in 95% methyl alcohol for 10 minutes. In instances of heavy bloodstaining of the sample, additional cytospin samples were prepared and lysed in 6% acetic acid in 95% methyl alcohol. Slides were stained using the Papanicolau method, and when appropriate, additional stains for mucin and / or cell marker studies were performed.

All cytological examinations were performed initially as part of the routine hospital service by a number of cytopathologists. All specimens were also reviewed independently by a Consultant Cytopathologist (EMcG). The results were documented on a standardised proforma (Appendix B).

2.5 RADIOLOGICAL IMAGING TECHNIQUES

2.5.1 Transabdominal ultrasonography

In Studies 3 and 4, transabdominal USS was performed after a fast of at least six hours using an Acuson 128 ultrasound machine (Mountain View, CA, USA) with 3.5 MHz or 4 MHz transducers. All scans were performed by one experienced radiologist (PLA). Colour Doppler and Doppler spectral analysis were used to assess the major peripancreatic blood vessels for tumour involvement. The presence of significant turbulence or an increase in velocity $\geq 100\%$ at, or beyond, the region of the tumour was taken as evidence of vascular invasion. The examinations were performed 'blind', and a protocol form (Appendix C) was completed for each examination by PLA. (Figure 34).

2.5.2 Dynamic CT

In Studies 3 and 4, CT scans of the abdomen were perfomed under the direction of one Consultant Radiologist (ARW), or by a nominated deputy according to the following protocol. Where CT scans had recently been obtained at a referring hospital, the films were reviewed by ARW, and the examination only repeated if the quality of the original scans were regarded as poor. The scans were interpreted 'blind', and a protocol form (Appendix D) was completed by ARW for each examination.

Abdominal CT scanning was performed using a General Electric 9800 whole body CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). Contiguous 10mm slices were acquired through the entire liver and pancreas before the administration of intravenous contrast. The examination was repeated following the injection of a 100 ml bolus of iodinated contrasted medium (Iopamidol 370®). Ten mm contiguous slices were obtained with scan acquisition performed in a craniad direction to optimise contrast opacification of the superior mesenteric and portal veins (Figures 35 and 36).

Latterly, several CT scans were performed using the technique of 'spiral' CT scanning with a Siemans Somatom Plus spiral-acquisition CT scanner. Scans were performed before and during intravenous contrast enhancement with 100-120 ml of Iopamidol 300®. For the precontrast scans, the liver and pancreas were scanned during a single breath-hold using 10 mm nominal slice thickness and a 10 mm / sec table speed. For the post-contrast scan, 5 mm slice thickness and 5 mm / sec table speed or 10 mm slice thickness with 10 mm / sec table speed was used depending on the volume of interest.

2.5.3 Selective visceral angiography

All angiographic examinations in Studies 2-4 were perfomed and interpreted 'blind' by one Consultant Radiologist (DNR). A protocol form (Appendix E) was completed for each examination by DNR.

A 7 Fg Cordis® superior mesenteric or Sidewinder® catheter was introduced percutaneously into the right common femoral artery by the Seldinger technique, and advanced into the abdominal aorta. The coeliac axis was initially selected, and 60-70 ml of non-ionic contrast (Niopam 370E®, Merck Pharmaceuticals) was injected at a rate of 6ml / sec and at a pump pressure of 600 psi. Following an initial delay of one second, ten films were obtained at a speed of one film every two seconds. This provided an anatomical display of the branches of the coeliac axis, and during the venous phase, visualisation of the splenic and portal vein (Figure 37 and 38).

The catheter was then placed within the superior mesenteric artery, and 70 ml of contrast are again injected at the same rate and pressure settings. A long film delay of 9-10 secondss was employed, and ten radiographs obtained at a rate of one film every two seconds. This sequence of films demonstrated any arterial anomalies involving the superior mesenteric artery, such as an accessory or replaced right or common hepatic artery (Figure 39). The longer delay ensured optimal visualisation of the superior mesenteric and portal veins.

Where the meso-portal venous pathway lay across the plane of the vertebral column, and imaging was consequently impaired, the examination was repeated with a 17° right posterior oblique view with the catheter still in the superior mesenteric artery and employing the same settings. Thus, the opacified veins were projected away from the bony structures and clearer images obtained.

2.6 VALIDATION OF RESULTS

Validation of the study endpoint of tumour unresectability was achieved in a number of ways:

2.6.1 Laparoscopic findings

Tumour unresectability was regarded as having been validated when distant intraabdominal metastases or malignant regional lymphadenopathy were discovered during laparoscopy. Histological confirmation of the diagnosis was required in each case. This was achieved by laparoscopic needle biopsy, fine needle aspiration cytology and / or scissor-biopsy of the lesion.

2.6.2 Surgical assessment

Exploratory laparotomy was the ultimate arbiter of tumour resectability in the majority of patients, and was always performed by a consultant surgeon who was experienced in pancreatic surgery (DCC, OJG and / or SPB). The findings were documented on a standardised proforma by TGJ (Appendix F). Laparotomy was performed under general anaesthesia with endotracheal intubation, muscle relaxation, mechanical ventilation and invasive monitoring (central venous pressure, arterial pressure line and urethral catheterisation). A right subcostal incision was performed, extended to the left where appropriate. A careful inspection of the peritoneal cavity and viscera was performed, with palpation of the liver, mesenteries, peripancreatic tissues and serosal surfaces for metastases, malignant lymphadenopathy or extra pancreatic tumour invasion. Histological proof of such findings was sought in each case by biopsy. Intraoperative ultrasonography of the liver was performed using a 7.5 MHz 'T-probe' to search for intrahepatic metastases (Aloka UST-576-T, KeyMed Ltd, Southend-on-Sea, UK; or Tetrad 6C, Englewood, CO, USA).

Exploration of the pancreas itself was performed to assess local tumour resectability (i.e. T-stage)[285]. The size and fixity of the tumour were assessed by superficial palpation. Local tumour invasion of the tissues of the hepatoduodenal ligament, mesenteric root, major arteries and stomach was regarded as evidence of unresectability. The pancreatic head and duodenum were mobilised from the inferior vena cava and aorta by the Kocher manoeuvre. Tumour infiltration of this plane (Figure 40), including the paraaortic lymphoid tissue and origin of the superior

mesenteric artery, was regarded as evidence of unresectability. Bi-digital palpation of the pancreatic head and mesenteric root was performed to evaluate tumour mobility and local tumour extension. Tumour invasion of the major peripancreatic veins was assessed by dissection of the superior mesenteric vein at the inferior pancreatic border between the third part of the duodenum and uncinate process, the portal vein at the superior pancreatic border and its course through the retropancreatic tunnel (Figure 41). Patients in whom limited tumour invasion of the superior mesenteric and portal vein was suspected were regarded as unresectable, and portal vein resection was not attempted.

Exposure of the anterior surface of the pancreas was achieved by entering the lesser sac through division of the gastrocolic and gastrohepatic omenta. Direct invasion of the posterior stomach wall was assessed by this manoeuvre. Evaluation of local retroperitoneal invasion in patients with cancers of the pancreatic body and tail was performed during mobilisation of the spleen and distal pancreas. Palliative resections comprising gross transection of tumour in patients with locally invasive disease were not performed.

In general, patients with cancers of the pancreatic head or periampullary region were treated by a Whipple pancreaticoduodenectomy, patients with cancers of the pancreatic body and tail underwent distal pancreatectomy, and total pancreatectomy was reserved for a patient with carcinoma of the head and body.

Patients with periampullary tumours apparently localised to the papilla and considered potentially resectable by local excision were evaluated superficially by means of a longitudinal duodenotomy. Such tumours were regarded as resectable when transduodenal local excision, or ampullectomy, could be achieved with tumour-free resection margins.

2.6.3 Non-operative findings

Occasionally, patients were deemed to have locally unresectable pancreatic cancers due to portal - superior mesenteric vein invasion on the basis of of the concurring radiological findings of USS, CT, LapUS and / or SVA, together with the clinical observation of a rapid death from carcinomatosis. In Studies 2-4, independent validation of these findings during laparotomy was not obtained because an *a priori* clinical decision had been made to palliate the patient non-operatively by means of biliary stent insertion. The combined evidence of the various staging investigations

and clinical findings were accepted as validation of tumour unresectability. Such findings were documented on a standardised proforma by TGJ (Appendix F).

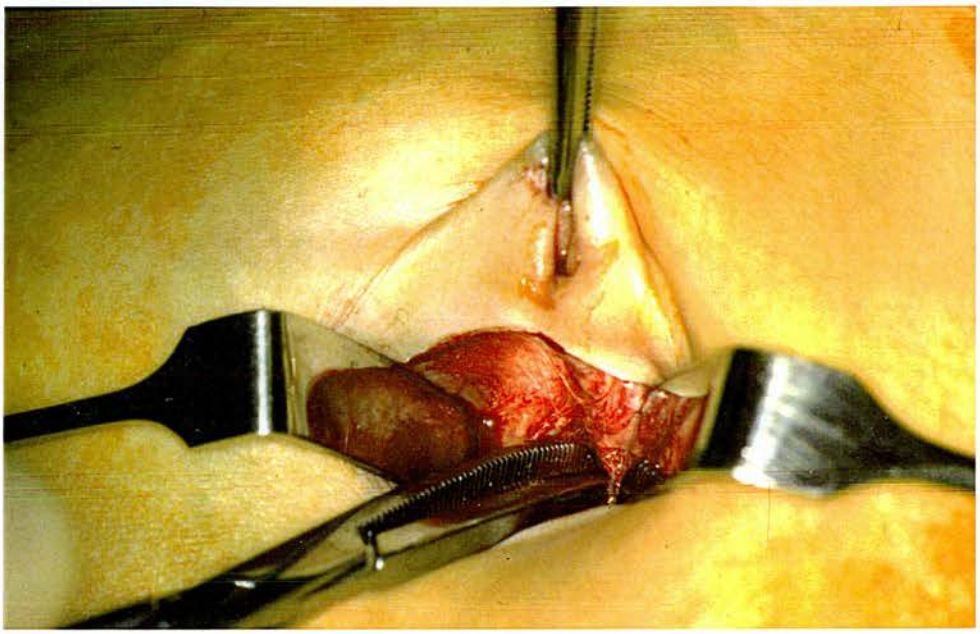
2.6.4 Histopathological findings

Validation of tumour resectability for cure in Studies 3 and 4 required the demonstration of microscopically tumour free resection margins and regional lymph nodes following routine histopathological examination of the resection specimens by the staff of the University of Edinburgh Department of Pathology. Particular attention was paid to the surgical transection lines of the stomach, common duct, pancreas, duodenum and retropancreatic fascia. The findings were documented on a standardised proforma by TGJ (Appendix F).

2.6.5 Documentation of data

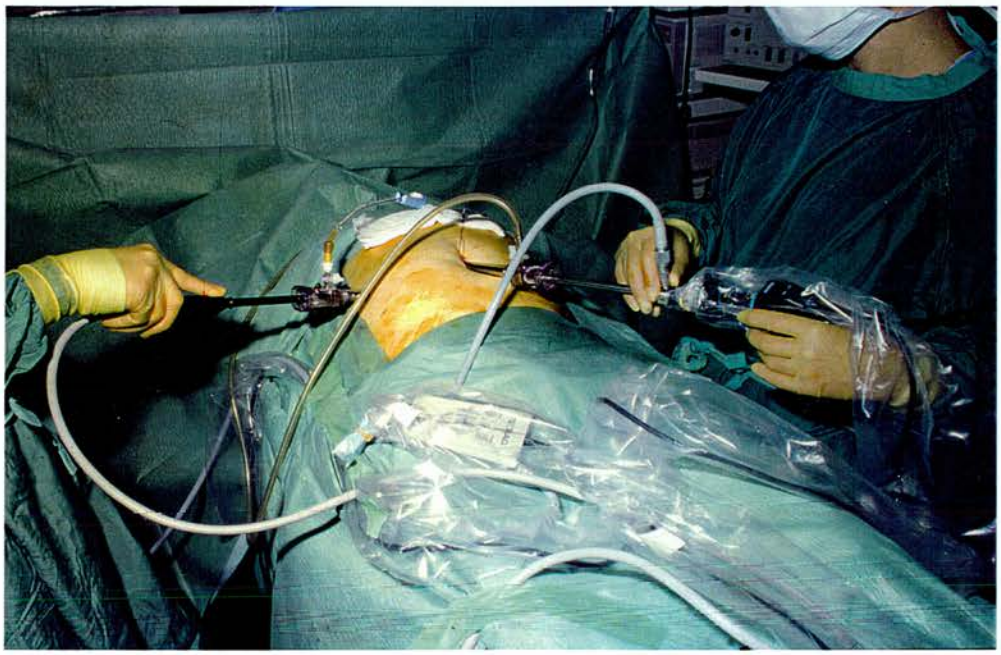
The data recorded on standardised proformas for Studies 1-4 (Appendices B-F) were collected and stored using a desktop computer database programme (Claris™ Filemaker Pro 2.1 Bv2 used with a Macintosh Centris 610 or Macintosh LC475), the database format having been created by TGJ.

Figure 1



Technique of "open" laparoscopy by direct cutdown. The umbilicus has been everted and the umbilical tube and parietal peritoneum incised. This provides direct access to the peritoneal cavity (as demonstrated by forceps) facilitating insertion of the laparoscopic port under direct vision.

Figure 2



Technique of laparoscopy with LapUS. The telescope (with attached camera and light source) has been inserted via the umbilical port (note insufflation tubing attached to side port). The LapUS probe has been inserted through the right flank port (note attached tubing for the instillation of saline via the side port). The "remote control" handset has been placed within a sterile plastic sleeve.

Figure 3

Aloka SSD-500 portable ultrasound scanning machine (back left) with Sony thermal printer (back right). A 7.5 MHz linear array LapUS probe (Aloka UST-5521-7.5), a 5 MHz intraoperative ultrasound "T probe" (Aloka UST-576-7.5) (and a 5 MHz intraoperative ultrasound "I probe") are pictured in the foreground (from back to front).

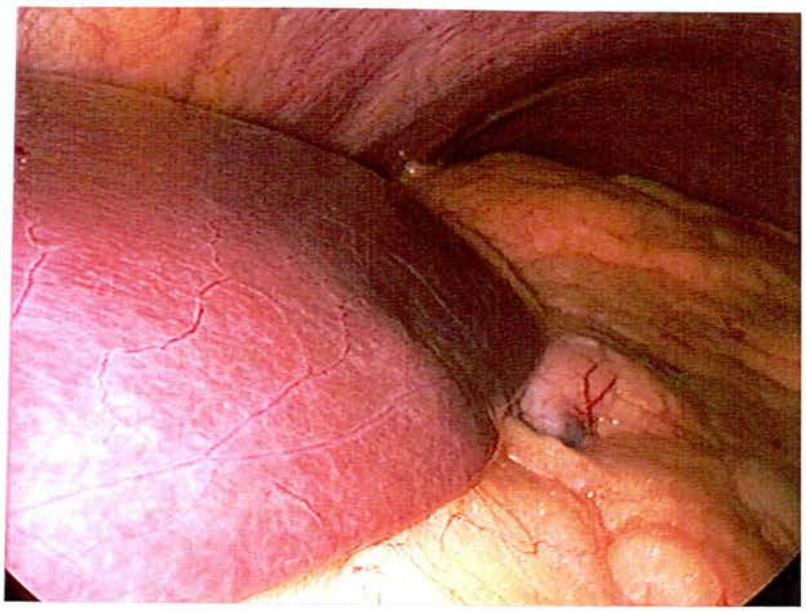
Figure 4

Tetrad 2200 portable ultrasound scanning machine
(Tetrad Corp, CO, USA)

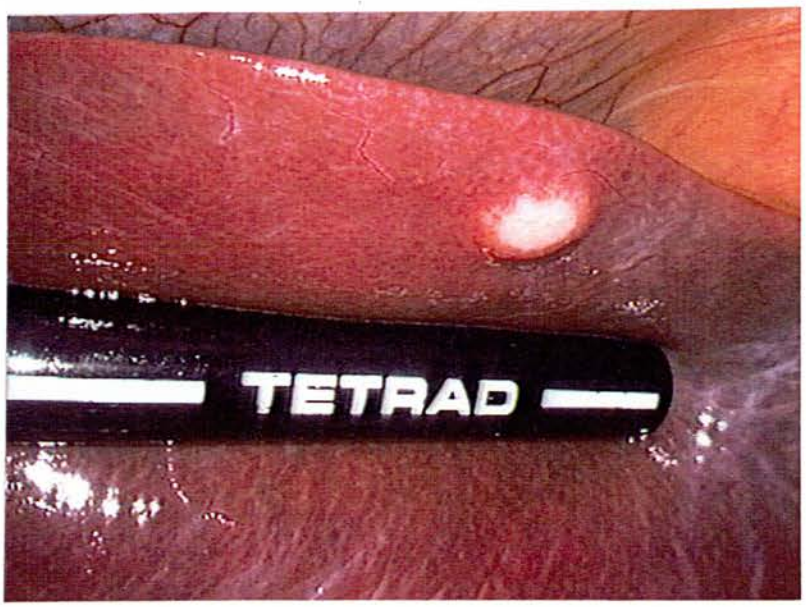
Figure 5

Close-up view of the 4 cm "footprint" of the 7.5 MHz linear array transducer at the end of the 9 mm diameter rigid shaft of the Aloka UST-5523L-7.5 laparoscopic ultrasound probe (KeyMed Ltd, Southend-on-Sea, UK).

Figure 6

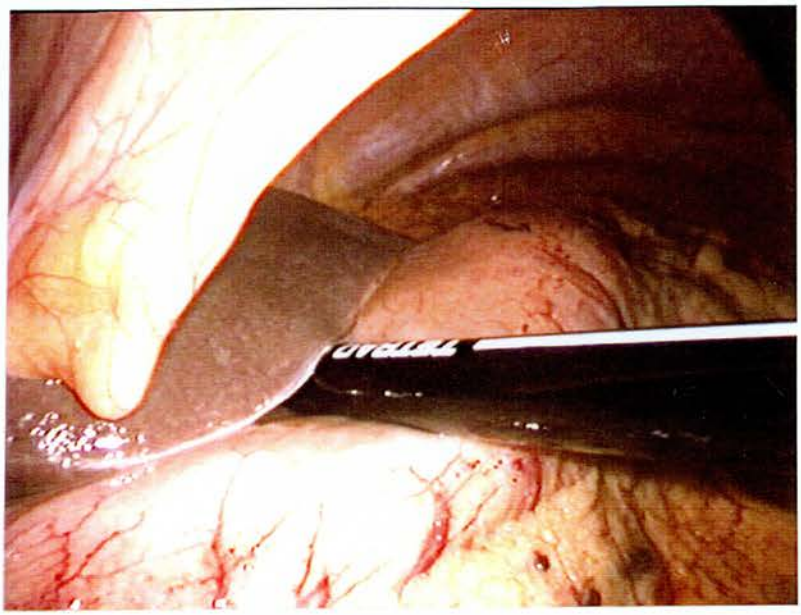


A. Inspection of the left hepatic lobe during staging laparoscopy in a patient thought (on the basis of spiral CT scanning) to have a potentially resectable periampullary carcinoma revealed a subtle contour change near the inferior edge.

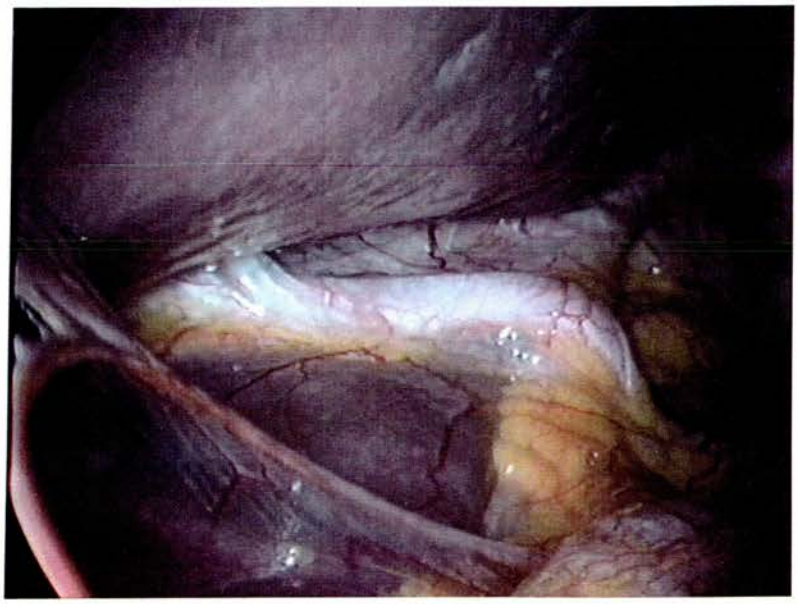


B. Retraction of the liver edge with the LapUS probe revealed a small metastasis breaching the capsule of its undersurface.

Figure 7

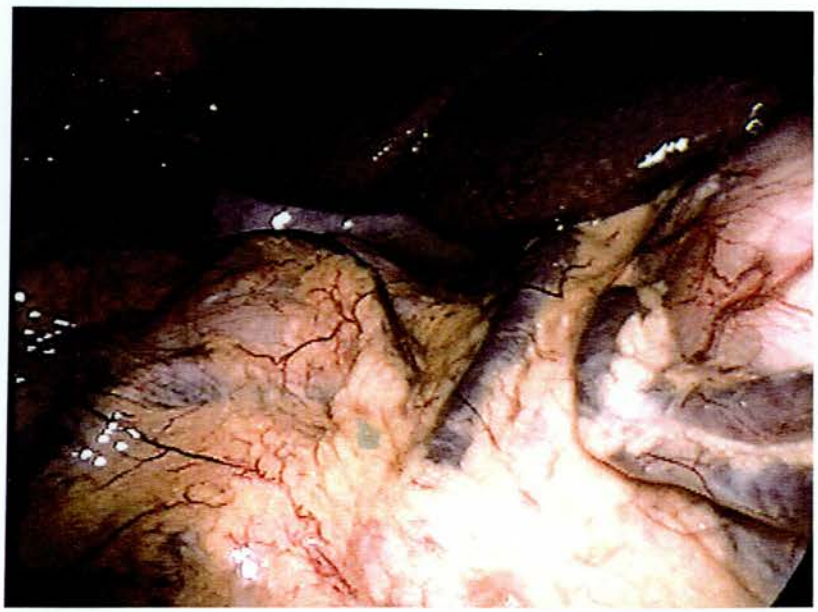


A. "Palpation" of the pancreas using a rigid LapUS probe during laparoscopy. The probe has been inserted through the umbilical port, and LapUS images of the pancreatic body and peripancreatic tissues are generated about the parasagittal plane.

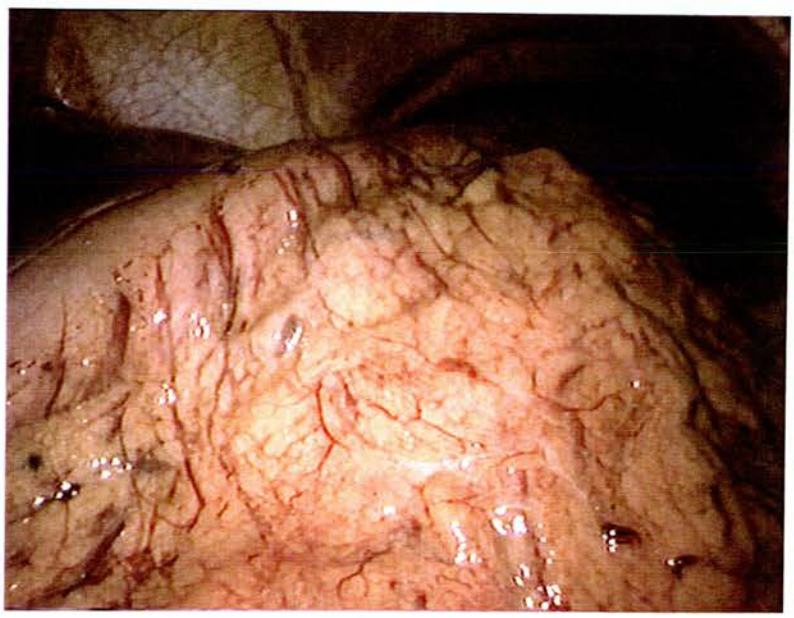


B. Elevation of the left hepatic lobe to demonstrate the lesser omentum, and the caudate lobe, common hepatic artery (lower right) and accessory left hepatic artery (from the left gastric artery) within the lesser sac. No nodes are identified.

Figure 8

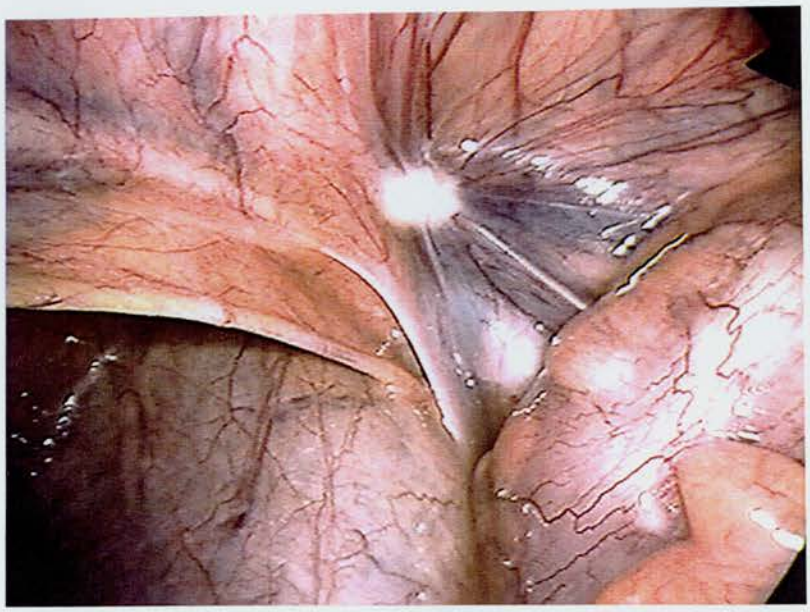


A. Distended gastroepiploic veins and ascitic fluid in the region of the porta hepatis providing indirect evidence of portal vein invasion by carcinoma of the pancreatic head during staging laparoscopy.

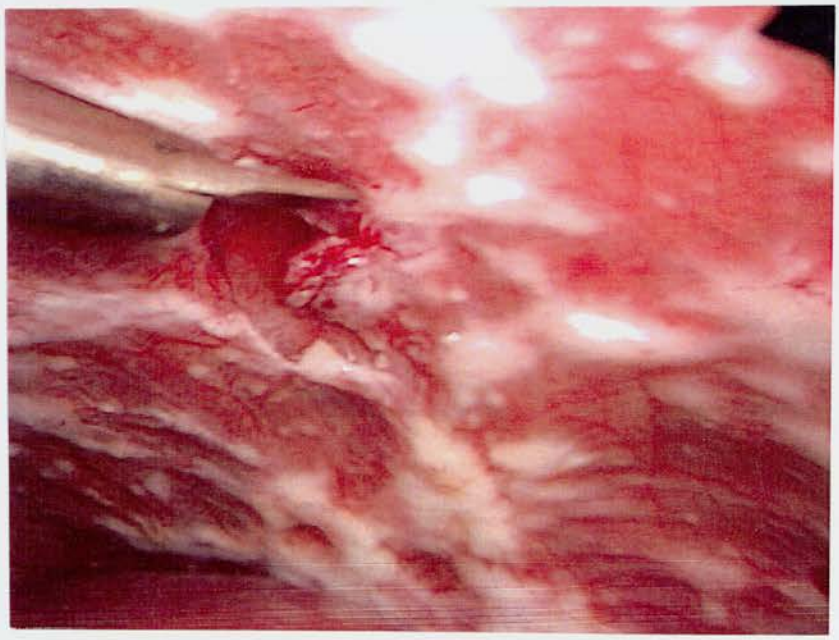


B. Anterior displacement of the stomach and gastrocolic omentum by a carcinoma of the pancreatic body as viewed during laparoscopy.

Figure 9

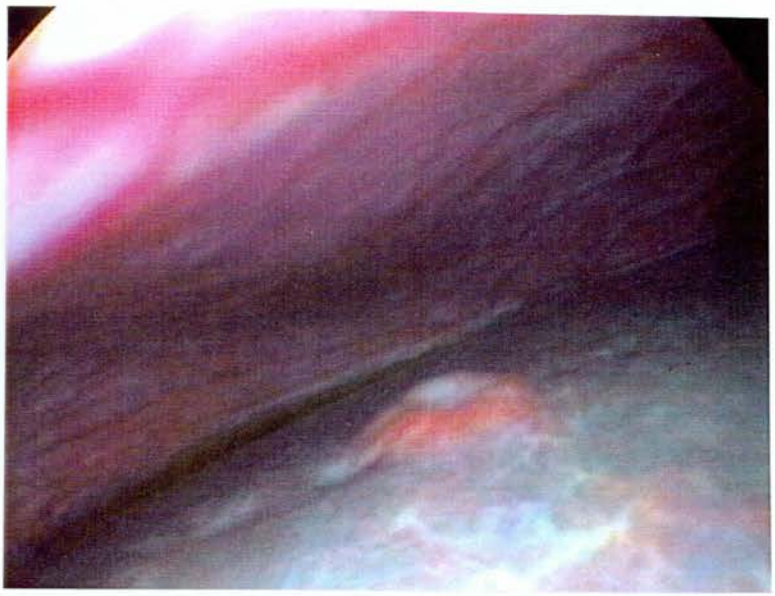


A. Previously unsuspected malignant peritoneal seedlings discovered over the parietal peritoneum of the left inguinal region during staging laparoscopy.

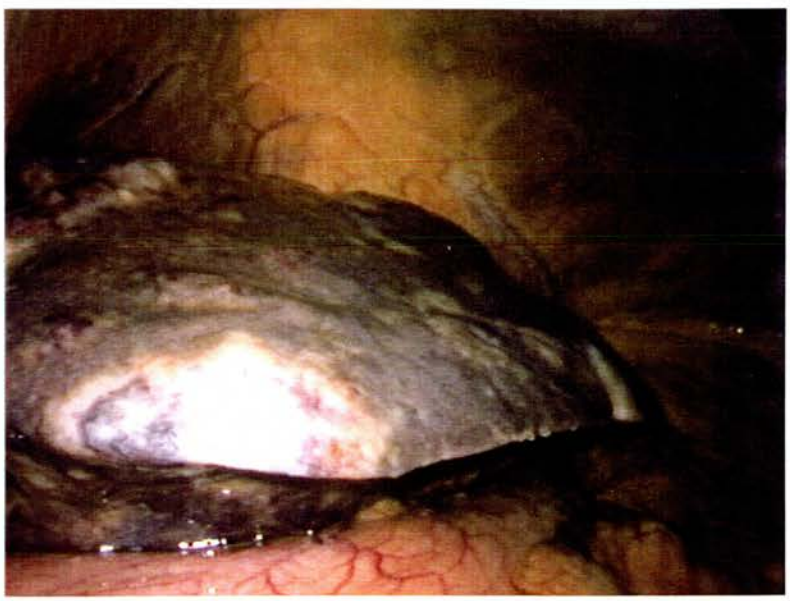


B. Malignant peritoneal seedlings covering the parietal peritoneum of anterior abdominal wall and biopsied with straight-bladed laparoscopic scissors.

Figure 10

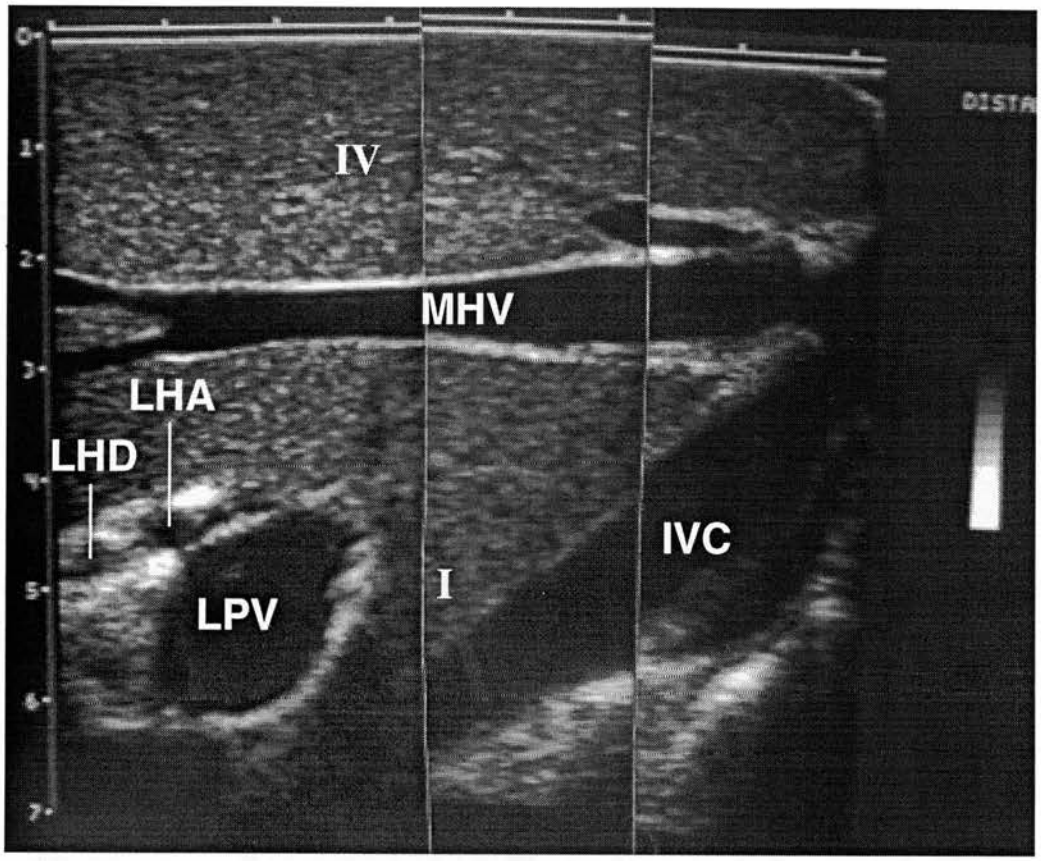


A. A small umbilicated liver metastasis arising superficially within the right hepatic lobe and undetected until staging laparoscopy in a patient with periampullary cancer.



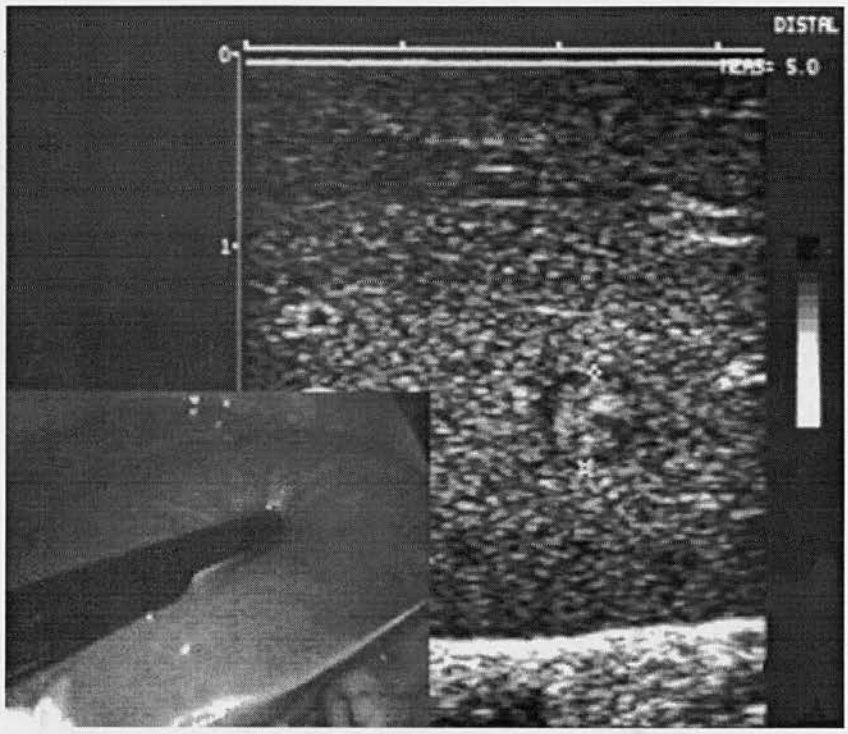
B. Extensive tumour replacement of the left hepatic lobe associated with ascites in a patient with pancreatic cancer.

Figure 11

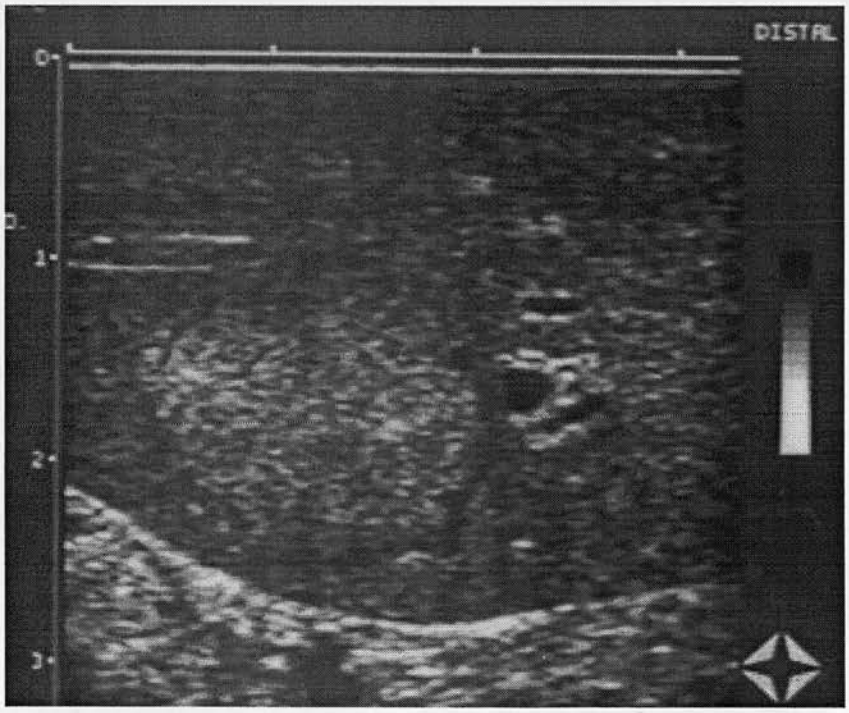


Laparoscopic sonograms through the liver in a parasagittal plane slightly to the left of the midline of the liver. The probe was inserted through the umbilical port, and succesive cuts obtained as it was gradually withdrawn to show the convergent courses of the middle (MHV) and left hepatic vein (unlabelled) with the inferior vena cava (IVC). The hilar structures (left portal vein (LPV), left hepatic artery (LHA) and left hepatic duct (LHD) surrounded by the hyperechoic Glissonian sheath are shown in cross-section and separate hepatic segments I and IV inferiorly.

Figure 12

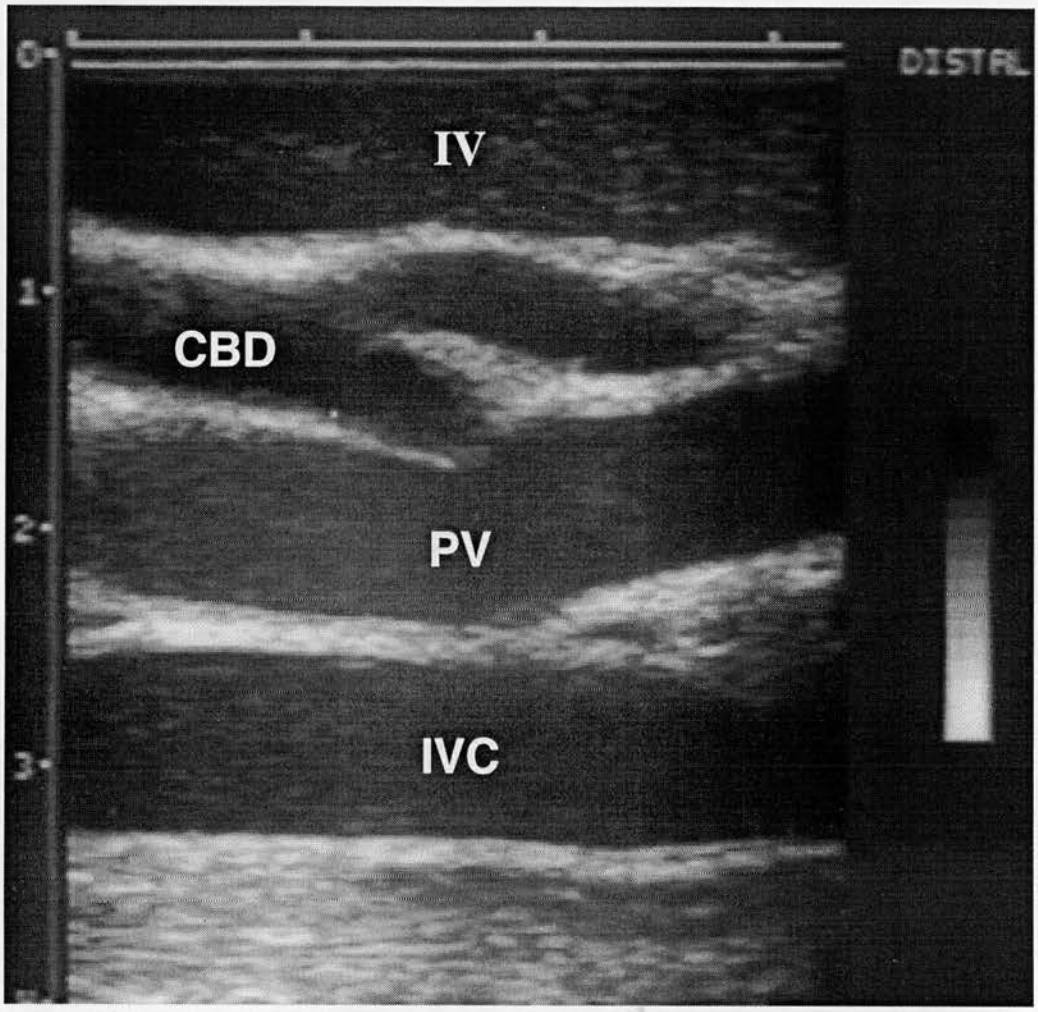


A. Isoechoic intrahepatic metastasis detected by LapUS with the probe placed on the right hepatic lobe (insert). An anechoic halo circumscribes the lesion, and electronic calipers indicate a tumour diameter of five millimetres (small print / top right).



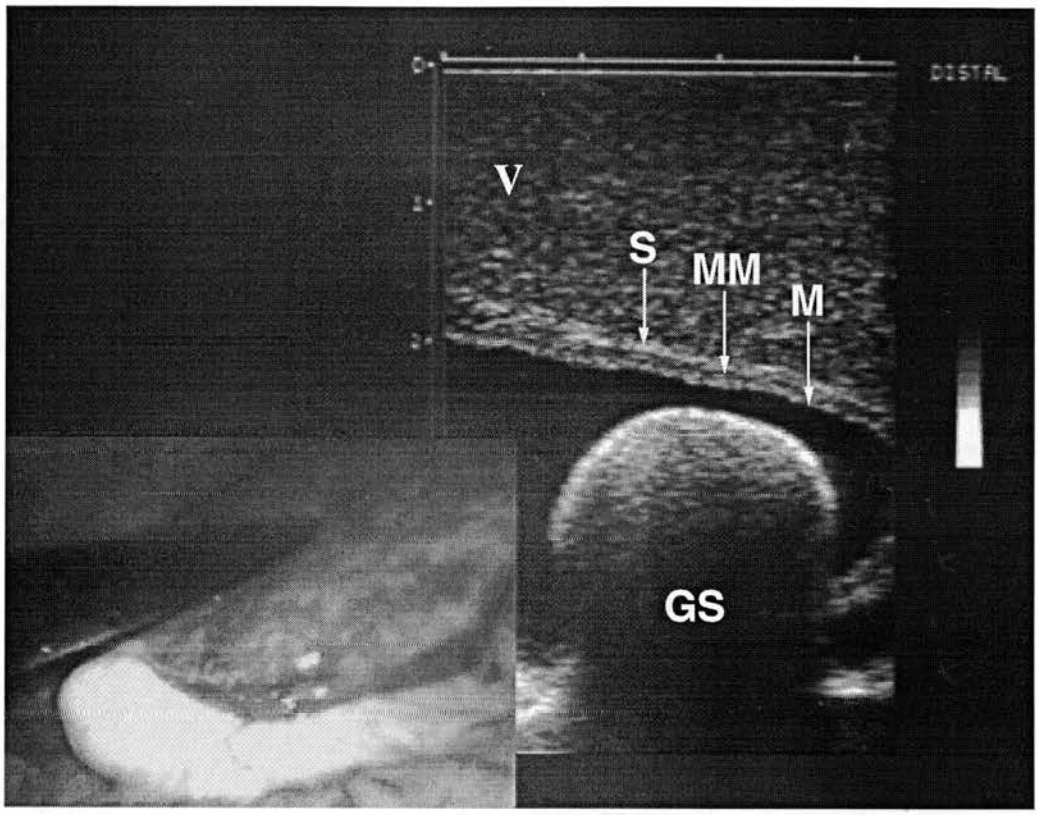
B. Laparoscopic sonogram of a hyperechoic metastasis (18 mm in diameter) within the left hepatic lobe and also showing an anechoic halo. Neither of these tumours were visible laparoscopically.

Figure 13



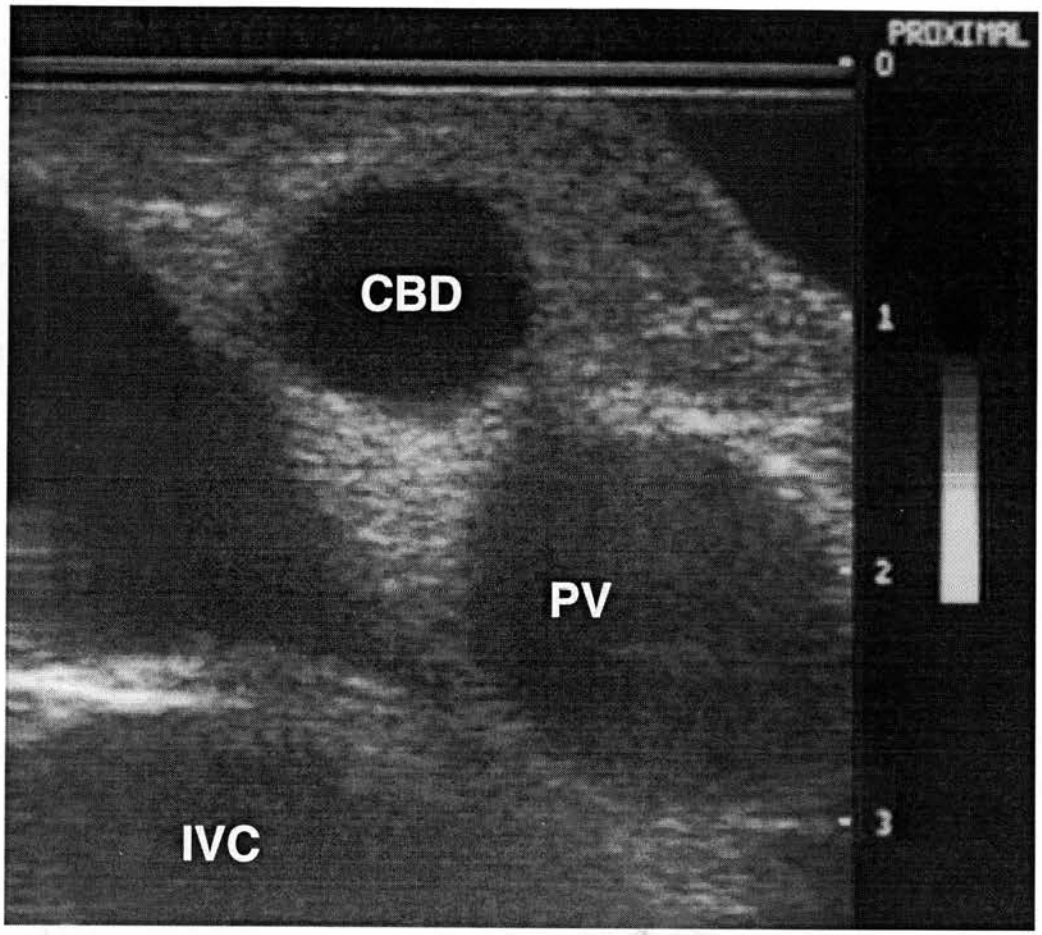
Laparoscopic sonogram in the longitudinal plane of the hepatoduodenal ligament with the LapUS probe inserted through the umbilical port and the transducer placed upon hepatic segment IV as an "acoustic window". The divergent courses of the portal vein (PV) and inferior vena cava (IVC) enclose the inferior tip of the caudate lobe in the cephalad direction (right of image). The suprapancreatic common bile duct (CBD) lies anterolaterally, and its diameter is estimated to be 4 mm by comparison with the 1 cm gaduated scale (left margin of image). The cystic duct / common hepatic duct confluence is also demonstrated. Laminar blood flow is just visible within the PV and IVC (*c.f.* the bile duct).

Figure 14



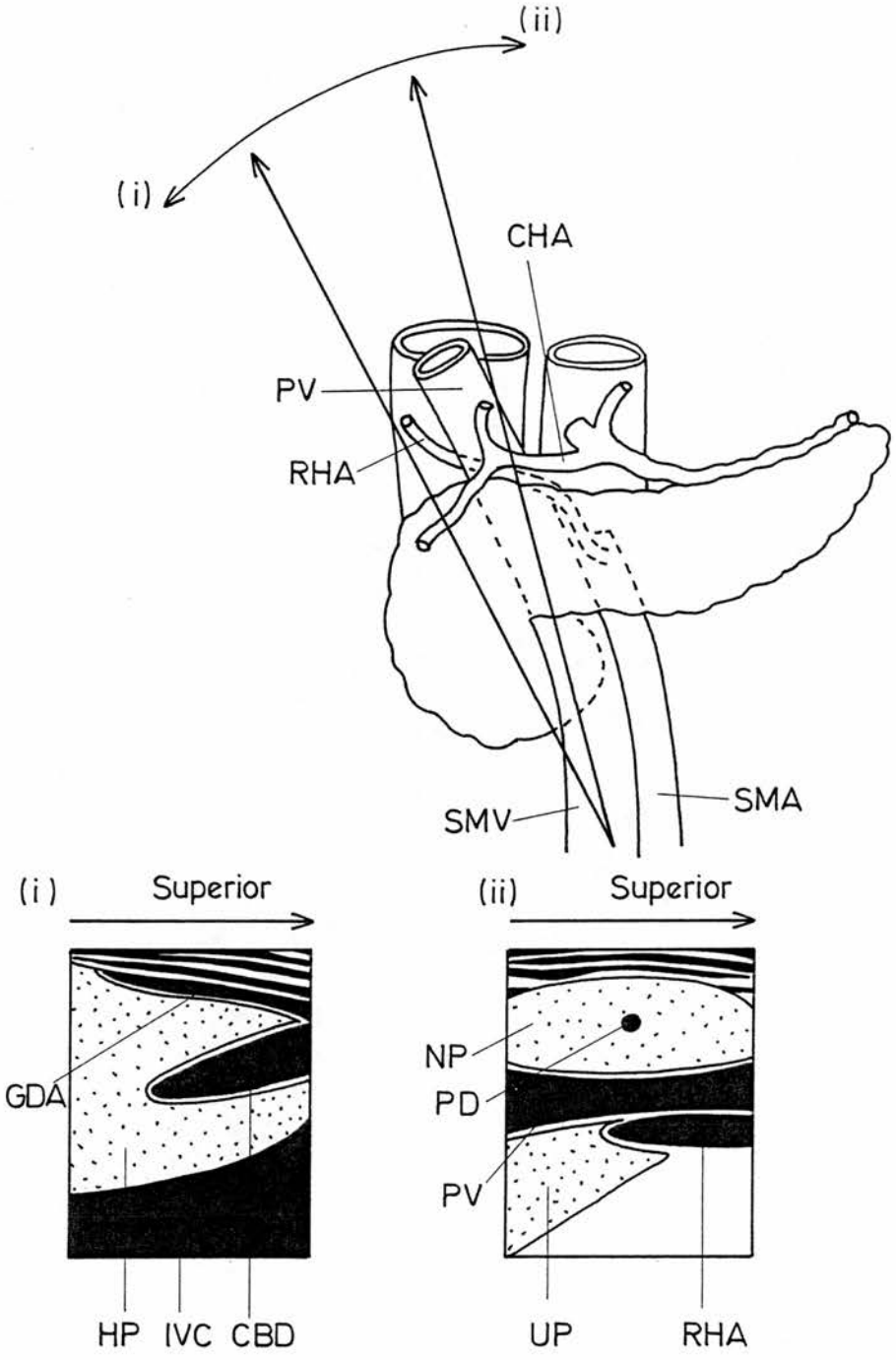
Laparoscopic sonogram of the gall bladder obtained with the LapUS transducer placed upon hepatic segment V as an "acoustic window" (insert). A single large gallstone (GS) casts a posterior acoustic shadow, and the three echo-layers of the thin gall bladder wall are demonstrated (M = mucosa (hyperechoic); MM = muscularis (hypoechoic); S = serosa (hyperechoic)).

Figure 15



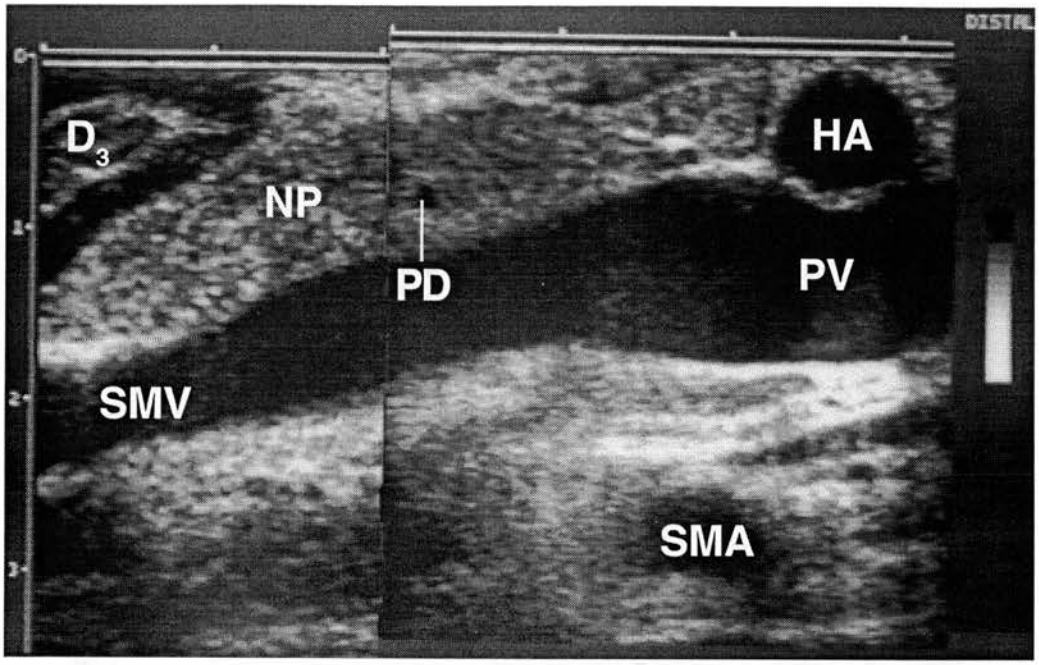
Cross-sectional LapUS image of the structures of the hepatoduodenal ligament obtained with the LapUS probe inserted via a right flank and orientated in a transverse plane. CBD = common bile duct; IVC = inferior vena cava; PV = portal vein.

Figure 16



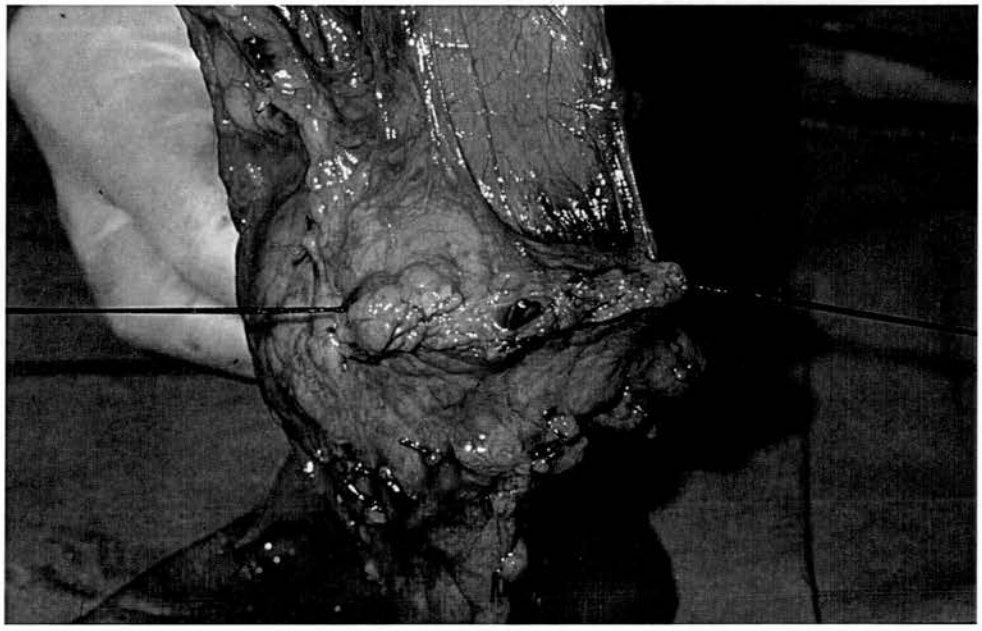
Schematic diagram showing LapUS of the pancreas and peripancreatic anatomy in a sagittal / oblique direction with the probe in the umbilical port, (i) in the plane of the common bile duct, and (ii) in the plane of the portal vein. CBD = common bile duct; IVC = inferior vena cava; PV = portal vein; HP = pancreatic head; GDA = gastroduodenal artery; NP = pancreatic neck; PD = pancreatic duct; UP = uncinate process; RHA = accessory right hepatic artery; SMV = superior mesenteric vein; SMA = superior mesenteric artery; CHA = common hepatic artery.

Figure 17



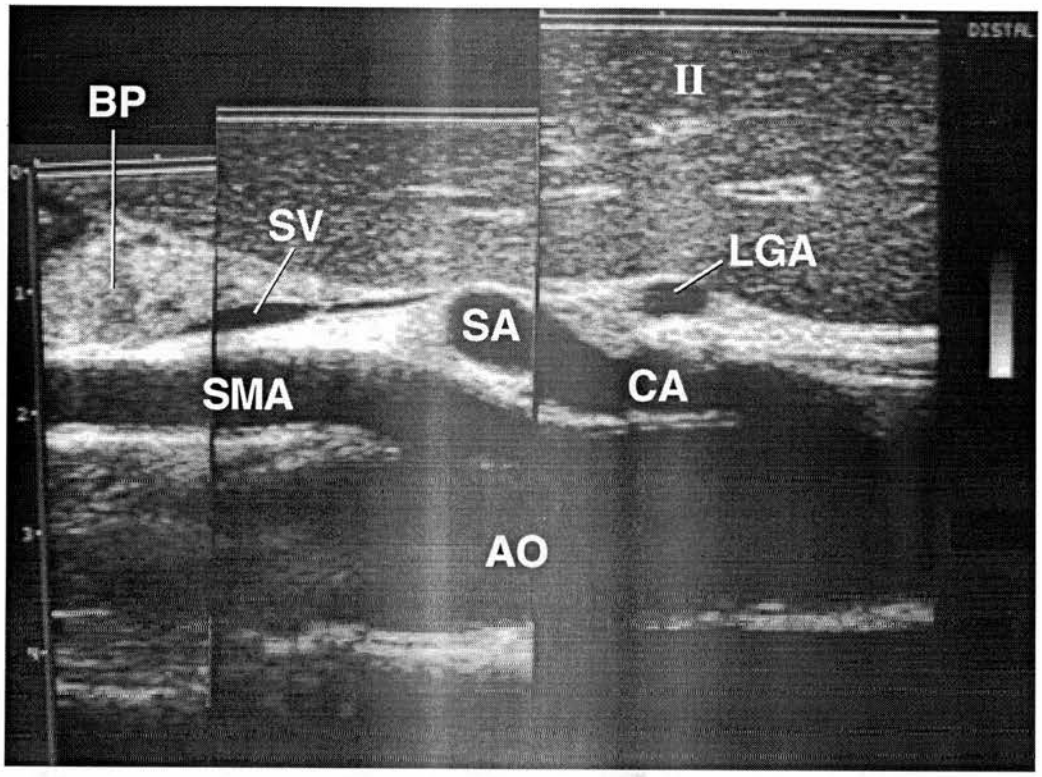
Laparoscopic sonograms obtained in a parasagittal plane through the normal pancreatic neck (NP) by withdrawal the LapUS probe through the umbilical port. The course of the superior mesenteric vein (SMV) and portal vein (PV) is shown posteriorly, with a cross-sectional view of the pancreatic duct as it traverses the pancreatic neck. D3 = duodenum (third part); HA = common hepatic artery; SMA = superior mesenteric artery.

Figure 18



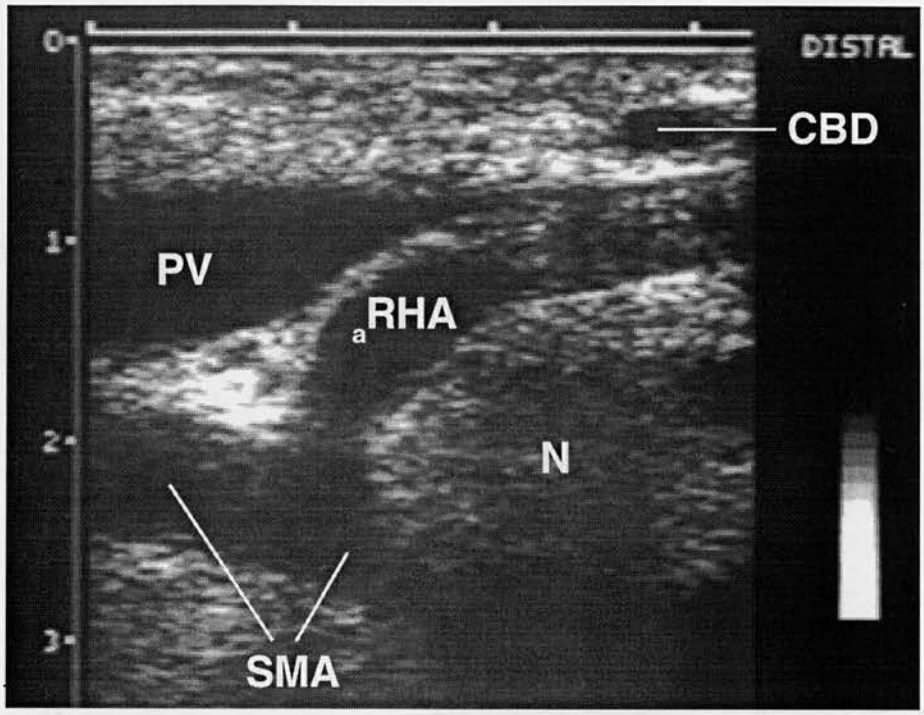
A pancreaticoduodenectomy specimen obtained from a patient with periampullary carcinoma and photographed to demonstrate the cross-sectional anatomy depicted in Figure 17. The neck is the thinnest part of the pancreas as it arches over the portal vein (measuring < 1 cm in this specimen), and the pancreatic parenchyma is transected in this plane during pancreaticoduodenectomy. A metal probe identifies the cut end of the dilated pancreatic duct. Stay sutures mark the inferior (left) and superior (right) borders of the pancreas.

Figure 19

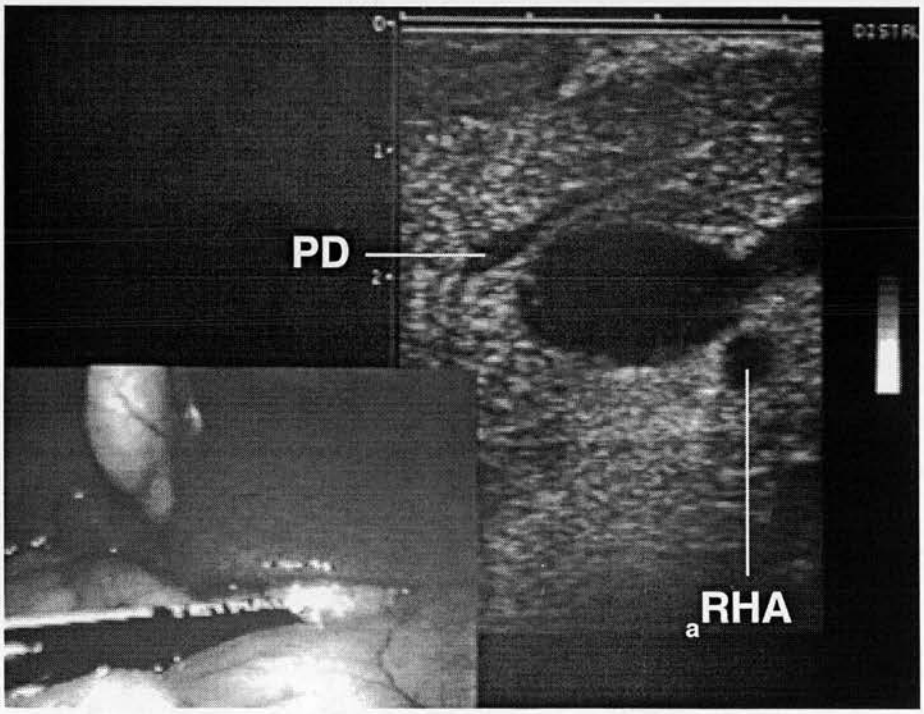


LapUS imaging of the paraaortic region with the transducer positioned on the left hepatic lobe (segment II). Withdrawal of the probe through the umbilical port generates a sequence of images in the parasagittal plane. The pancreatic body (BP) is imaged in cross-section, with the splenic vein closely applied posteriorly (and in this example is compressed by probe pressure). The origins of the superior mesenteric artery (SMA) and coeliac axis (CA) from the abdominal aorta (AO) are demonstrated. In this case, no lymphadenopathy has been identified in the paraaortic region, nor adjacent to the left gastric (LGA) and splenic arteries (SA).

Figure 20

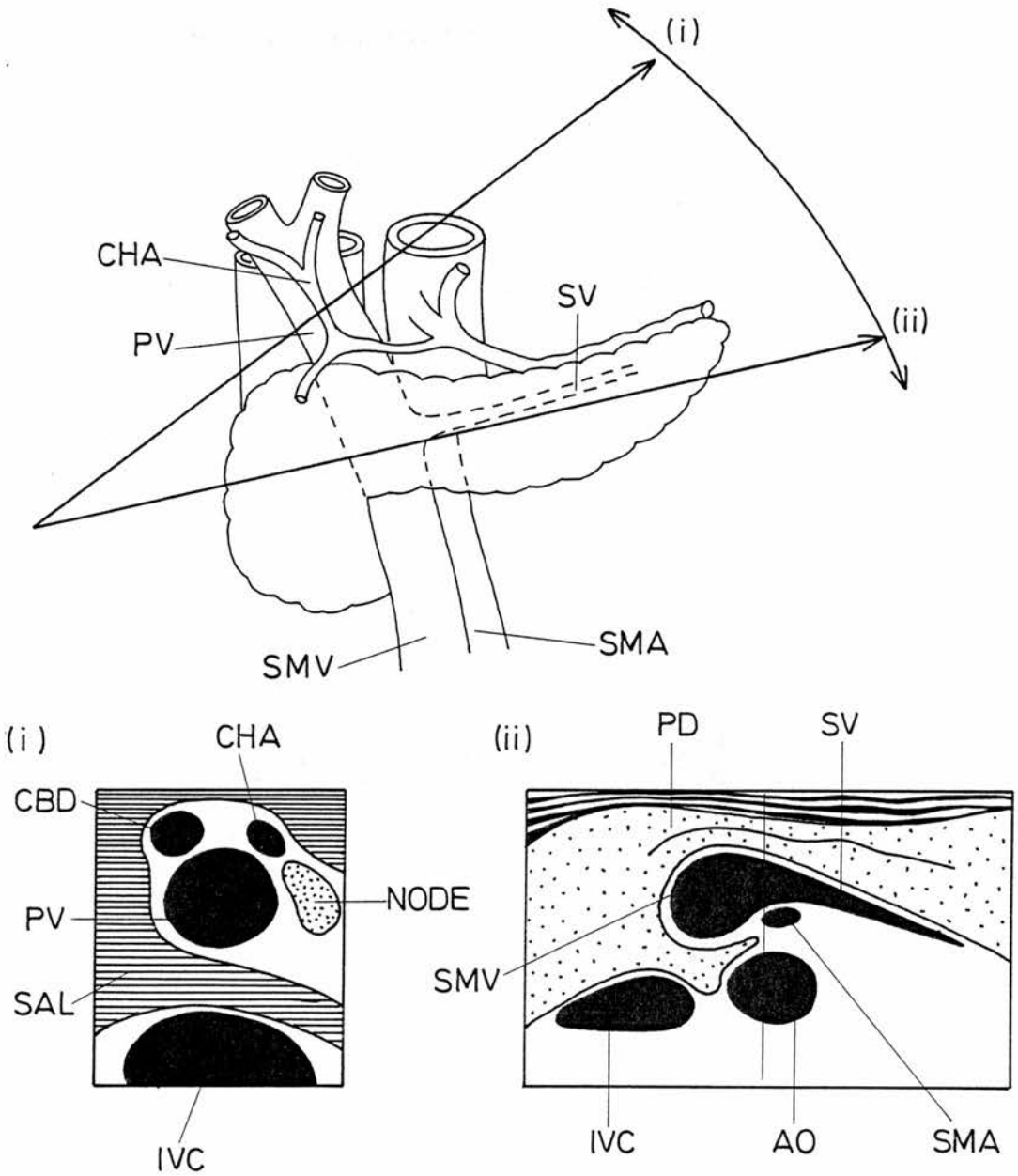


A. Laparoscopic sonogram showing an accessory right hepatic artery ($_a$RHA) arising from the superior mesenteric artery (SMA) and passing dorsal to the portal vein (PV) and common bile duct (CBD). An enlarged lymph node (N) at the origin of the SMA is identified.



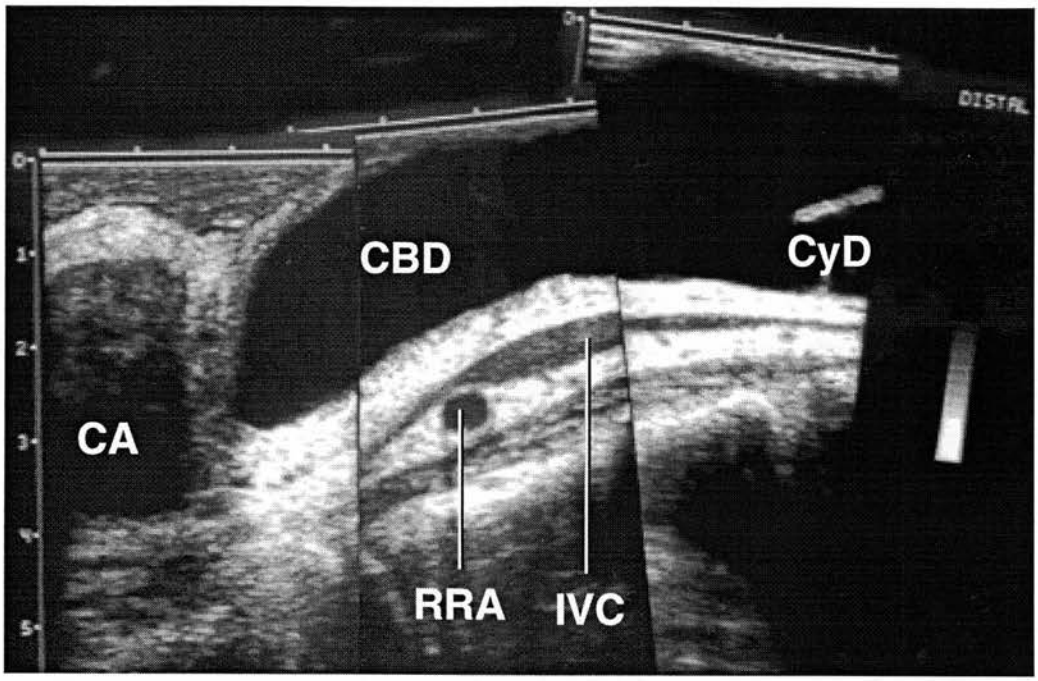
B. Transverse LapUS scan through the pancreatic head and neck (via the right flank port (see insert)) showing an accessory right hepatic artery ($_a$RHA) passing posterior to the confluence of the splenic and superior mesenteric vein. The pancreatic duct is shown arching over the portal vein within the pancreatic neck.

Figure 21



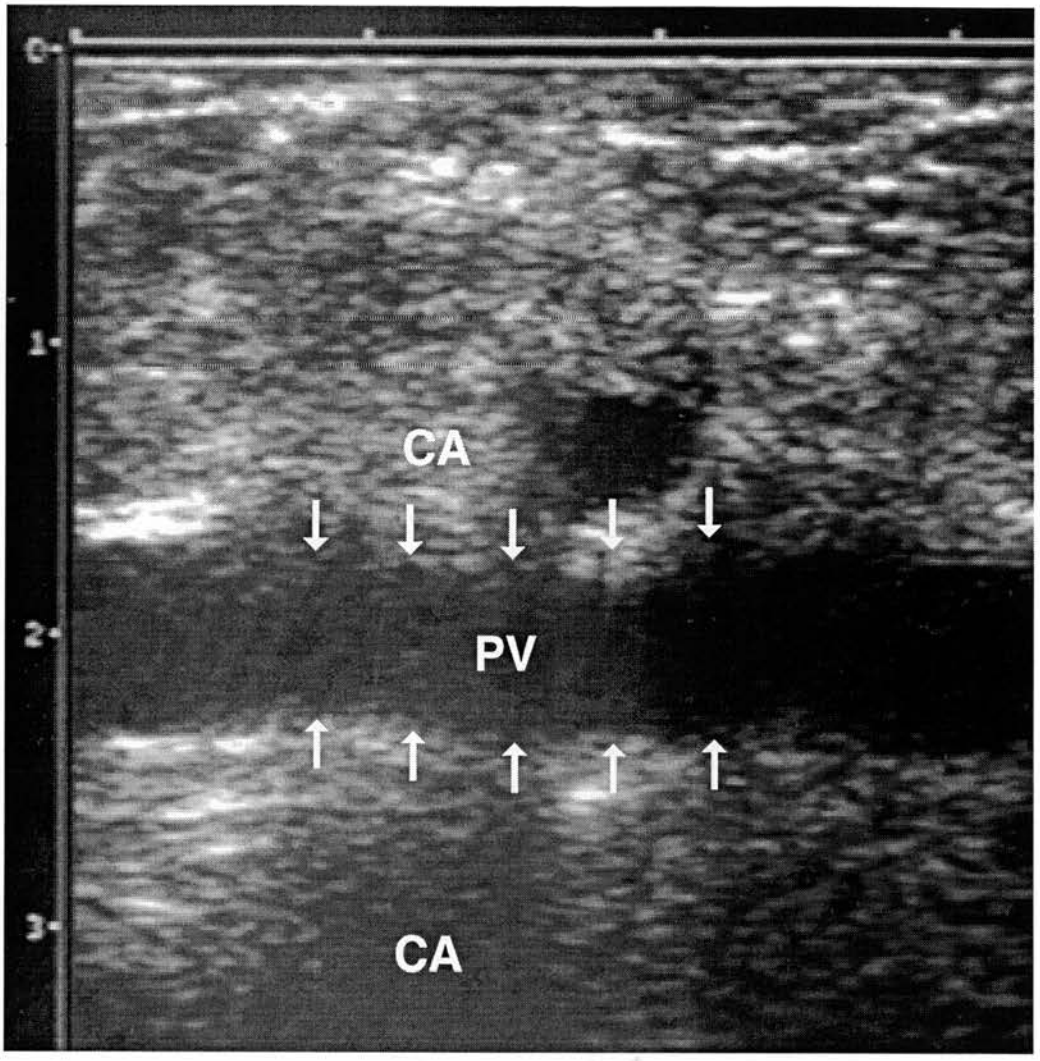
Schematic diagram showing LapUS of the pancreas and peripancreatic anatomy in a transverse / oblique direction with the probe in the right lateral port, (i) across the hepatoduodenal liagment at the superior pancreatic border, and (ii) across the head, neck and body of pancreas. CBD = common bile duct; IVC = inferior vena cava; PV = portal vein; HP = pancreatic head; CHA = common hepatic artery; SAL = saline instilled into the subhepatic space; PD = pancreatic duct; SV = splenic vein; AO = aorta; SMV = superior mesenteric vein; SMA = superior mesenteric artery.

Figure 22



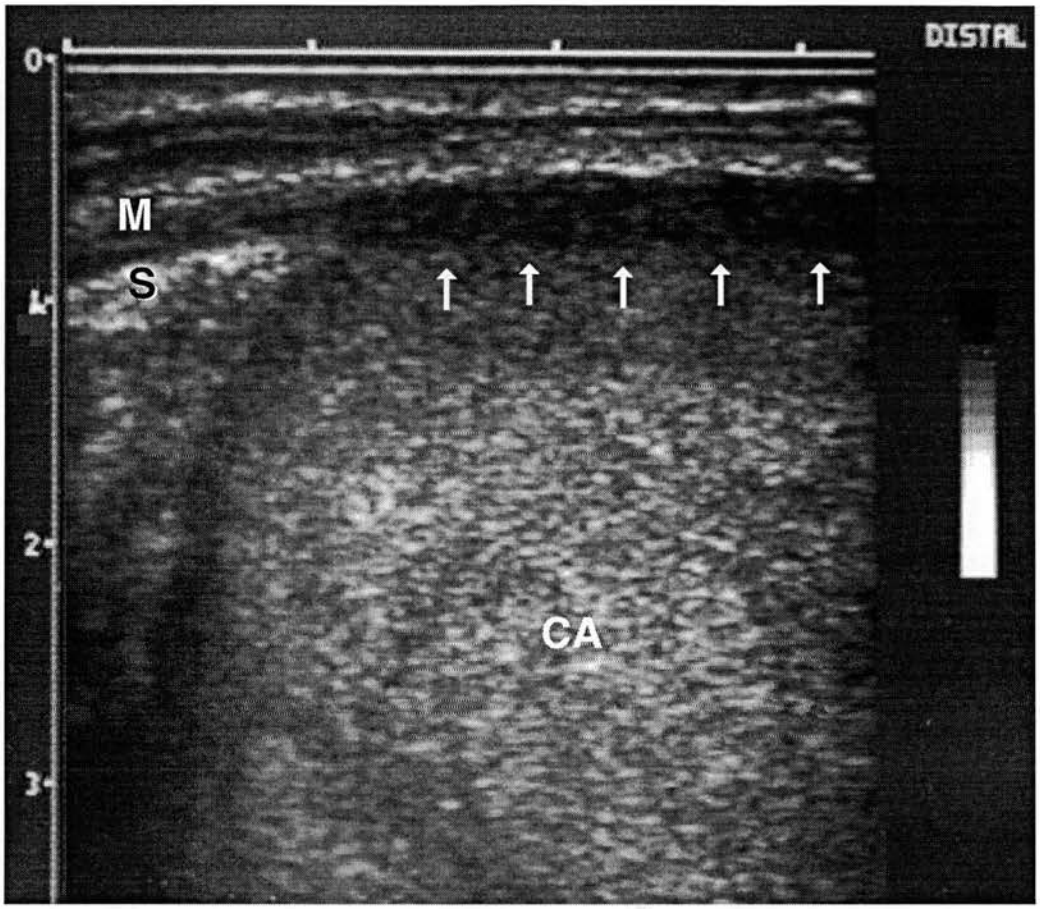
A sequence of laparoscopic sonograms orientated in the long axis of the common bile duct and obtained with the transducer positioned on the hepatoduodenal ligament and withdrawn via the umbilical port. A well circumscribed hypoechoic cancer of the pancreatic head is demonstrated (CA), measuring three centimetres in diameter and obstructing the CBD and cystic duct (CyD) (duct diameter approximately 2 cm). Probe down pressure has compressed the inferior vena cava (IVC). The right renal artery (RRA) is identified in cross-section posteriorly.

Figure 23



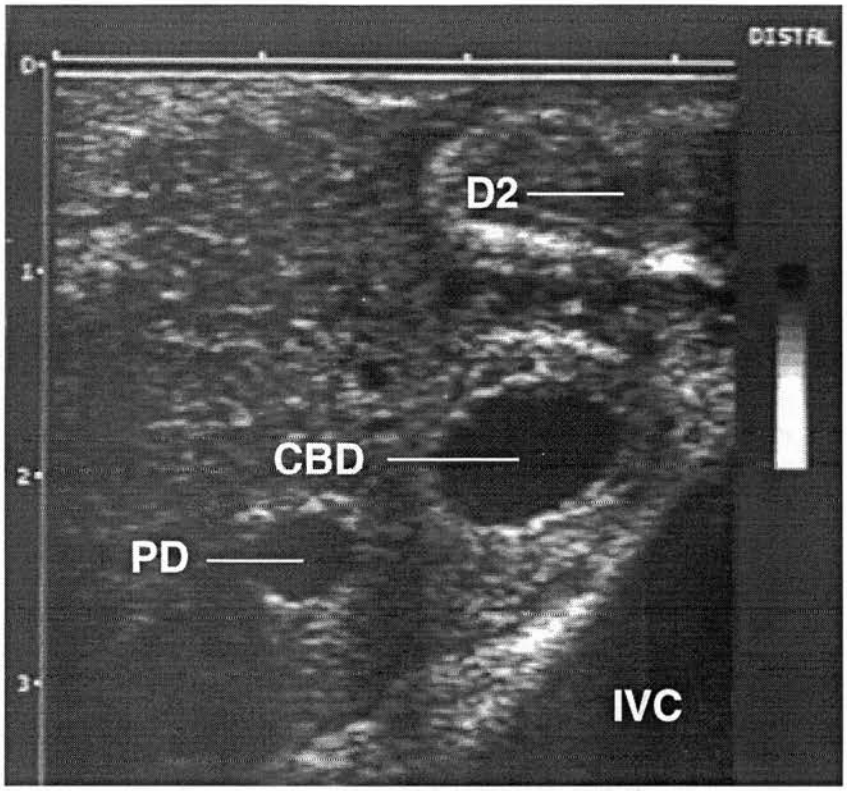
Intraoperative sonogram through a thickened pancreatic neck obtained during exploratory laparotomy. A diffusely infiltrating isoechoic carcinoma (CA) arising from the pancreatic head, enveloping the portal vein (PV) and associated with loss of the hyperechoic portal vein - parenchymal interface (arrows) was demonstrated. These findings had not been recognised during staging laparoscopy with LapUS.

Figure 24

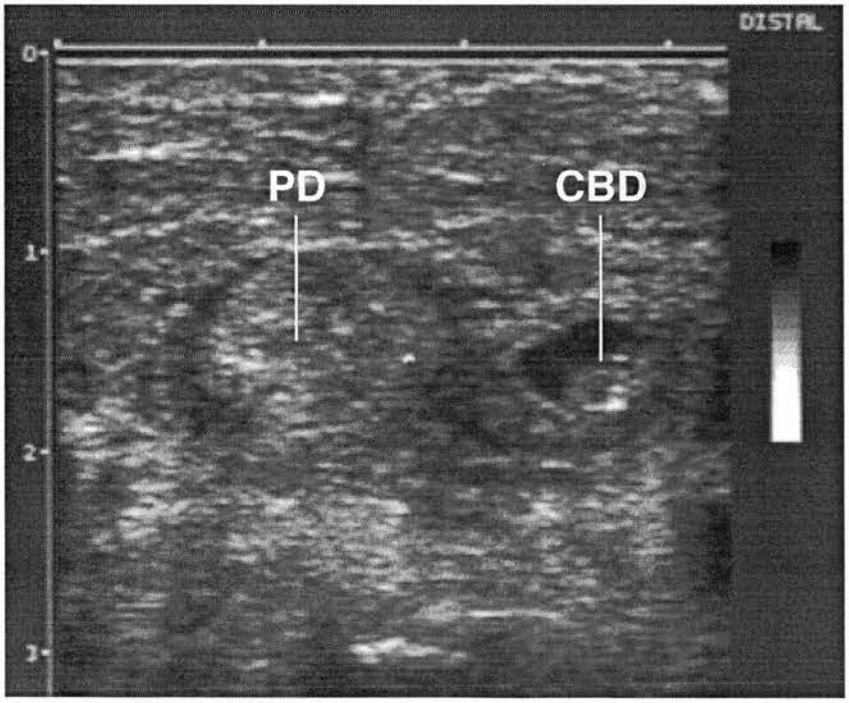


Intraoperative sonogram of the pancreatic body obtained during exploratory laparotomy with the "T-probe" positioned on the gastric antrum. An isoechoic cancer of the pancreatic body (CA) is shown invading the posterior wall of the stomach (arrows). The five echo-layers of the stomach wall are shown, and there is loss of the hyperechoic interface between tumour and gastric serosa (S), with tumour infiltration of the hypoechoic muscle layer (M). These findings had not been identified during staging laparoscopy with LapUS.

Figure 25

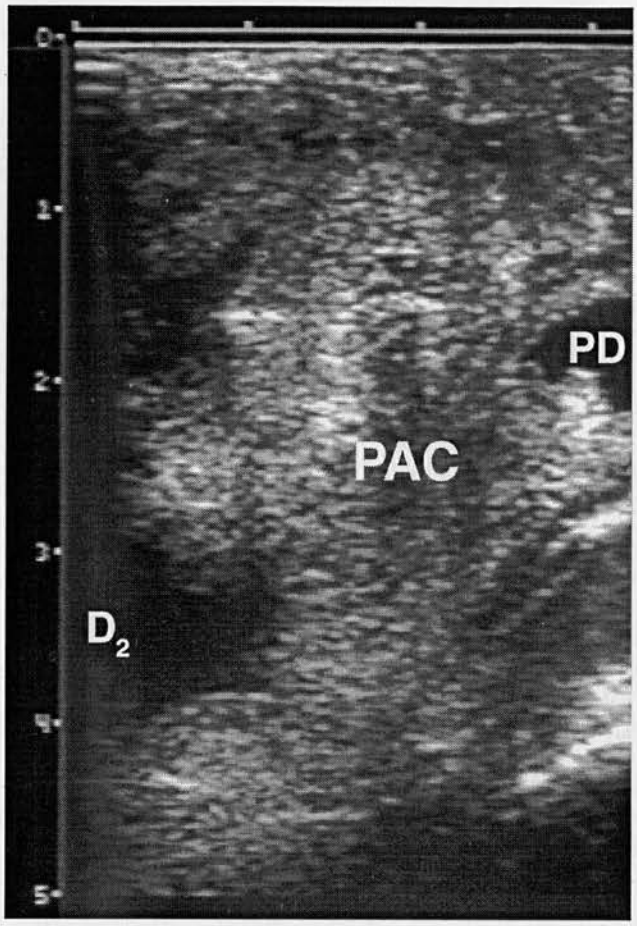


A. LapUS scan showing the convergent terminal portions of the pancreatic duct (PD) and common bile duct (CBD) are traced through the pancreatic head alongside the inferior vena cava (IVC) to the papilla. D2 = second part of duodenum.



B. LapUS scan showing infiltration of isoechoic periampullary carcinoma into the lumens of the distal pancreatic duct (PD) and common bile duct (CBD) within the pancreatic head.

Figure 26



A. LapUS scan obtained with the transducer pressed against the lateral wall of the duodenum to show a sessile, isoechoic periampullary carcinoma (PAC) ulcerating into the lumen of the second part of the duodenum (D_2). Tumour is also identified prolapsing into the lumen of the pancreatic duct within the pancreatic head.

B. Transverse LapUS scans showing pancreatic duct (PD) and common duct (CBD) dilatation due to an isoechoic periampullary cancer invading the pancreatic head (left of picture). The inferior vena cava (IVC), aorta (AO), splenic vein (SV) and superior mesenteric vein (SMV) and artery (SMA) are clear of tumour.

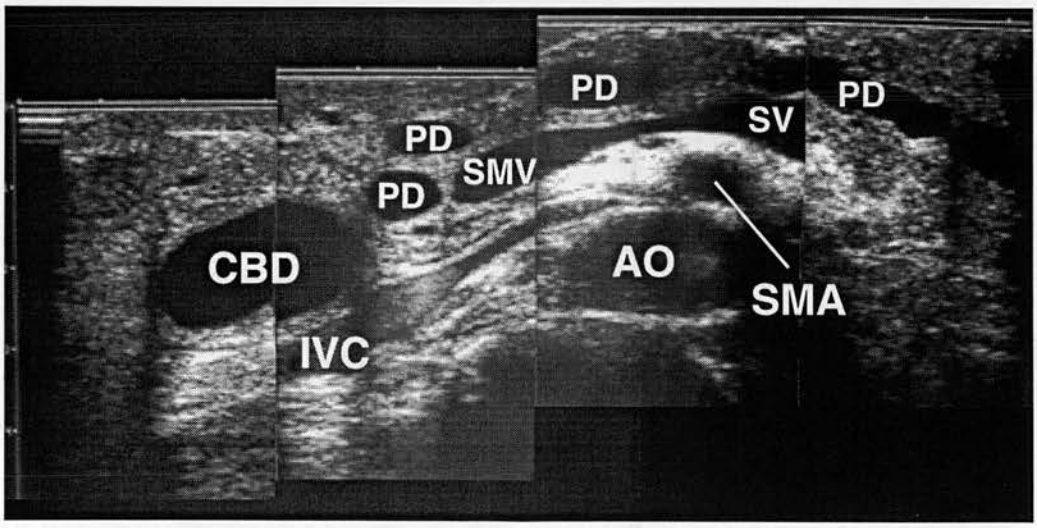
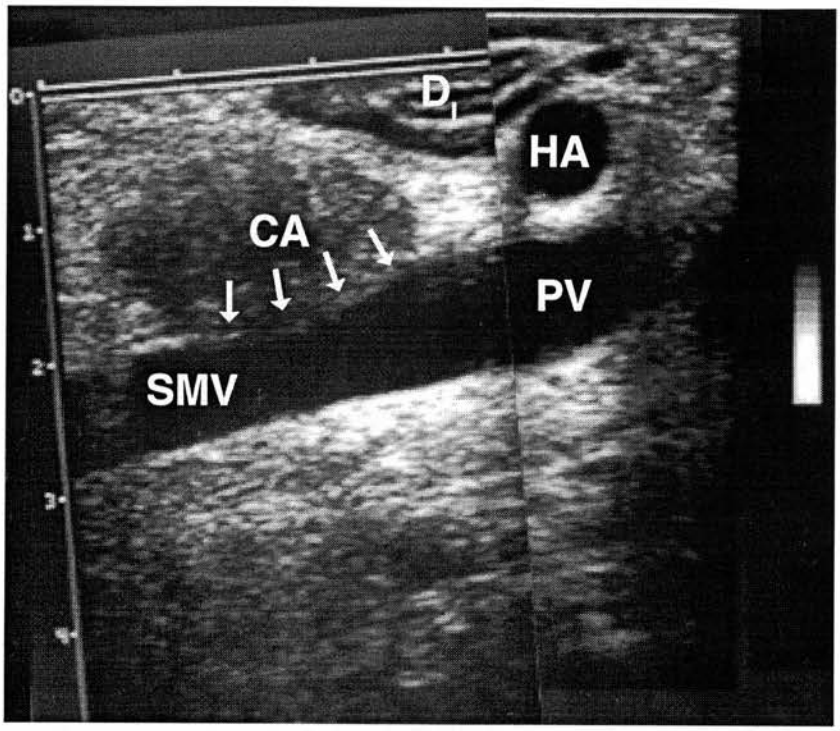
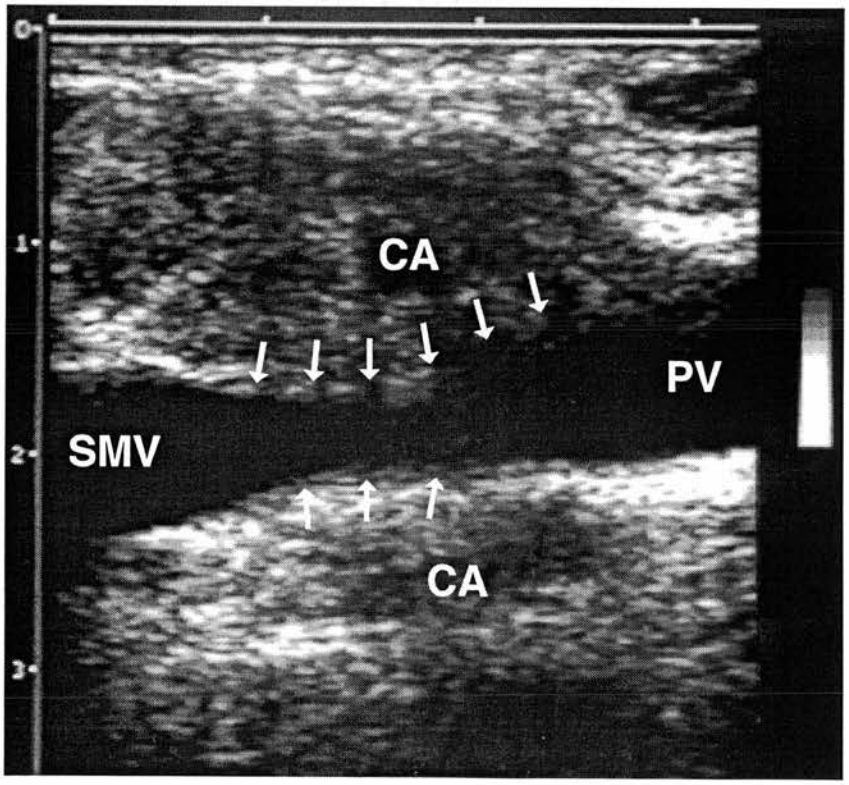


Figure 27

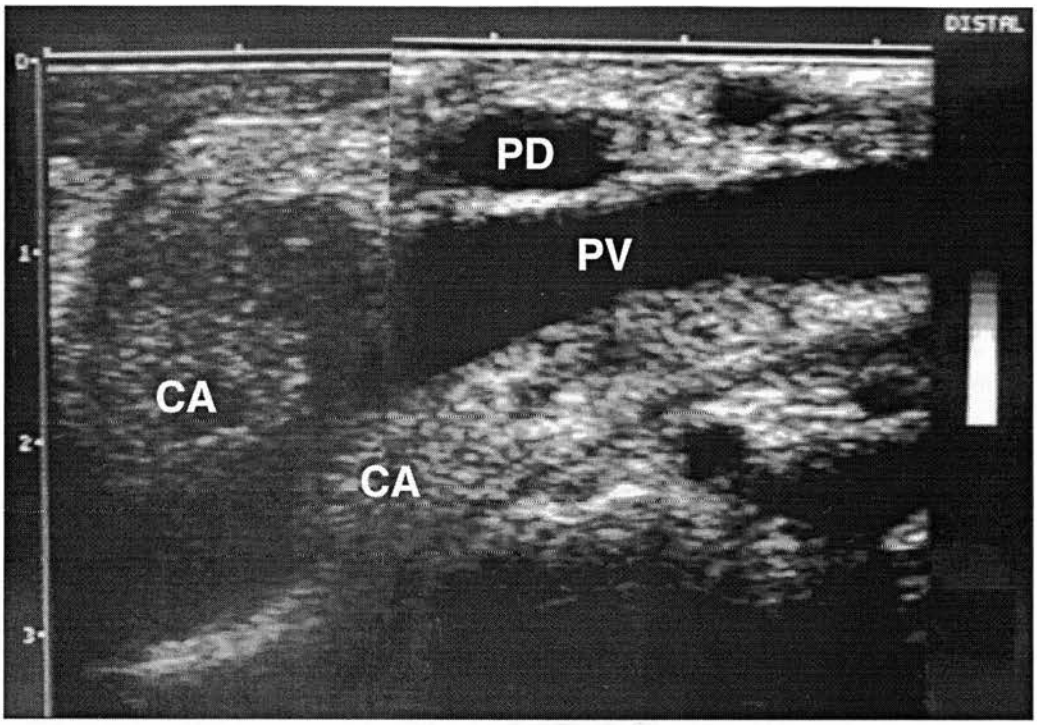


A. Hypoechoic cancer of the pancreatic head (CA) indenting the superior mesenteric (SMV) and portal veins (PV) with loss of the hyperechoic vessel - parenchymal interface (arrows). D1 = first part of duodenum; HA = common hepatic artery.



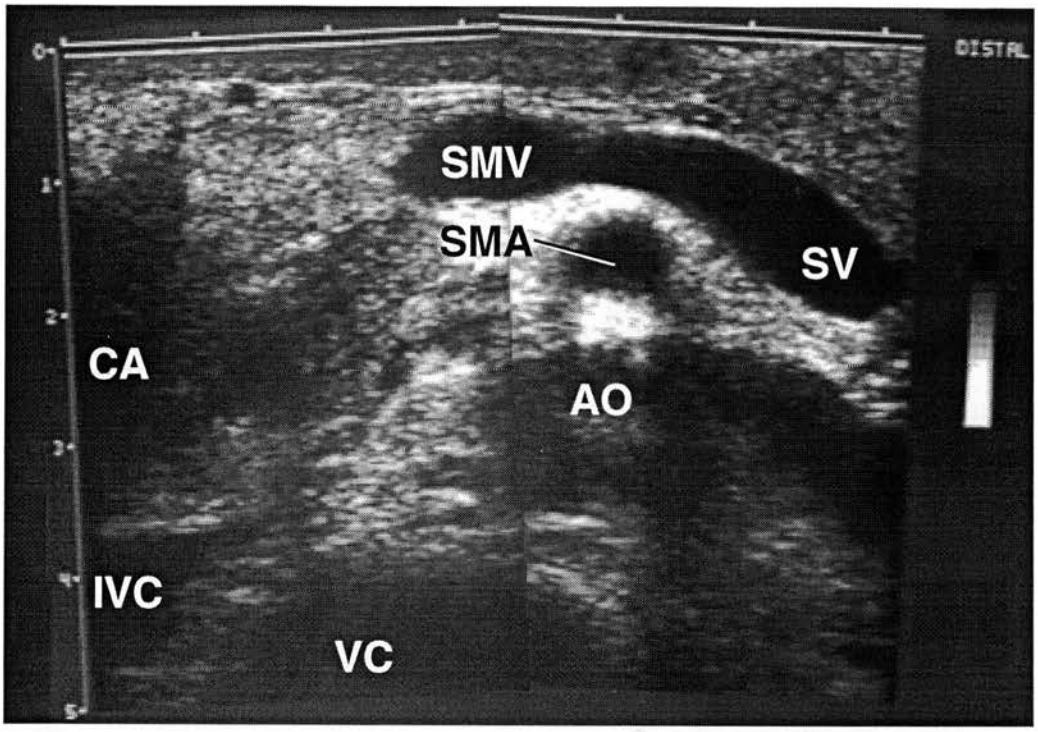
B. Magnified view of same LapUS examination as shown in Fig 26A. Slight rotation of the LapUS probe demonstrates the "cuffing" effect of the pancreatic head cancer causing an "hourglass deformity" of the portal vein.

Figure 28



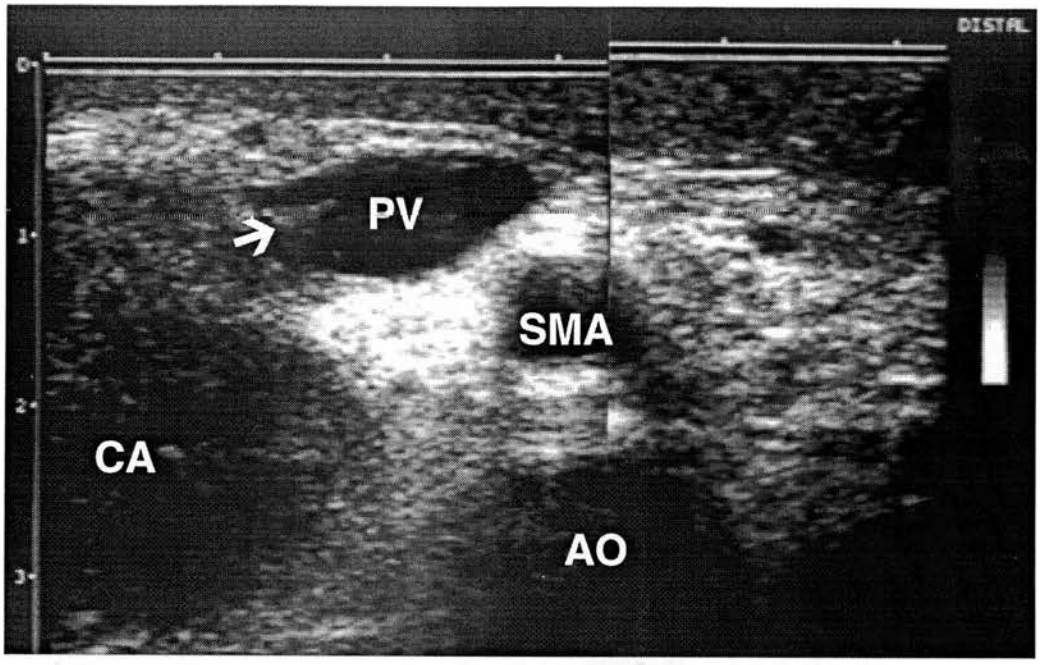
Laparoscopic sonograms obtained in a parasagittal plane through the pancreatic neck while withdrawing the probe through the umbilical port. A hypoechoic cancer of the pancreatic head and uncinate process (CA) is shown invading the lumen of the superior mesenteric vein at the level of the inferior pancreatic border, immediately proximal to the formation of the portal vein (PV). A dilated pancreatic duct (measuring approximately 6 mm in maximum diameter) is shown in cross-section traversing the pancreatic neck which appears otherwise normal.

Figure 29



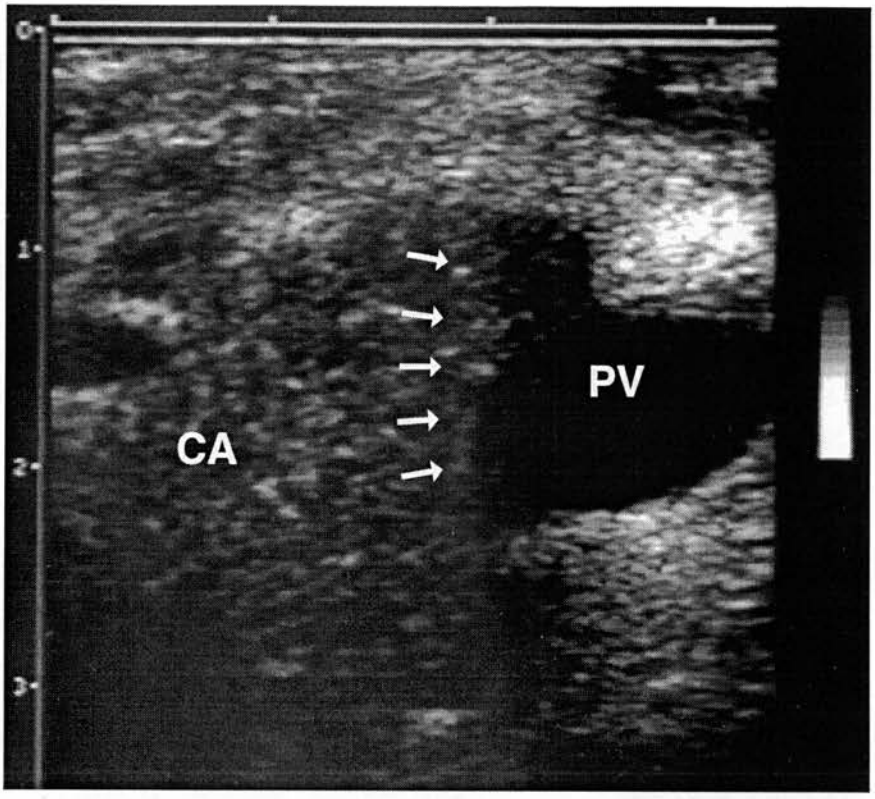
Laparoscopic sonograms obtained in the transverse direction at the level of the confluence of the superior mesenteric (SMV) and splenic veins (SV) with the probe inserted via the right flank port. An irregular, hypoechoic carcinoma of the pancreatic head (CA) is demonstrated. There is no evidence of tumour involvement of the peripancreatic blood vessels in this section.
SMA = superior mesenteric artery; AO = abdominal aorta; VC = vertebral column; IVC = inferior vena cava.

Figure 30



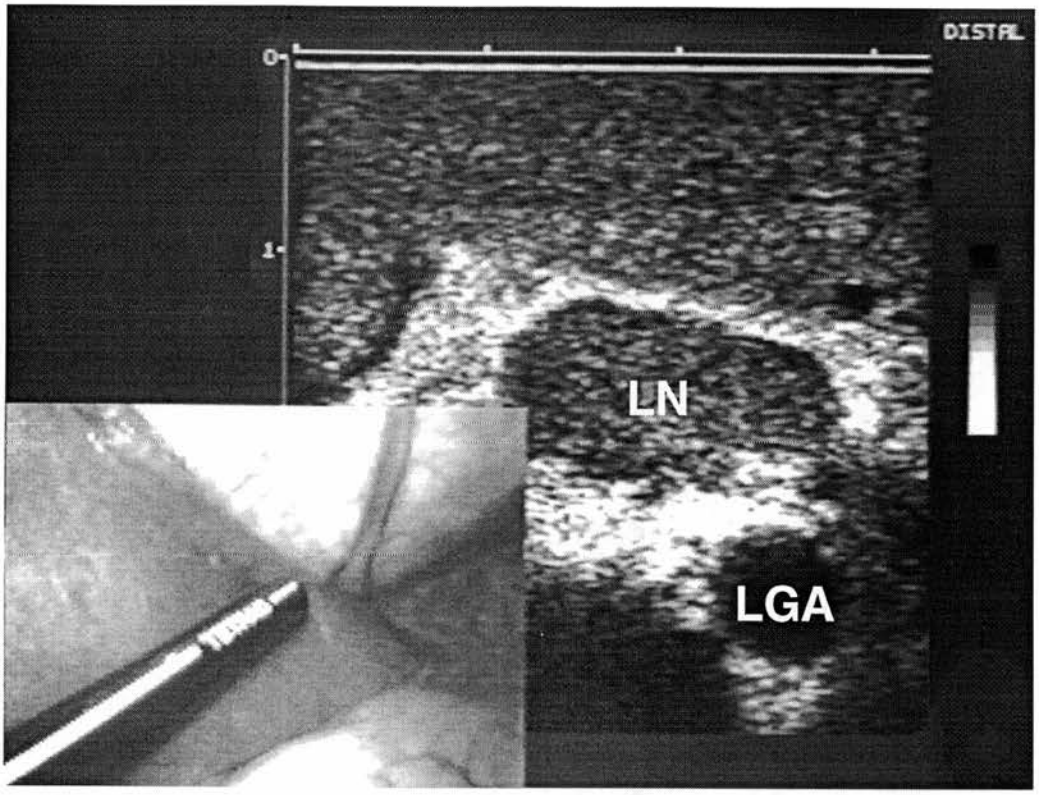
Laparoscopic sonograms during the same examination and at a slightly superior level to that shown in Figure 29. Hypoechoic carcinoma (CA) extends to invade the right lateral wall of the portal vein (PV) with loss of the normal hyperechoic parenchyma - vessel interface and irregularity of the vein wall (arrow). The superior mesenteric artery (SMA) and aorta (AO) appear to be clear of tumour.

Figure 31



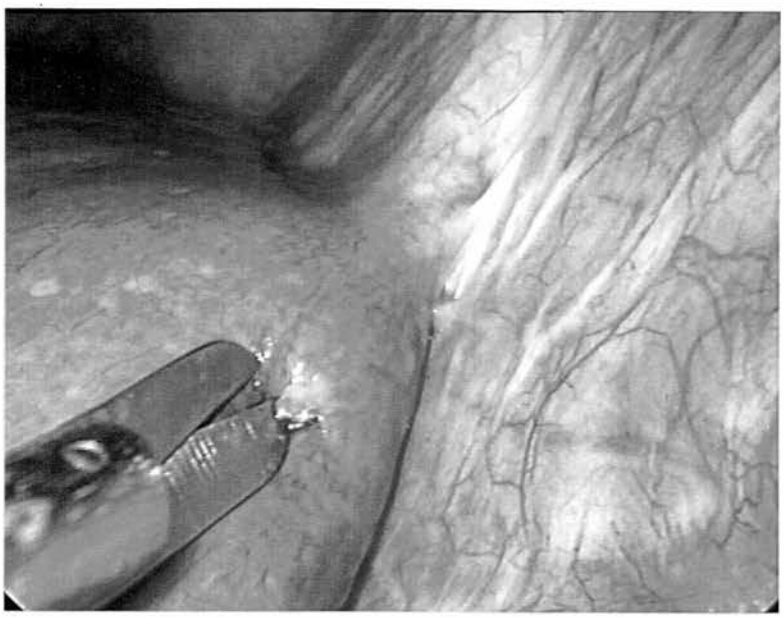
High magnification laparoscopic sonogram examining detail of the relationship between tumour (CA) and portal vein (PV) in a patient thought to have potentially resectable cancer of the pancreatic head. Loss of the parenchyma - vessel interface along the right lateral wall of the vein (arrows) indicates the unresectable nature of this tumour.

Figure 32

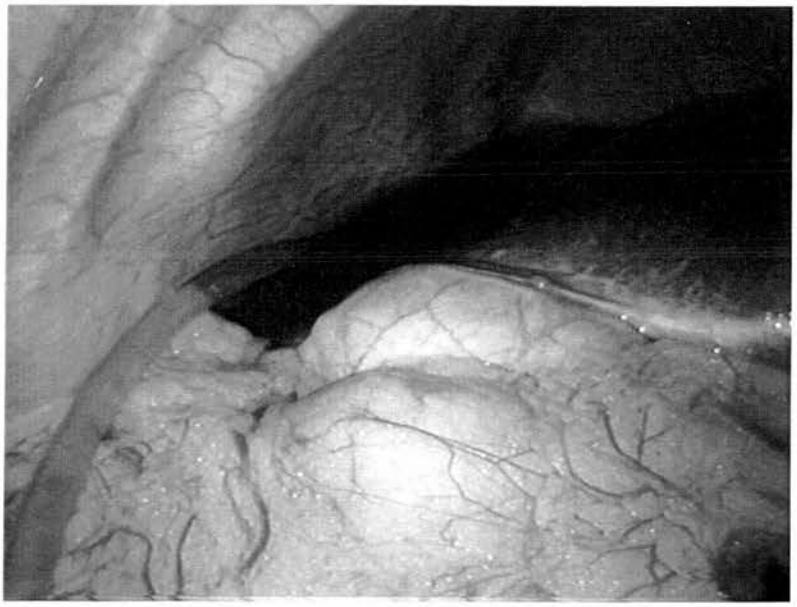


Laparoscopic ultrasound appearances of malignant regional lymphadenopathy. With the LapUS probe positioned on the left hepatic lobe as an "acoustic standoff" (insert photograph), a well defined, hypoechoic lymph node measuring 2 cm in maximum diameter is demonstrated alongside the left gastric artery (LGA). Operative biopsy confirmed metastatic adenocarcinoma.

Figure 33

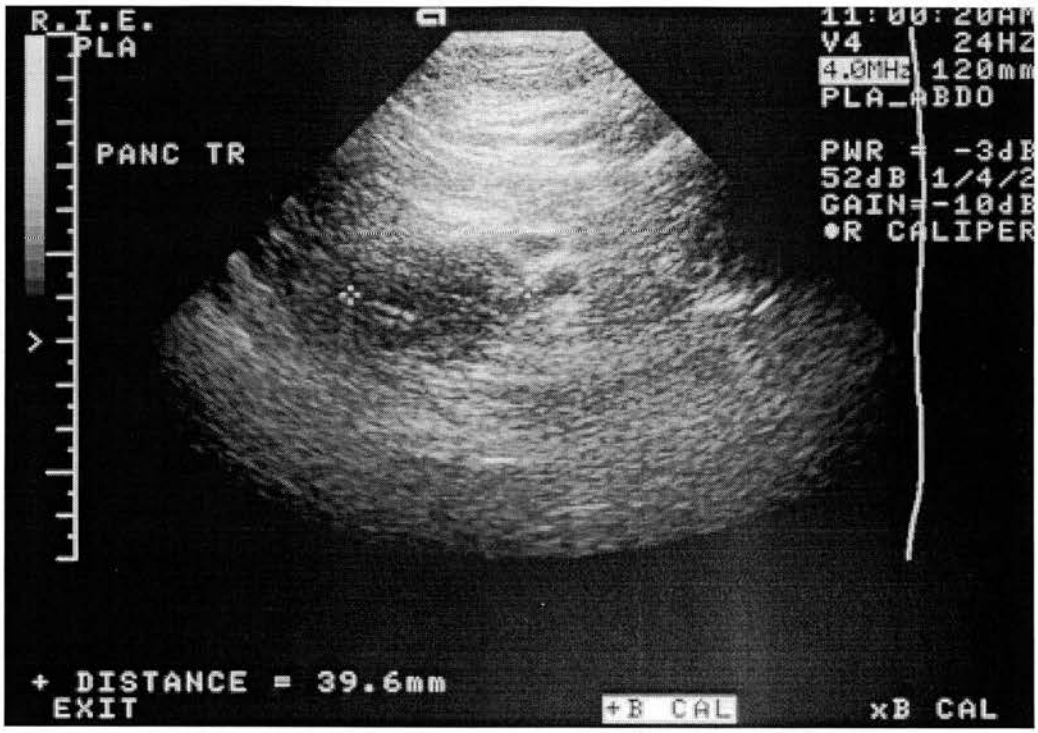


A. Staging laparoscopy in a patient otherwise considered to have potentially resectable pancreatic cancer revealed barely perceptible whitish plaques scattered over the capsule near the free edge of hepatic segment IV. Biopsy with straight-bladed laparoscopic scissors documented metastatic adenocarcinoma.



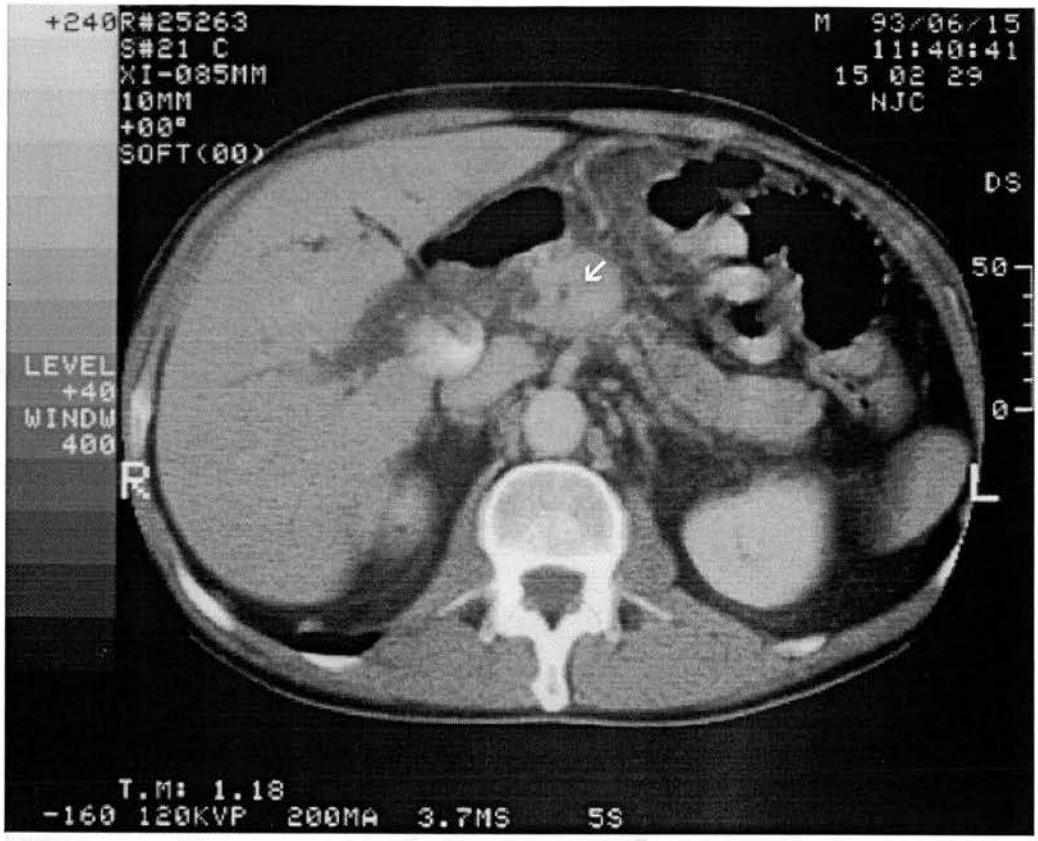
B. Retrieval of peritoneal washings from the right sub-phrenic space during staging laparoscopy using a catheter inserted through the right flank port.

Figure 34



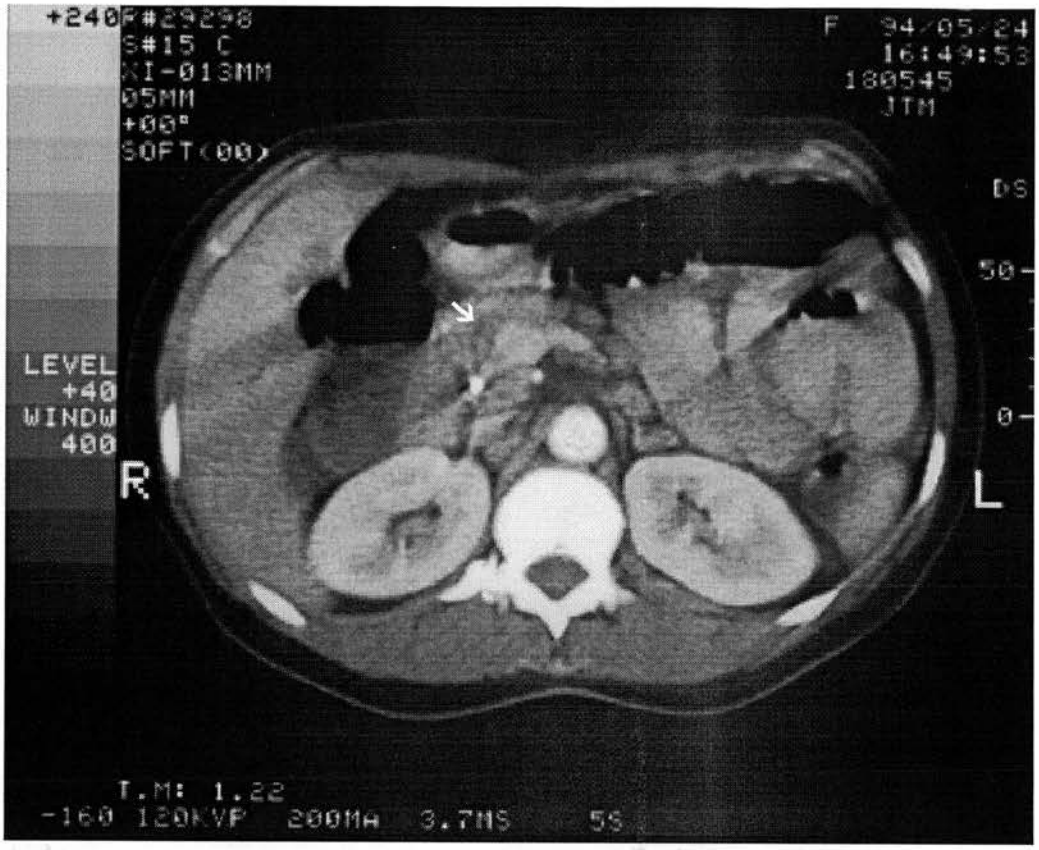
Transabdominal ultrasonography in a patient with suspected carcinoma of the pancreatic head using a 4 MHz curvilinear array probe. This transverse image through the pancreatic head has identified a hypoechoic tumour mass, which has been measured with the electronic calipers to show a diameter of 39.6 mm (see text bottom left of image). The hyperechoic artefact caused by a plastic biliary endoprosthesis is identified traversing the tumour. The duodenal lumen is demonstrated on the left side of the tumour, and the portal vein (right side of tumour) appears to be free from invasion. Pancreaticoduodenectomy for "cure" was later performed.

Figure 35



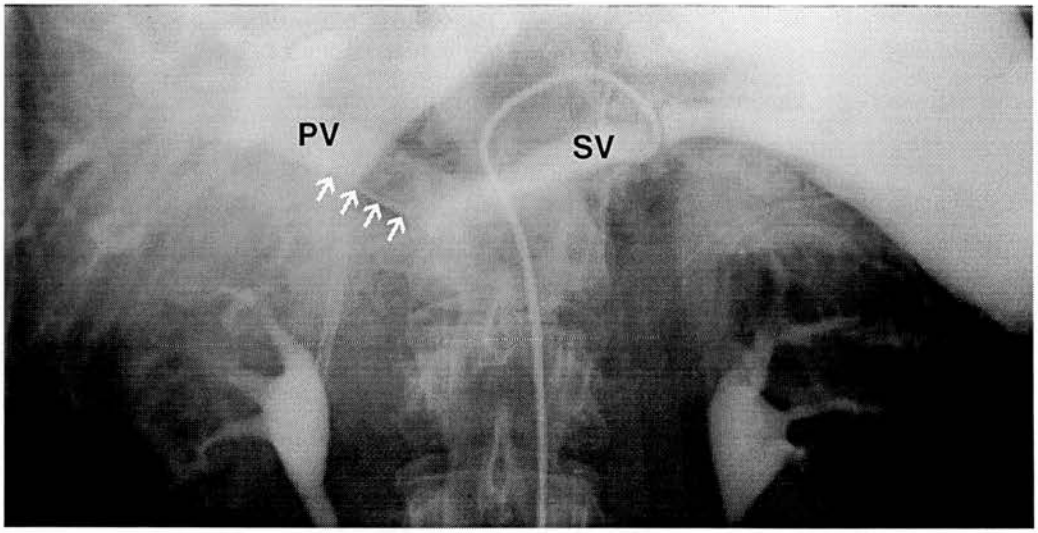
Dynamic abdominal CT scan demonstrating a carcinoma of the pancreatic head (arrow) causing gross biliary dilatation. The tumour was reported as well circumscribed, localised to the pancreas and potentially resectable. Exploratory laparotomy revealed malignant infiltration of the mesenteric root in the region of the duodeno - jejunal flexure and of the retroduodenal soft tissues. Palliative surgical biliary bypass was performed.

Figure 36



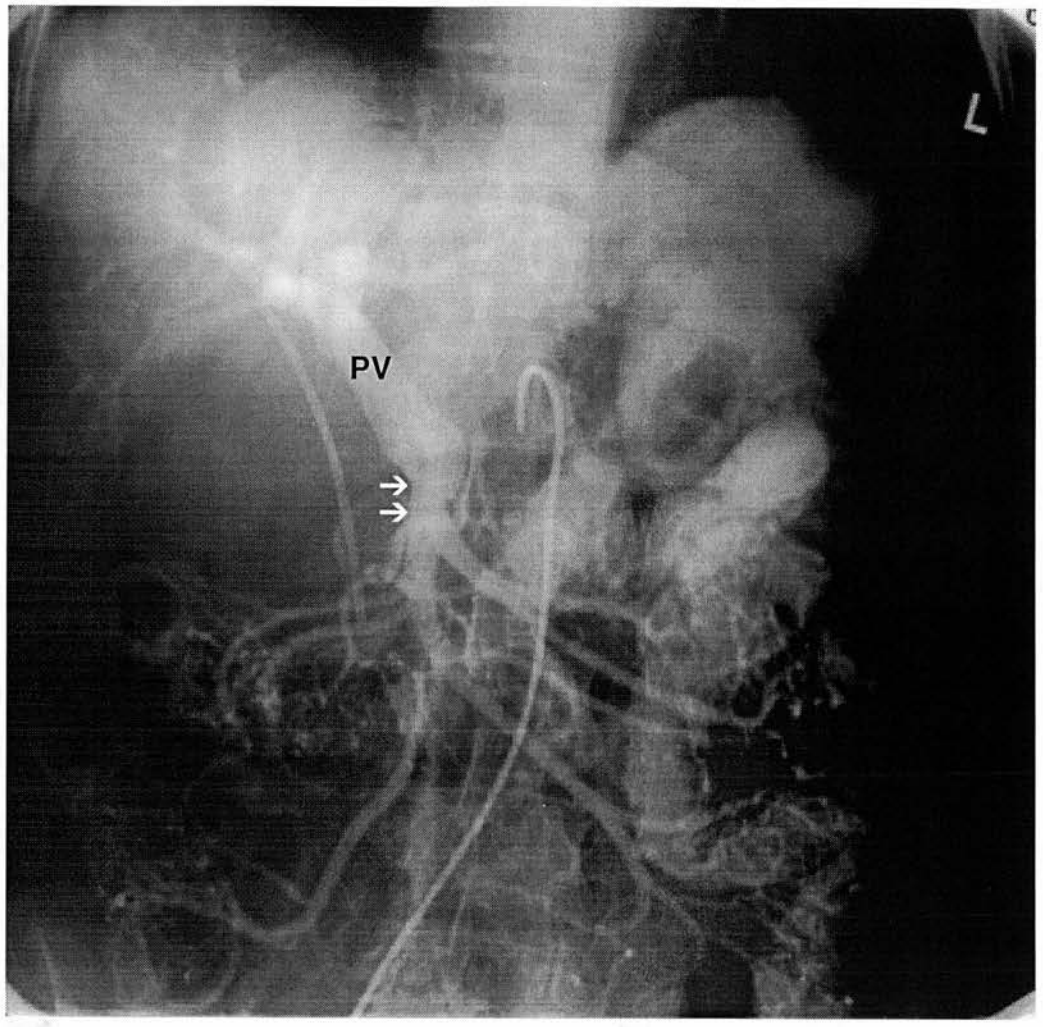
False positive staging CT scan. A poorly - defined tumour of the pancreatic head was identified (note the hyperattenuating appearance of the biliary endoprosthesis traversing the tumour to enter the duodenal lumen). Malignant invasion of the superior mesenteric vein in the region of its confluence with the portal vein (arrow) was reported. Infiltration of the mesenteric root was also identified. Pancreaticoduodenectomy for "cure" was later performed. An accessory right hepatic artery arising from the superior mesenteric artery is identified passing immediately posterior to the portal vein (*c.f.* Figure 39 (same patient)).

Figure 37



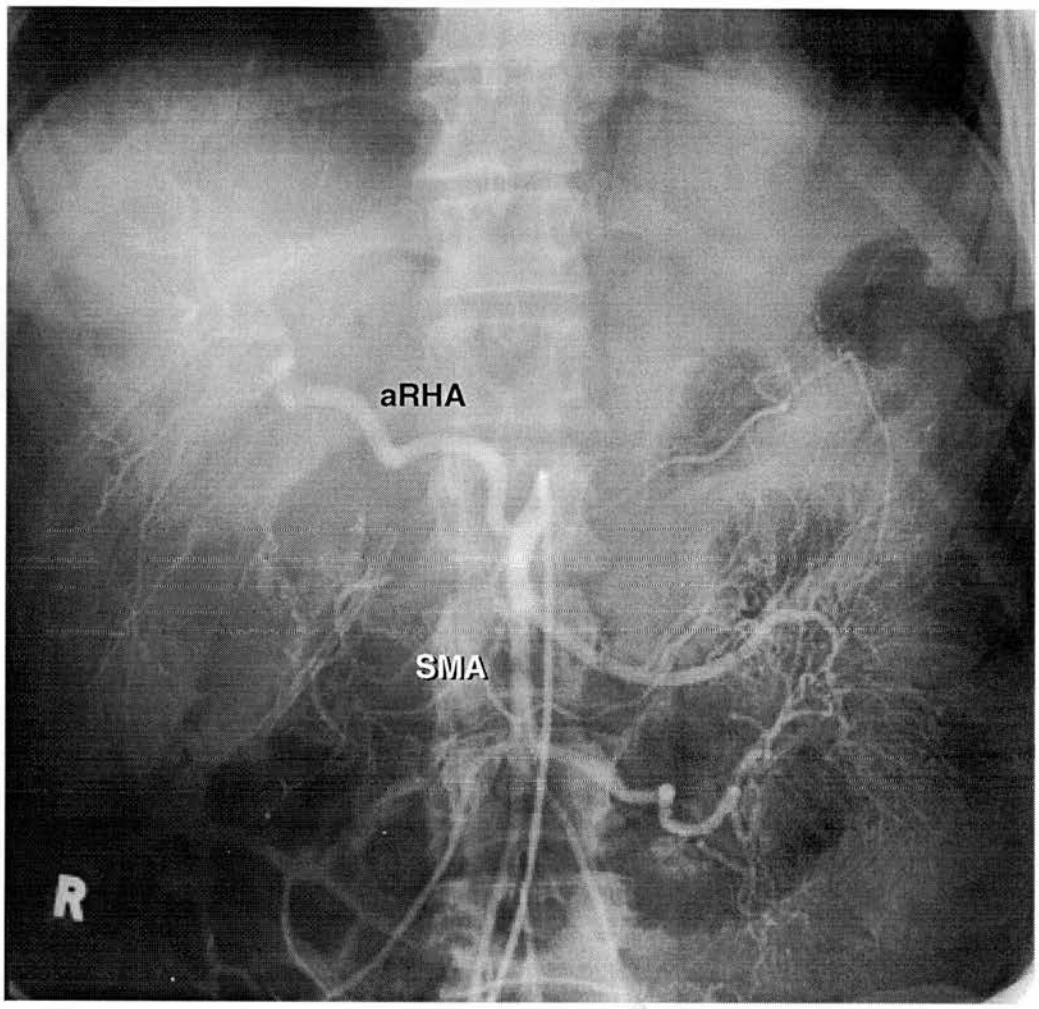
Portal venous phase of selective visceral angiography (catheter tip in the splenic artery) in a patient with cancer of the pancreatic head. A subtle indentation in the lateral wall of the portal vein (PV) indicating tumour invasion is demonstrated (arrows). Local tumour invasion was confirmed during laparotomy and trial dissection of the pancreas. A 7FG plastic biliary endoprosthesis marks the site of bile duct obstruction by the tumour.
SV = splenic vein.

Figure 38



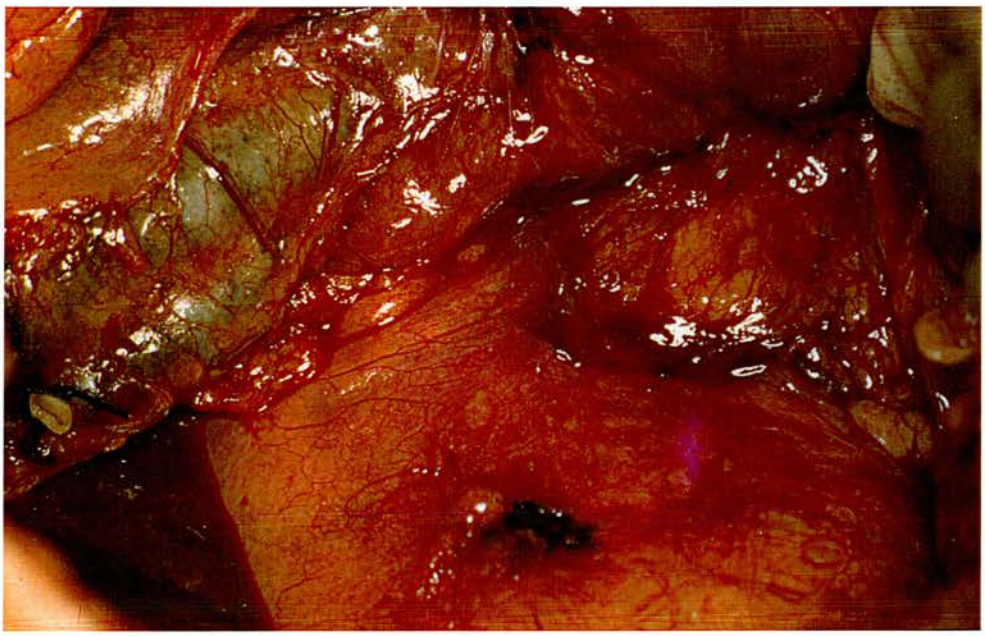
False positive staging angiogram. Portal venous phase of selective visceral angiography (catheter tip in the superior mesenteric artery) in a patient considered to have potentially resectable cancer of the pancreatic head. An indentation in the right lateral wall of the portal vein (PV) in the vicinity of the portal - superior mesenteric venous confluence ("notching") was interpreted as showing tumour invasion (arrows). The patient later underwent "curative" pancreaticoduodenectomy. A 7FG plastic biliary endoprosthesis marks the site of bile duct obstruction by a carcinoma of the pancreatic head which was later resected for "cure". PV = portal vein.

Figure 39



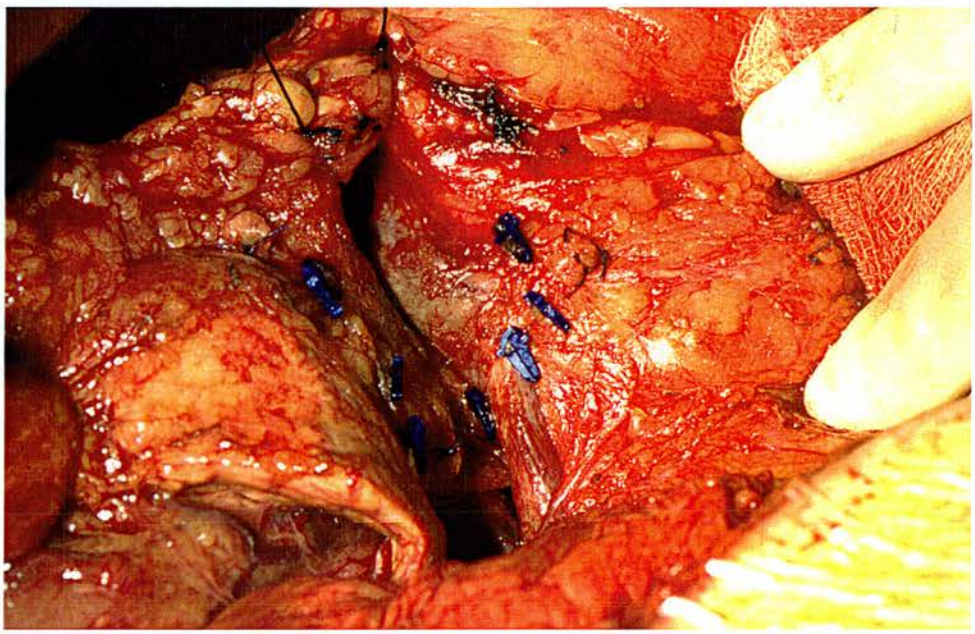
Selective superior mesenteric arteriogram demonstrating an accessory right hepatic artery (aRHA) arising from the proximal superior mesenteric artery (SMA). No evidence of mesenteric arterial invasion is identified. A 7FG plastic biliary endoprosthesis marks the site of bile duct obstruction by a carcinoma of the pancreatic head which was later resected for "cure".

Figure 40



Exploratory laparotomy and trial dissection of pancreatic carcinoma. Following mobilisation of the duodenum and pancreatic head from the inferior vena cava (top left), exposure of the retropancreatic plane revealed several small areas of fascial induration (note local charring following use of diathermy). Biopsy confirmed local soft tissue invasion which had not been detected by any preceding investigation.

Figure 41



Exploratory laparotomy and trial dissection as a prelude to the performance of pancreaticoduodenectomy for resectable carcinoma of the pancreatic head. The superior mesenteric vein has been dissected free of the pancreatic head and uncinate process with division of multiple small pancreaticoduodenal veins (marked by blue Absolok® clips (Ethicon Ltd, Edinburgh, U.K.). A tunnel has been established between the portal vein and pancreatic neck in readiness for transection of the pancreas (marked by black stay sutures at the inferior pancreatic border (top left of photograph)).

Chapter 3 Study 1

Imaging of the hepatobiliary and pancreatic anatomy using laparoscopic ultrasonography

3.1 INTRODUCTION

If LapUS is to be used to evaluate hepatobiliary and pancreatic diseases then its efficacy in imaging normal anatomical structures should first be ascertained. As there are no circumstances which permit the evaluation of LapUS in entirely normal human subjects or healthy volunteers, an attempt was made to quantify the success of LapUS in demonstrating anatomical landmarks as described in Section 2.3 in two different groups of patients. The first comprised patients undergoing elective laparoscopic cholecystectomy, in whom LapUS was being performed routinely to detect common duct calculi, and in whom no major distortion of the biliary anatomy was anticipated. The second group comprised patients undergoing elective staging LapUS to investigate suspected pancreatic malignancy, accepting that anatomical abnormalities wer expected in many of these patients.

3.2 PATIENTS AND METHODS

3.2.1 Laparoscopic ultrasonography during laparoscopic cholecystectomy

Laparoscopic ultrasonography was performed by a defined laparoscopic ultrasonographer (the author) during elective laparoscopic cholecystectomy in 80 consecutive patients (median age 56 years (range 21-82 years); male : female ratio = 26 : 54) during a 14 month period (5/1/93 - 21/2/94). The indications for laparoscopic cholecystectomy were: chronic cholecystitis / biliary colic syndrome (n = 67); previous acute gall stone related pancreatitis (n = 10); empyema of the gall bladder (n = 2); gall bladder polyps (n = 1).

Laparoscopic cholecystectomy was always performed by the "four port technique" (a 10 mm port at the umbilicus, a 10 mm sub xiphoid port, a 5 mm port in the right mid clavicular line and 5 mm port laterally in the right flank). Laparoscopic ultrasonography was performed early in the course of laparoscopic cholecystectomy

to minimise the degrading effects of gas within tissue planes or metal clips upon image quality. A time limit of 10 minutes was imposed for the LapUS examination. The technique of LapUS was performed as described in Sections 2.3.6 - 2.3.7 with the exception that laparoscopic cholecystectomy did not require the insertion of a 10 mm right flank port. To have done so would not have been considered justifiable in terms of potential morbidity and cost. The LapUS probe was therefore limited to use via the umbilical port, and LapUS was performed in a predominantly sagittal plane in all cases. The laparoscope was inserted through the sub-xiphoid port, which allowed manoeuvre of the LapUS probe under direct vision.

The ability of the laparoscopic ultrasonographer to satisfactorily image the following structures was documented prospectively using proforma sheets (see Appendix B):

Gall bladder (GB)
The whole gall bladder, including fundus, body and Hartmann's pouch.

Suprapancreatic common bile duct ($_{s}$CBD)
The entire length of the common duct from the confluence of the right and left hepatic ducts to the level of the superior pancreatic border

Intrapancreatic common bile duct ($_{i}$CBD)
The distal common duct as it passes behind or through the pancreatic head, and anterior to the inferior vena cava, until its termination at the Papilla of Vater.

Portal vein (PV)
The entire length of the portal vein from its bifurcation into right and left branches in the hilum, to its position posterior to the pancreatic neck inferiorly.

Common hepatic artery proper (CHA)
The entire length of the common hepatic artery, proximally from the "takeoff" of the gastroduodenal artery at the superior pancreatic border to its bifurcation into right and left branches in the hilum.

Pancreatic duct (PD)
The pancreatic duct imaged in transverse section traversing the pancreatic neck anterior to the portal vein, and passing obliquely across the pancreatic head to terminate at the papilla of Vater.

Papilla of Vater (Amp)
The confluence of the distal CBD and PD at a point within the medial duodenal wall which was recognisable by visible peristalsis.

The frequency with which these structures were identified was expressed in the context of four consecutive groups of LapUS examinations, each consisting of 20 procedures, performed between the following dates: Group A (5/1/93 - 15/3/93); Group B (16/3/93 - 6/5/93); Group C (11/5/93 - 9/9/93); Group D (10/9/93 - 21/2/94).

3.2.2 Laparoscopic ultrasonography during staging laparoscopy for pancreatic carcinoma

Laparoscopic ultrasonography was performed by one of two defined laparoscopic ultrasonographers (the author and / or OJG) between March 1993 and April 1995. All examinations were performed as part of elective staging LapUS in 50 consecutive patients with a diagnosis of pancreatic or periampullary carcinoma (31 male, median age 62 years (range 42 - 78 years)) (see Chapter 5 / Study 3). A biliary stent had been inserted in the common bile duct of thirty patients, and a cholecystojejunostomy had previously been performed in one patient at the referring hospital.

The technique of LapUS was performed as described in Sections 2.3.5 - 2.3.7, with the liver, biliary tree and pancreas examined in two planes using both umbilical and right flank ports. The ability of the laparoscopic ultrasonographer to satisfactorily image the following structures was documented prospectively using proforma sheets (see Appendix B):

Common bile duct (CBD)
The entire length of the common duct from the confluence of the right and left hepatic ducts to the papilla, or to the level of obstruction by tumour.

Portal / superior mesenteric venous trunk (PV / SMV)
The entire length of the venous trunk from its formation from tributaries in the mesenteric root at the inferior pancreatic border, through its course immediately posterior to the pancreatic neck, to the bifurcation of the PV into right and left branches in the hilum.

Splenic vein (SV)

The course of the splenic vein posterior to the pancreatic body and anterior to the SMA to its confluence with the PV / SMV. Imaging of the SV at its origin in the vicinity of the splenic hilum and pancreatic tail were not routinely made.

Coeliac axis (CA)

The origin of the CA from the abdominal aorta, its trifurcation into left gastric artery, splenic artery and CHA, and the bifurcation of the CHA into GDA and CHA proper at the superior pancreatic border.

Superior mesenteric artery (SMA)

The origin of the SMA from the abdominal aorta and its course posterior to the pancreatic neck to enter the mesenteric root.

Pancreatic duct (PD)

The pancreatic duct imaged in transverse and longitudinal section traversing the pancreatic body, neck and head.

Selective visceral angiography was performed in 32 patients as described in Section 2.5.5 (see also Chapter 5 - Study 3), and always after LapUS had been performed. The ability of LapUS to identify an anomalous right or common hepatic artery was correlated with the findings of SVA (Figure 39).

Anomalous right (or common) hepatic artery ($_a$RHA)

The presence of an accessory or replaced right (or common) hepatic artery originating from the SMA or aorta, and coursing in a cephalad direction posterior to the PV / SMV (see Figure 20).

3.3 RESULTS

3.3.1 Laparoscopic ultrasonography during laparoscopic cholecystectomy

Laparoscopic ultrasonography was successfully performed in every case. The median time taken for LapUS was 9 minutes (range 3 - 10 minutes). The frequency with which defined anatomical landmarks were identified using LapUS in Groups A-D are shown in Table 3.1. The gallbladder and PV were easily identified in every case. The suprapancreatic CBD and CHA were identified during every LapUS examination only during later stages of the study. Most difficulty was initially

experienced in demonstrating the distal CBD, pancreatic duct and papilla (60%, 45% and 35% of examinations in Group A), although the frequency with which these structures were identified improved to 85%, 85% and 75% of examinations, respectively, in Group D.

Table 3.1 - Imaging of the pancreaticobiliary anatomy by LapUS: results of 80 examinations performed during laparoscopic cholecystectomy

	Group A (n=20) (5/1/93 - 15/3/93)		Group B (n=20) (16/3/93 - 6/5/93)		Group C (n=20) (11/5/93 - 9/9/93)		Group D (n=20) (10/9/93 - 21/2/94)	
GB	20	(100)	20	(100)	20	(100)	20	(100)
sCBD	18	(90)	19	(95)	20	(100)	20	(100)
iCBD	12	(60)	17	(85)	18	(90)	17	(85)
PV	20	(100)	20	(100)	20	(100)	20	(100)
CHA	14	(70)	19	(95)	19	(95)	20	(100)
PD	9	(45)	15	(75)	17	(85)	17	(85)
Amp	7	(35)	16	(80)	17	(85)	15	(75)

3.3.2 Laparoscopic ultrasonography during staging laparoscopy for pancreatic carcinoma

Access to the peritoneal cavity was achieved in all cases. However, access to the region of the pancreas and porta hepatis was limited in three cases by adhesions associated with previous open cholecystectomy or cholecystjejunostomy. The frequency with which defined anatomical landmarks were identified using LapUS are shown in Table 3.2. The demonstration of the PV / SMV trunk in each case served to demonstrate the pancreatic neck, from which position the head of the pancreas could be successfully imaged. Inability to define the confluence of the splenic vein with the superior mesenteric vein in six cases was associated with the presence of tumours directly invading this area. The 11 cases where there was unsatisfactory imaging of the coeliac axis and / or superior mesenteric artery

occurred in the chronological sequence: 1, 2, 3, 4, 6, 8, 10, 11, 21, 30 and 42. In the latter case, adhesions had prevented satisfactory transducer contact with the area of interest.

Table 3.2 - Imaging of the pancreaticobiliary anatomy by LapUS: results of 50 examinations performed during staging laparoscopy for pancreatic or periampullary carcinoma

	n / 50	(%)
CBD	49	(98)
PD	47	(94)
PV / SMV	50	(100)
SV	44	(88)
CA	39	(78)
SMA	40	(80)
$_a$RHA	6	(12)

An anomalous right or common hepatic artery arising from the superior mesenteric artery or aorta was demonstrated in eight of the 32 patients (25%) who underwent SVA. This finding had been identified during LapUS in four out of eight cases (50%). In addition, LapUS identified this variant in two of the remaining 18 patients (11%) in whom SVA was not performed.

3.4 DISCUSSION

3.4.1 Laparoscopic ultrasonography during laparoscopic cholecystectomy

This study demonstrates that successful LapUS imaging of the biliary and pancreatic anatomy is feasible in the majority of patients. However, several problems were identified. All ultrasound techniques are inherently operator dependent, and the results of LapUS performed during laparoscopic cholecystectomy by a laparoscopic ultrasonographer who was relatively inexperienced in the technique at the start of the

study suggest a "learning curve" effect. While the gallbladder and portal vein were easily identified as landmarks from the outset of the study, the improvement in the frequency with which the other structures were identified is likely to reflect increasing competence with experience. The CHA and suprapancreatic CBD could be demonstrated consistently following the first 20 examinations, whereas the distal CBD, PD and papilla prove to be more difficult to image. Nevertheless, these structures have small dimensions in the absence of pathology, and their position in the retroperitoneum behind the gastric antrum and duodenum increases the likliehood of interference from luminal gas. Although no contemporaneous comparison with another imaging technique such as transabdominal USS was performed, the observation that following 40 examinations, the terminal CBD was visible in 85-90% of examinations, and the papilla itself in 75-85%, could be interpreted as evidence for the utility of LapUS in imaging this difficult anatomical region.

Moreover, the terminal retro- / intrapancreatic portion of the CBD would be expected to be collapsed in a proportion of patients without biliary obstruction. It is also possible that even slight LapUS probe pressure over this area may have caused obliteration of the duct and duodenal lumen. Several investigators have since recognised the possible limitations of LapUS imaging of this region during laparoscopic cholecystectomy, citing the potential to overlook impacted CBD stones adjacent to the papilla[286, 287]. However, any consideration of the accuracy of LapUS in detecting CBD stones, and hence its influence on clinical management, was outwith the aims of the study.

These results appear to concur with those reported by Jakimowicz[249, 250], who had previously acquired considerable personal experience with IOUS in the examination of the biliary tract during open cholecystectomy[245]. In his pilot study, in which LapUS was performed in 79 patients undergoing laporoscopic cholecystectomy, successful examination of the biliary tract was performed in 96% of cases, with a 4% failure rate because the bile duct could not be identified[249]. Using subjective criteria, an "optimal or good" examination was achieved in 87% of cases. In his subsequent study of 133 patients during laporoscopic cholecystectomy, in which similar LapUS equipment to this study was used, failure to visualise the CBD again occurred in 4% of cases[250]. The CBD was visualised up to the liver in 122 / 133 cases (92%) and to the papilla in 121 / 133 (91%).

There are technical factors which also may have potentially influenced the success of the examination. Although the LapUS system used in this study did not include the facility for Doppler sampling, other workers have recommended its use as a convenient means of distinguishing ducts from arterial and venous structures, and thus increasing diagnostic yield[250, 253-255]. Other workers have also suggested that the linear array LapUS probe may be operated through the sub-xiphoid port during laparoscopic cholecystectomy[253, 254, 287-289]. This manoeuvre allows the LapUS transducer to be placed perpendicularly alongside the free edge of the hepatoduodenal ligament, thereby generating cross-sectional images of the underlying structures, and permitting LapUS to be performed in two planes. Further experience with the technique has since supported the adoption of this technique during laparoscopic cholecystectomy.

Röthlin and co-workers also investigated the ability of LapUS to define the anatomy of the hepatoduodenal ligament using a different transducer configuration[290, 291]. They employed a 360° radial scanning probe which was inserted through the umbilical port and "dragged" alongside the hepatoduodenal ligament. In this way, they reported their ability to create a detailed "map" of the anatomy of the hepatoduodenal ligament, including the detection of biliary and arterial anomalies. Normal examinations were obtained in 52 out of 75 patients (69%), and a diverse range of anatomical variations were detected with a sensitivity of 82% (compared with 100% for intraoperative cholangiography)[290]. However, the potential role of LapUS using this technique in patients with suspected hepatobiliary and pancreatic malignancy is not clear given the limited tissue penetration associated with this type of LapUS transducer (≤ 4 cm), and the lack of additional information regarding its ability to detect other peripancreatic structures.

3.4.2 Laparoscopic ultrasonography during staging laparoscopy for pancreatic carcinoma

This study shows that LapUS is able to demonstrate the important structures comprising the pancreatic and peripancreatic anatomy in most patients with pancreatic or periampullary malignancy. Again, the ability of LapUS to define the pancreatic anatomy was not compared with that of alternative imaging techniques. However, the relative success of LapUS in this task is illustrated by historical comparison with the results of Kamin and colleagues who, using transabdominal USS, failed to demonstrate the pancreas in 38% of examinations due to interference

attributed to factors such as ascites and bowel gas[292]. Similarly, Arger and co-workers had succeeded in visualising the pancreatic head and body in just 77% and 70% respectively, of 500 consecutive transabdominal USS examinations[293].

Adhesions following previous operations can limit the efficacy of LapUS, although this was limited to a minority of patients in this study (6%). Anatomical distortion caused by the presence of tumours in the pancreatic head or periampullary region may make recognition of anatomical landmarks more difficult, and it must be recognised that failure to demonstrate structures such as the splenoportal-mesenteric venous junction during staging LapUS may be due to tumour obliteration rather than technical failure (12% in this study). Conversely, malignant obstruction and dilatation of the biliary and pancreatic ducts may facilitate the identification of these structures, while the presence of a biliary stent allowed rapid identification of the collapsed CBD. These factors help explain the higher frequency with which these structures were demonstrated compared with the results obtained during the early stages of the previous study.

Least success was experienced in imaging the coeliac trunk (78%) and SMA (80%) from their aortic origins, an area which is probably the least accessible of all those studied. Reasons for this again include the "learning curve" phenomenon as unsuccessful examinations tended to occur earlier in the study, in addition to the technical factors already enumerated. This aspect of the LapUS examination tended to be performed last, and would have attracted the least emphasis in cases where metastatic dusease had been demonstrated and biopsy required. In this way, "breaches of protocol" may have contributed to the poorer results.

This study also confirms that the $_{a}$RHA can be detected by LapUS, and it is pertinent to emphasise that all LapUS examinations preceded SVA. Röthlin and colleagues have also described this anatomical variant in six out of 100 LapUS examinations (6%) performed during laparoscopic cholecystectomy[291]. They also reported the detection of other "anomalies" consisting of hepatic or cystic arteries crossing ventral to the CBD in 16% of LapUS examinations, although none of these findings were confirmed by angiography. The anomaly of the $_{a}$RHA may have important implications for surgeons attempting pancreatic resection, and has been reported with an incidence of 14 - 27% in angiographic series[153, 174, 175, 180, 186, 188] (see Table 1.6 / Section 1.2.6). Its incidence as proven by SVA in this study was 20%, LapUS having achieved the same diagnosis with a sensitivity of 50%, with no misdiagnoses. However, the acquisition of this type of information is clearly

operator dependent and subject to inter-observer variations. This may explain the increased frequency with which the $_{a}$RHA anomaly was detected by LapUS in the present study (12%), compared with six out of 100 cases in Röthlin's series (6%). Therefore, while LapUS may provide useful additional information of this type, the surgeon should be aware that absence of this arterial anomaly during LapUS does not exclude its presence.

Chapter 4 Study 2

Laparoscopy and laparoscopic ultrasonography in the staging of patients with potentially resectable carcinoma of the pancreatic head and periampullary region

4.1 INTRODUCTION

As discussed in Section 1.2.7, initial reports suggested that laparoscopy could be used to demonstrate intraabdominal metastases in a high proportion of surgical patients with pancreatic cancer[83, 85, 229]. However, many of the patients in the aforementioned studies had advanced tumours or pancreatic body cancers, and the findings could be regarded to be of dubious clinical value as there had been little prior patient selection using less invasive imaging techniques. Subsequent work by Warshaw and colleagues suggested that truly unsuspected metastases had been apparent during laparoscopy in up to 41% of patients considered to be candidates for pancreatic resection on the basis of prior USS and / or CT[84, 86].

However, the concept of preoperative staging laparoscopy failed to achieve widespread popularity in the management of patients with pancreatic cancer. A recently reported survey of national patterns of care for pancreatic cancer at 978 American institutions conducted by The Commission on Cancer of the American College of Surgeons reported that laparoscopy had been performed in only 6% of cases, a figure which had remained static between the 1983-1985 period and 1990[294]. The present study was therefore undertaken to evaluate the reproducibility of earlier claims for the utility of laparoscopy, and to assess the clinical value of staging laparoscopy in preventing unnecessary laparotomy in patients with potentially resectable pancreatic or periampullary cancer.

Apart from a preliminary study of 12 patients performed at the Royal Infirmary, Edinburgh[158], experience with LapUS in the evaluation of pancreatic and periampullary cancer comprised a small selection of anecdotal reports[239-242, 250] as discussed in Section 1.2.8. Having evaluated the ability of LapUS to demonstrate the hepatobiliary and pancreatic anatomy in Study 1, the diagnostic accuracy of laparoscopy aided by LapUS in the assessment of tumour resectability was

investigated. To assess the contribution of LapUS to the laparoscopic examination, these findings were compared with those obtained for laparoscopy alone.

4.2 PATIENTS AND METHODS

From January 1991 to September 1993, 40 consecutive patients diagnosed as having pancreatic or periampullary carcinoma underwent staging laparoscopy (22 female, 18 male; median age 59 years (range 36-78 years)), of whom 38 also underwent LapUS. Endoscopic insertion of a biliary stent had previously been performed in 21 patients (53 per cent). Failure to achieve laparoscopic access to the peritoneal cavity occurred in one other patient with adhesions from a previous laparotomy, and this patient was excluded from analysis.

All patients were considered, on the basis of USS and / or CT, to be candidates for tumour resection with curative intent either by pancreatoduodenectomy or by transduodenal local resection. A variety of scanning techniques and equipment had been employed by the referring hospitals. Histopathological confirmation of periampullary or pancreatic carcinoma was obtained in each case, either following examination of the surgically resected specimen, by needle biopsy of the primary tumour, by luminal biopsy of periampullary tumours during ERCP and / or by biopsy of metastatic deposits during laparoscopy or laparotomy.

Decisions regarding tumour resectability were documented prospectively for staging laparoscopy alone, and in conjunction with LapUS, at the time of the examination. Predictions of tumour unresectability due to locoregional tumour invasion, malignant regional lymphadenopathy and / or distant metastases were defined by the staging convention outlined in Section 2.1.1. Laparoscopic and LapUS staging criteria were interpreted as described in Sections 2.3.3 and 2.3.7. Validation of the end-point of tumour resectability was achieved by laparoscopic, surgical or non-operative methods as described in Section 2.6.1. Thus, surgical resectability was determined by clinical means, and histopathological examination of resection margins for microscopic tumour involvement was not used as an endpoint in this study. Summary measures of diagnostic accuracy were calculated by 2 x 2 matrix analysis as defined in Section 2.1.2.

4.3 RESULTS

4.3.1 Patient outcome

Twenty two patients (55 per cent) progressed to laparotomy and operative assessment of resectability of whom 12 patients were considered to be resectable for "cure" (30 % overall resectability rate). Pancreatoduodenectomy was performed in 10 patients and one patient underwent transduodenal resection of a periampullary adenocarcinoma. Another patient, in whom resectability of a periampullary carcinoma was confirmed at laparotomy, became profoundly hypotensive during the procuedure. It was considered appropriate to perform an expeditious biliary bypass rather than attempt pancreatic resection on this occasion. Having refused further surgery, this patient was alive with CT evidence of tumour progression two years later. For the purposes of this study, he has been classified as having 'resectable' disease. Palliative biliary and duodenal bypass procedures were performed in ten patients in whom tumour unresectability was confirmed at laparotomy.

Criteria confirming tumour unresectability were confirmed by laparoscopic means in 14 patients (see below), and unresectability due to locally advanced tumour with vascular invasion was validated non-operatively in four patients.

4.3.2 Laparoscopy (n=40)

Procedure-related complications were encountered in one patient (2.5 per cent complication rate) in whom a port site haemorrhage had occurred with the discovery of intraperitoneal blood at laparotomy six days later. A fall in the haemoglobin concentration by 3.2 g/dl was measured in this patient and two units of blood were transfused on day 2. However, the patient had remained haemodynamically stable and asymptomatic, and no sequelae to this event were ientified.

In no patient was it possible to inspect the primary tumour directly during the laparoscopic examination, although it was occasionally possible to 'palpate' a retrogastric mass with the tip of a probe.

Previously unsuspected metastatic tumour spread to the liver (ten patients), peritoneal surfaces (eight patients) and / or hilar lymph nodes (two patients) were identified during laparoscopy in a total of 14 patients (35 per cent). Biopsy material was obtained and metastatic carcinoma confirmed in each case. Exploratory

laparotomy was withheld from these patients, who in terms of predicting resectability, were regarded as having undergone 'true positive' laparoscopic staging examinations.

Laparoscopy failed to detect malignant dissemination to distant sites within the abdominal cavity in three patients (i.e. 'false negative' procedures). In one patient, a cluster of tiny peritoneal tumour seedlings were concealed by adhesions in the right subhepatic space having not been recognized by the laparoscopist. Failure to diagnose liver metastases during laparoscopy ocurred in three patients. In one case, laparoscopic biopsy of a suspicious subcapsular lesion yielded adiagnosis of biliary ectasia, although biopsy at open operation confirmed metastatic carcinoma. A 10mm diameter metastasis within the caudate lobe of the liver was demonstrated by LapUS in another patient. A small metastatic deposit on the free edge of the right hepatic lobe was only discovered during exploratory laparotomy in a third patient. A delay of two months had ensued between laparoscopy and laparotomy in this deeply jaundiced patient. Ultimately, unsuspected small liver and peritoneal tumour deposits were demonstrated following laparoscopy, LapUS and / or laparotomy in 17 of the 40 patients (43%).

Laparoscopy failed to identify locoregional tumour unresectability in 12 patients (30%). Overall, there were 14 'false negative' laparoscopic examinations including those where distant metastases were overlooked. The inability of laparoscopy to identify factors confirming tumour unresectability in these patients was reflected by a sensitivity of 46%, while the predictive value of a negative result was 50% (Tables 4.1 and 4.3).

Table 4.1
Diagnostic accuracy of laparoscopy in the staging of 40 patients with pancreatic or periampullary carcinoma

		Laparoscopy	
		Resectable	Unresectable
Outcome	Resectable	12	0
	Unresectable	14	14

Tumour resectability was correctly inferred from the absence of signs of dissemination within the abdominal cavity in all 12 patients considered resectable. The absence of a tendency for laparoscopy to overstage these patients was reflected by a specificity and PPV of 100% (Tables 4.1 and 4.3).

4.3.3 Laparoscopic ultrasonography (n=38)

Laparoscopic ultrasonography was deferred in two out of 40 patients undergoing laparoscopy because widespread peritoneal carcinomatosis had been encountered, and the insertion of a second 10mm laparoscopic port was considered unjustified under the circumstances. Satisfactory LapUS images of the primary pancreatic and periampullary tumours were recorded in 31 out of 38 patients (82 per cent).

Factors indicating tumour unresectability were correctly identified by LapUS in 23 out of 38 cases (61%). Liver metastases were identified in 10 patients, and / or tumour invasion of the peripancreatic soft tissues and / or portal-superior mesenteric vein in 24 patients. Regional lymphadenopathy was identified in 14 patients, and biopsies were obtained to confirm malignant nodal infiltration in three cases. In those patients with LapUS evidence of enlarged regional lymph nodes, but without histological proof of metastatic involvement, tumour unresectability was always validated by additional staging criteria and was never based upon an unconfirmed diagnosis of malignant lymphadenopathy.

Failure to recognize tumour invasion of the portal-superior mesenteric vein in one patient, and tumour infiltration of the suprapancreatic common bile duct and pylorus in another, yielded two instances of 'false negative' results for LapUS. In another patient, the diagnosis of retro-duodenal tumour infiltration from cancer of the pancreatic head was refuted at laparotomy, and the patient underwent a Whipple operation. This was the only 'false positive' LapUS examination in this series, which diminished the 100% specificity of staging laparoscopy to 92%, while the predictive value of positive LapUS findings were reduced to 96%. Conversely, the correct identification of tumour unresectability in 23 out of 26 patients when the findings of LapUS were considered improved the sensitivity of tumour staging to 88%, while the reduced incidence of 'false negative' results improved the predictive value of a negative examination from 46% to 79% (Tables 4.2 and 4.3).

In 20 patients (53%), information relevant to the assessment of tumour stage and not apparent following laparoscopy was derived from the LapUS examination. This

new staging information altered the laparoscopic decision concerning tumour resectability in 10 patients (25%). Local invasion of the peripancreatic soft tissues was defined in six of these 10 patients, invasion of the adjacent portal-superior mesenteric vein in eight patients and / or the discovery of metastastatic liver disease which had remained undetected during laparoscopy in one patient. Enlarged regional lymph nodes were also demonstrated in six of these patients, although biopsies were not obtained.

Table 4.2

Diagnostic accuracy of laparoscopy and LapUS in the staging of 38 patients with pancreatic or periampullary carcinoma

		Laparoscopy / LapUS	
		Resectable	Unresectable
Outcome	Resectable	11	1
	Unresectable	3	23

Table 4.3

Diagnostic accuracy of laparoscopy compared with laparoscopy and LapUS in the diagnosis and staging of patients with pancreatic and periampullary cancer

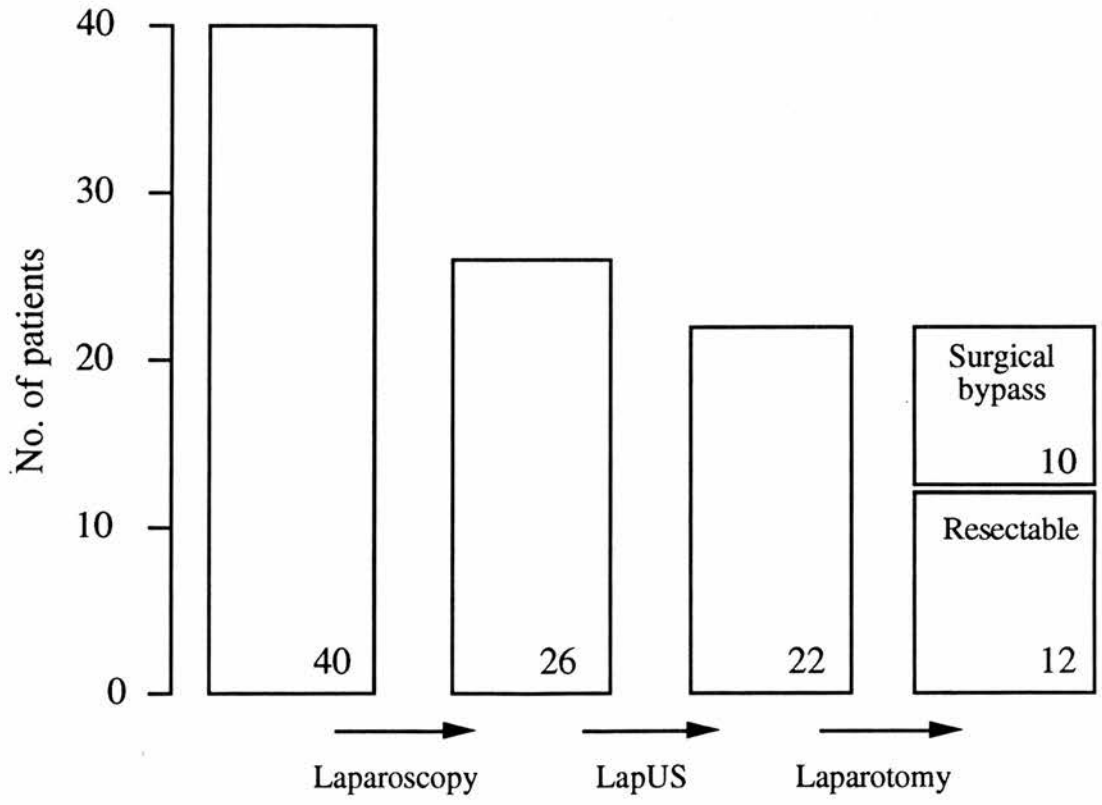
	Laparoscopy (n=40)	Laparoscopy & LapUS (n=38)
Diagnosis	-	31 / 38 = 82%
Sensitivity	14 / 28 = 50%	23 / 26 = 88%
Specificity	12 / 12 = 100%	11 / 12 = 92%
PPV	14 / 14 = 100%	23 / 24 = 96%
NPV	12 / 26 = 46%	11 / 14 = 79%

4.3.4 Clinical value of staging laparoscopy with LapUS

The effect of laparoscopy and LapUS on patient treatment is illustrated in Figure 42. Of the 40 patients with potentially resectable tumours who underwent laparoscopy, unnecessary laparotomy was avoided in 14 (35%) due to the discovery and biopsy of intraabdominal metastases. In a further four patients, local tumour invasion was identified by LapUS, but not by laparoscopy, the findings corroborated by non-operative means and surgery was avoided. Exploratory laparotomy was performed in the remaining 22 patients, confirming tumour resectability in 12 patients (11 of whom had been correctly identified as such by laparoscopy and LapUS), and tumour unresectability in 10 patients (8 of which had been predicted as such by LapUS).

Figure 42

The impact of staging laparoscopy and LapUS on selection for surgery in 40 patients with potentially resectable pancreatic and periampullary cancer



4.4 DISCUSSION

This study has confirmed that small intraabdominal metastases are present in a substantial proportion of patients considered, on the basis of conventional radiological techniques, to have potentially resectable pancreatic and periampullary cancers. Such findings were ultimately proven in 42% of such patients in this study. While this incidence may appear suprisingly high, it is not at variance with the experience reported by Warshaw and colleagues in their reports of 1986 (43%)[84] and 1990 (31%)[86]. However, the same group have since reported a diminished incidence of unsuspected intraabdominal metastases of 24%, with a further reduction to 18% when patients with carcinoma of the pancreatic head only were considered[295]. They speculate that improvements in radiological imaging techniques, earlier patient presentation and / or a change towards a more favourable tumour biology are possible explanations for this apparent change.

The patient population comprising this study should be considered in the context of a tertiary referral practice where a degree of prior patient selection will have been inevitable. The relatively high resectability rate of 30% may be considered indicative of this "centripetal bias". This contrasts with resectability rates ranging from 4% in Gudjonsson's series[26] and 2.6% in Bramhall and co-workers' epidemiological study of practice in the West Midlands[296], through mean resection rates of 10-15% in Watanapa and Williamsons' collective review[62], to a figure of 21% recently reported by the collaborative experience of the French Association of Surgery[297]. Nevertheless, prior screening with USS and / or CT scanning in patients in the present study had failed to identify metastatic lesions, although variations in equipment and personnel may have accounted for suboptimal examinations, and methodological flaws could not be excluded using this non-standardized approach. However, this situation did reflect clinical practice at the time of the study, and represented the basis for decision-making prior to the adoption of laparoscopic staging which supports the validity of these findings.

Laparoscopy was highly effective in identifying such unsuspected lesions (83% sensitivity) and afforded the opportunity for their biopsy, thus providing a tissue diagnosis without resort to unnecessary laparotomy. Warshaw and colleagues previously used laparoscopy to detect intraabdominal metastases with reported sensitivities of 82%[84], 96%[86] and more recently 93%[295]. Independent and contemporaneous evaluation of staging laparoscopy in this role by other workers has since been reported. Between 1993 and 1994, Bemelman and colleagues at the

University of Amsterdam performed staging laparoscopy with LapUS in 73 patients with carcinoma of the pancreatic head or periampullary region and considered to have stage 1 disease on the basis of ERCP and Doppler USS[298]. The incidence of unsuspected metastases was 24%, and these were identified laparoscopically in 16 out of 21 patients (76%). Conlon and co-workers at the Memorial Sloane Kettering Cancer Center, New York, also performed preoperative laparoscopy in 115 patients with "radiologically resectable" pancreatic cancer between 1992 and 1994, defining liver metastases in 17%, peritoneal carcinomatosis in 14% and / or visible malignant lymphadenopathy in 7%[299]. These reports have corroborated the conclusions of the present study that in patients with pancreatic or periampullary cancer, "occult" intraabdominal metastases are encountered commonly despite imaging with contemporary radiological techniques, and that staging laparoscopy is a sensitive method for their detection.

Staging laparoscopy was also shown to be fallible in a proportion of patients, both in detecting metastatic lesions, and in predicting overall tumour resectability where locoregional tumour spread was overlooked. Adhesions, intrahepatic metastases, delay to laparotomy and unrepresentative biopsy were implicated in the three false negative laparoscopies performed in patients with overt liver metastases. These limitations, albeit in a minority of patients, have also been recognised by other workers[295, 298, 299]. The impact of LapUS in identifying previously imperceptible intrahepatic metastases in the present study was minimal, and occurred in one patient (3%). However, Bemelman and co-workers have since reported a different experience for which there is no obvious explanation[298]. In their study, laparoscopy identified liver metastases in seven out of 16 proven instances (44%), six cases were diagnosed exclusively by LapUS (38%) and there were three false negative procedures.

Ultimately, the actual false negative rate for distant intraabdominal metastases is likely to be even higher due to the presence of "occult" micrometastases. Evidence for this has been presented by Willet and colleagues, who reported distant metastases to the liver, peritoneum and pleura as the dominant pattern of recurrence among 12 "high risk" patients with periampullary carcinomas who had undergone exploratory laparotomy, pancreaticoduodenectomy and post-operative radiotherapy[68]. Also, by measuring the doubling times of cell lines derived from liver metastases in patients with resected pancreatic cancers, Japanese workers have extrapolated the size of "occult" liver metastases at the time of pancreatoduodenectomy to have been as small as 10 μm[300]. Patterns of recurrence

and long term follow-up were not assessed in the present study, and it therefore seems inevitable that the true incidence of "occult" extrapancreatic metastases would have been underestimated. Neverthless, this study has shown that staging laparoscopy was efficacious and of real clinical value when its impact was evaluated in clinically measurable terms at the time of surgical decision-making.

Laparoscopy was found to be an ineffective method of assessing locoregional tumour invasion in this study. On no occasion was vascular invasion inferred from secondary signs such as mesenteric venous congestion, and tumour infiltration of the mesenteric root was never identified. Although no attempts at peripancreatic dissection or instrumentation of the lesser sac were undertaken, routine observation of the gastrohepatic omentum and lesser sac yielded no useful staging information. This is at variance with the recent experience of Conlon and colleagues[299]. They described "extended laparoscopy" by a four port technique, where adhesiolysis was performed, periportal lymph nodes biopsied, the mesocolon retracted, the gastrohepatic omentum incised and the major peripancreatic blood vessels and lymph nodes examined. A complete examination was achieved in 94% of patients, with vascular invasion diagnosed in 16 patients (15%) and coeliac or portal lymphadenopathy proven in eight patients (7%). Vascular invasion was overlooked in one case, giving an overall predictive value for a positive result of 100%, whereas the negative predictive value was 91%[299].

Explanations for these contrasting results may include differences in patient populations. The latter study cites a 58% resectability rate, the prevalence of vascular invasion as the sole source of unresectability was only 9% and the incidence of cancer of the pancreatic body and tail was 25%[299]. The reproducibility of locoregional tumour staging by extended laparoscopy remains to be ascertained.

The present study has also demonstrated that LapUS successfully exploits the principles of IOUS in the assessment of patients with pancreatic cancer. The immediate benefit of LapUS over laparoscopic inspection was illustrated by its ability to image a focal pancreatic mass lesion in 82% of patients, whereas the primary diagnosis could not be established by laparoscopy in any cases. Summary measures of diagnostic accuracy for staging laparoscopy and LapUS have approximated those reported by Machi and colleagues for IOUS in assessing portal vein invasion[236]. The improved staging sensitivity (88%) conferred by LapUS reflects its ability to evaluate retroperitoneal tumour spread, and the resultant

diminished incidence of 'false negative' findings was reflected by a negative predictive value of 79%.

Nevertheless, local tumour staging by LapUS was fallible, and yielded two false negative assessments where direct invasion of portal vein and suprapancreatic common bile duct were not identified. Of more concern, however, was the instance where the tumour was overstaged by LapUS, retroduodenal tumour invasion having been identified in error. In this case, which was the fourth performed in this series, it seems likely that dense acoustic shadowing posterior to a carcinoma of the pancreatic head had been misinterpreted as tumour extension. It is, therefore, tempting to ascribe this interpretative error to a "learning curve" phenomenon.

Nevertheless, this study may be considered as having validated the diagnostic accuracy of laparoscopy combined with LapUS in the staging of pancreatic and periampullary cancer. Furthermore, contemporaneous work with staging laparoscopy and LapUS performed between 1993 and 1994 by Bemelman and colleagues in Amsterdam has reproduced the findings[298]. Their study was similar inasmuch as the majority of patients had undergone insertion of a biliary endoprosthesis and an identical 7.5 MHz linear array LapUS probe was employed. They performed surgical exploration and trial pancreatic dissection in 49 out of 73 evaluated patients with pancreatic or periampullary cancer, for an overall resectability of 41%. In addition, segmental resection of the portal vein was performed in three patients, allowing histological validation.

There was one false positive LapUS prediction of portal vein invasion in a patient with retroperitoneal radiation fibrosis, histological examination of the resected portal vein indicating no direct tumour invasion. The specificity and PPV of LapUS in predicting vascular invasion were therefore reported to be 96% and 93% respectively[298]. Failure to detect intraabdominal metastases in five patients, together with the discovery of positive resection margins in seven patients accounted for an overall sensitivity and negative predictive value of 67% and 65% respectively. These latter parameters were slightly inferior to those obtained in our study, which partially reflects the authors' use of stringent histopathological criteria in validating tumour resectability. However, similar findings to our own were reported in that staging laparoscopy with LapUS had changed therapeutic strategy in 25% of patients, avoided unnecessary laparotomy in 19% and upstaged the tumour in 41%[298]. By contrast, other workers have reported difficulty in evaluating the peripancreatic region using LapUS in patients with pancreatic malignancy, although

the same group claimed success in detecting "occult" intrahepatic metastases[251]. While it is not possible to ascertain the reasons for the latter group's limited success with LapUS in this context, the inherent operator dependency of the technique does not make such findings wholly unexpected.

The provision of a tissue diagnosis of metastatic disease permitted clinical management decisions to be based upon the laparoscopic findings. If one accepts the rationale for avoiding unnecessary laparotomy in such patients as outlined in Section 1.1.2, the impact of laparoscopy alone in averting an inevitable unnecessary laparotomy in 35% of patients may have had a beneficial effect on the quality of palliative care provided to the patient, as well as health economic implications. This must remain speculative as these issues were not explicitly investigated in this study. Nevertheless, surveys from France[297] and the West Midlands region of the U.K.[296] have indicated that the incidence in the 1980's of laparotomy alone in patients with pancreatic cancer was 12% and 14.5% respectively. Clearly these are areas where the clinical management of patients with pancreatic or periampullary cancer might be improved.

The present study has provided further evidence that incorporation of staging laparoscopy into the preoperative investigative algorithm may be beneficial to the management of such patients. Furthermore, the adoption of LapUS may further facilitate the selection of patients with pancreatic or periampullary cancer for appropriate surgery. However, further prospective validation of the technique in comparison with alternative imaging investigations is indicated before the adoption of LapUS into clinical practice can be recomended. The next study investigates this matter.

Chapter 5 Study 3

A prospective comparison of USS, CT , SVA and laparoscopy with LapUS in the staging of patients with carcinoma of the pancreas and periampullary region

5.1 INTRODUCTION

The previous chapter (Study 2) demonstrated the clinical value of staging laparoscopy in the management of patients with pancreatic and perwiampullary carcinoma. Also, the high diagnostic accuracy of LapUS both in establishing the primary diagnosis and determining tumour resectability was documented. However, LapUS was evaluated in a series of patients already identified as potentially resectable on the basis of USS and / or CT, with the endpoint of locoregional tumour resectability determined largely by the decision of the operating surgeon. To date, no direct comparison between LapUS and other imaging modalities in the diagnosis and staging of pancreatic and periampullary cancer has been performed. An attempt to address these deficiencies was undertaken in a second cohort of patients.

A more rigorous method of validation was adopted in a prospective study which compared LapUS with alternative imaging techniques (USS, CT and SVA). Special reference was made to the various components of the TNM classification presented in Table 2.1 / Section 2.1.1[272] , as well as to overall tumour staging, in an attempt to define the strengths and weaknesses of the individual modalities. Also, a more stringent histopathological evaluation of resection margins was included in the determination of tumour resectability.

5.2 PATIENTS AND METHODS

5.2.1 Patient details

Fifty consecutive patients presenting with carcinoma of the pancreas or periampullary region were studied (31 male, median age 62 years (range 42 - 78 years)). Staging laparoscopy with LapUS (LapUS) was performed in all patients between March 1993 and April 1995. A histological diagnosis of pancreatic or periampullary carcinoma was obtained in 44 patients by percutaneous (four patients)

or operative (n=10) needle biopsy of the pancreas, laparoscopic (n=15) or operative (one patient) biopsy of metastatic lesions in the liver, serosal surfaces or regional lymph nodes, histopathological examination of the pancreatic resection specimen (n=14) and / or endoluminal biopsy of periampullary lesions (n=10). No biopsy diagnosis was obtained in the other six patients, although a pancreatic mass lesion was documented by imaging investigations, and death from carcinomatosis was observed in each case (crude mean survival 34 weeks (range 12 - 67 weeks)). The primary tumour was situated in the pancreatic head (33 patients), pancreatic body (five patients), pancreatic head and body (one patient) and periampullary region (11 patients). A biliary stent had been inserted in thirty patients by the endoscopic (22 patients) or percutaneous route (eight patients), and a cholecystjejunostomy had previously been performed in one patient at the referring hospital.

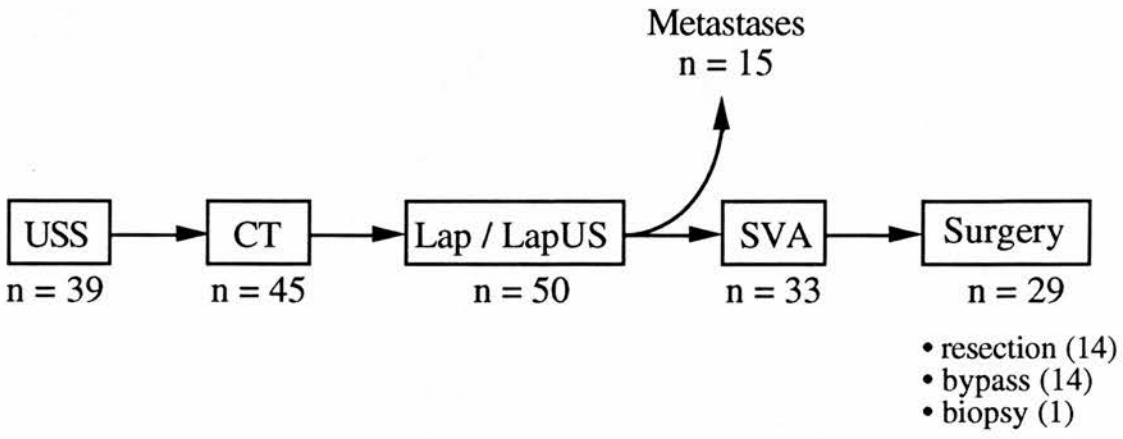
5.2.2 Staging investigations

Patients were managed according to the investigative algorithm depicted in Figure 43. Staging investigations were performed and interpreted by defined personnel as described previously for USS (Section 2.5.1), CT (Section 2.5.2), LapUS (Section 2.3) and SVA (Section 2.5.5). The various investigations were interpreted 'blind' without reference to the results of preceding staging investigations. Results were recorded prospectively on standardised proformas (Appendix) and compared for each stage.

Breaches of protocol occurred inasmuch as some patients failed to undergo all four investigative modalities. Eleven patients did not undergo USS according to protocol, either because of unavailability of the defined ultrasonographer during the patients' hospital admission, or because of logistic difficulties in the timing of the various interventions. CT scans which had been performed at the original hospital within two months prior to referral, and which were regarded as being of satisfactory quality, were not repeated in 12 cases (27%). However, five other patients did not undergo repeat CT, despite the original scans having been deemed to be of insufficient quality for inclusion in this study. Thirty three out of fifty patients underwent SVA. The demonstration of biopsy proven metastases during laparoscopy in 15 patients accounted for a decision to avoid operative intervention in these patients, and SVA was accordingly regarded as unjustified as it would have contributed nothing further to these patients' management. Breaches in protocol accounted for a failure to perform SVA in two patients who progressed to surgical staging.

Figure 43

Investigative algorithm employed in the diagnosis and staging of 50 patients with pancreatic and periampullary cancer



5.3.3 Evaluation and validation of resectabilty by TNM stage

The results were expressed in terms of the TNM classification presented in Table 2.1 / Section 2.1.1[272] , and in terms of overall tumour resectability in the context of pancreatic resection with the intention of cure.

Evaluation of T stage

As documented in Section 2.1.1, patients were considered as having pancreatic or periampullary cancers which were resectable with curative intent when there was no evidence of extrapancreatic tumour invasion (T_1), or when local tumour invasion was limited to the distal common bile duct or medial duodenal wall (T_2). However, local tumour invasion of the peripancreatic fat, or tissues of the hepatoduodenal ligament, were regarded as indicating unresectable tumour (also T_2). Similarly, tumour invasion or encasement of major peripancreatic blood vessels, stomach, spleen or colon indicated tumour unresectability (T_3). Local tumour resectability by T stage was validated by surgical staging in 29 out of 50 patients as described in Section 2.6.1, and by non-operative means in six patients when all four staging modalities and the patients' clinical course were indicative of advanced cancer. Histopathological examination of pancreatic resection specimens was performed

with particular attention to microscopic involvement of the resection margins with tumour. For the purposes of this study, patients found to have positive resection margins were regarded as having been 'unresectable' in the context of 'cure'. Fifteen patients in whom metastases had been discovered, and who were neither assessed by laparotomy or SVA, were not evaluable by T stage (T_X).

Evaluation of N and M stages

For the purposes of this study, patients with distant metastases (M_1) or malignant regional lymphadenopathy (N_1) documented by laparoscopic or operative biopsy, and including those patients found to have lymph node metastases following histological examination of the pancreatic resection specimen, were regarded as having 'unresectable' tumours (see Section 2.1.1). Further investigation by SVA or surgery was avoided in patients with biopsy proven distant metastases or malignant lymphadenopathy. The absence of distant metastases (M_0) or regional lymph node spread (N_0) was accepted only after full operative staging, including sampling of suspicious lesions by frozen section histology where appropriate. Lymph node status was unevaluable in 23 patients in whom operative staging was not performed, while the M stage of three patients could not be validated for similar reasons (i.e. 'N_X' and 'M_X').

Overall staging

All fifty patients were classified overall as 'resectable' or 'unresectable', taking account of the findings for each of the T, N and M stages. Overall unresectability was therefore denoted by the demonstration of defined criteria contraindicating tumour resection for any aspect of the TNM staging system, recognising that other TNM criteria may have been classified as being 'resectable' in the same patient.

5.3.4 Analysis of results

Summary measures of diagnostic accuracy were calculated and compared as described in Section 2.1.2 (Table 2.2). The predictive values of positive results in determining tumour unresectability, and of negative findings in predicting tumour resectability were calculated in the knowledge of the prevalence of tumour unresectability within the population of evaluable patients by reference to Study 2. A prevalence of tumour unresectability of 70% was therefore observed.

5.3 RESULTS

5.3.1 Patient outcome

Exploratory laparotomy was performed in 29 patients, 14 of whom underwent tumour resection (Whipple operation in nine patients; transduodenal local resection for periampullary carcinoma in three patients; total pancreatectomy in one patient; distal pancreatectomy in one patient). Palliative bypass surgery was performed in 14 patients (duodenal and biliary bypass in eight patients; duodenal bypass alone in five patients; biliary bypass alone in one patient), and laparotomy with tumour biopsy was performed in one patient found to have invasion of the posterior wall of the stomach from a pancreatic body carcinoma. However, three patients who underwent tumour resection had either peripancreatic lymph node metastases (two patients), or invasion of the peripancreatic soft tissues with tumour involvement of the posterior resection margin (one patient), and for the purposes of this study these tumours were considered to have been 'unresectable' for cure. Conversely, three patients in whom transduodenal local resections were not possible due to pancreatic tumour infiltration were, nevertheless, judged as having tumours which were potentially resectable by pancreaticoduodenectomy. However, it was elected to forego pancreatic resection in these frail patients of high cardiovascular risk status, and palliative bypass operations were performed instead. Therefore, for the purposes of this study, the prevalence of patients with 'unresectable' tumours was 72% (36 out of 50 patients).

Post operative morbidity following LapUS was encountered in one patient with carcinoma of the pancreatic body who previously had undergone percutaneous needle biopsy. Peritoneal carcinomatosis was revealed at laparoscopy and the patient developed an umbilical port site metastasis six weeks later. The general health of another two patients deteriorated rapidly after LapUS had revealed histologically proven disseminated pancreatic cancer, with death occurring at six days and two weeks later.

5.3.2 Diagnosis of primary tumour

A focal mass lesion within the pancreas or periampullary region was revealed by USS in 32 out of 39 patients (82%) and by CT in 42 out of 45 patients (93%). Definition of a primary tumour mass was possible in 48 out of 50 patients (96%) using LapUS. The tumour typically appeared as a discrete, irregular, hypoechoic mass in cases of pancreatic cancer, or as an isoechoic or hypoechoic lesion prolapsing into the lumen of the second part of the duodenum, or infiltrating the pancreatic head in patients with periampullary carcinoma. There were two 'false negative' LapUS examinations where focal tumour could not be demonstrated. Both patients had diffuse isoechoic carcinomas of the pancreatic head, and in one the examination was limited by adhesions associated with a cholecystojejunostomy performed at the referring hospital.

The presence of the primary tumour was inferred from displacement of the pancreaticoduodenal arteries, or by the displacement or invasion of the portal or superior mesenteric veins in 21 out of 32 patients (66%) studied by SVA ($P = 0.005$ versus CT; $P = 0.0008$ versus LapUS). An anomalous right or common hepatic artery arising from the superior mesenteric artery or aorta was demonstrated in eight of the 32 patients (22%) as discussed in Section 3.3.2. Severe obliterative vascular disease with occlusion of the coeliac and superior mesenteric arteries was shown in one patient.

5.3.3 Evaluation of T stage

Validation of T stage status was achieved in 35 patients, by surgical staging in 29 patients and by non-operative criteria in six patients. Sixteen patients were staged T_1, three patients were staged T_2 (invasion of retropancreatic fat in one patient, invasion of mesenteric root in one patient and invasion of hepatoduodenal ligament in one patient) and 16 patients were staged T_3 (vascular invasion in 15 patients, and invasion of the posterior wall of the stomach in one patient). Tumour unresectability according to T stage was, therefore, documented in 19 out of 35 evaluable patients (prevalence 54%). The validated results of the various staging investigations in predicting tumour resectability by T stage are shown as 2 x 2 contingency matrices in Tables 5.1.1 - 5.1.4. The derived summary measures of diagnostic accuracy for T staging are summarised in Table 5.2.

There were six instances where LapUS failed to identify tumour unresectability due to T_2-T_3 local tumour invasion (Table 5.1.3). Invasion of the portal-superior mesenteric vein was not predicted in three patients, one of whom had a diffusely infiltrating isoechoic carcinoma of the pancreatic head, the extent of which was difficult to define, and another had a five centimetre diameter tumour in which dense posterior acoustic shadowing largely obscured the vein-tumour interface. In the third case, marked distortion of the portal-superior mesenteric vein by a three centimetre diameter carcinoma of the uncinate process was identified, although no direct venous invasion was identified and diagnosis of a potentially resectable "pushing" tumour was predicted. However, during surgical exploration the tumour was deemed to have extended too far posterior to the superior mesenteric vein to enable resection without necessitating gross tumour transection.

Infiltration of the posterior wall of the stomach was undetected in one patient with an eight centimetre diameter pancreatic body cancer, in which the tumour was discovered to have extended into the lesser sac to infiltrate the serosa during laparotomy. Retrospective review of the LapUS images in this patient revealed loss of the normal hyperechoic interface between the stomach serosa and the pancreas which had not been recognised during the procedure (see Figure 24). Infiltration of the retroperitoneal soft tissues alongside the inferior vena cava was discovered during Kocher's manoeuvre in one case (Figure 40). Retropancreatic fat invasion was discovered by histopathological examination of the distal pancreatectomy specimen of one patient. The sensitivities (60 - 71%) and negative predictive values (58 - 73%) of all investigations in identifying tumour unresectability due to direct extrapancreatic invasion did not differ significantly (Table 5.2).

There were 16 instances where overestimation of T stage by one or more investigations was demonstrated. These 'false positive' findings were attributable to USS in four patients (invasion of the portal vein (n=2), common bile duct (n=2) and / or peripancreatic fat (n=1)), CT in eight patients (invasion of peripancreatic fat (n=6), portal vein invasion (n=3) and / or colonic invasion (n=1)) (see Figure 36), and SVA in four patients (slight narrowing of the superior mesenteric-portal vein junction leading to the diagnosis of "encasement") (see Figure 38). All these patients were subsequently shown to have resectable tumour by surgical validation and histopathological examination of the resected specimen. There were no instances of overstaging of T stage by LapUS (Table 5.1.3), and accordingly its specificity and positive predictive value were significantly superior to that of both USS and CT (Table 5.2).

Table 5.1.1

Diagnostic accuracy of USS in the T staging of 26 evaluable patients with pancreatic or periampullary carcinoma

		USS	
		- ve	+ ve
Outcome	- ve	7	4
	+ ve	6	9

Table 5.1.2

Diagnostic accuracy of CT in the T staging of 32 evaluable patients with pancreatic or periampullary carcinoma

		CT	
		- ve	+ ve
Outcome	- ve	7	8
	+ ve	5	12

Table 5.1.3

Diagnostic accuracy of laparoscopy and LapUS in the T staging of 35 evaluable patients with pancreatic or periampullary carcinoma

		LapUS	
		- ve	+ ve
Outcome	- ve	16	0
	+ ve	6	13

Table 5.1.4

Diagnostic accuracy of SVA in the T staging of 31 evaluable patients with pancreatic or periampullary carcinoma

		SVA	
		- ve	+ ve
Outcome	- ve	9	4
	+ ve	6	12

Angiography failed to detect local tumour unresectability due to proven portal vein invasion or encasement in two out of six cases. The other false negative examinations were due to invasion of the peripancreatic soft tissues (hepatoduodenal ligament, mesenteric root and / or retropancreatic / retroduodenal fascia).

TABLE 5.2

Diagnostic accuracy of staging investigations in predicting tumour unresectability according to T stage in 35 patients with pancreatic or periampullary carcinoma

	Sensitivity	Specificity	PPV	NPV
USS	0.60	0.64*	0.66	0.58
CT	0.71	0.47‡	0.61*	0.58
LapUS	0.68	1.00	1.00	0.73
SVA	0.67	0.69	0.72	0.64

* $P \leq 0.05$; ‡ $P \leq 0.005$ (USS / CT *versus* LapUS)

5.3.4 Evaluation of N stage

Nodal status was evaluable in 27 patients, seven of whom had proven regional lymph node metastases at laparoscopy (three patients), laparotomy (two patients) or on histopathological examination of the pancreatic resection specimen in two patients (prevalence of N1 stage 26%). The sites of the involved nodes were para aortic (three patients), hilar (two patients), retroduodenal (two patients), mesenteric root (two patients) and / or peripancreatic tissues (two patients). The validated results of the various staging investigations in predicting tumour resectability by N stage are shown as 2 x 2 contingency matrices in Tables 5.3.1 - 5.3.4. The derived summary measures of diagnostic accuracy for N staging are summarised in Table 5.4.

Failure to detect lymph node metastases was associated with all four investigations (sensitivity range 20-83%), while 'false positive' results were also obtained with USS (two patients), CT (five patients) and LapUS (four patients), where histopathology revealed lymph node enlargement ≥ 10 mm to be due to reactive hyperplasia.

Table 5.3.1
Diagnostic accuracy of USS in the N staging of 19 evaluable patients with pancreatic or periampullary carcinoma

		USS	
		- ve	+ ve
Outcome	- ve	11	2
	+ ve	2	4

Table 5.3.2

Diagnostic accuracy of CT in the N staging of 23 evaluable patients with pancreatic or periampullary carcinoma

		CT	
		- ve	+ ve
Outcome	- ve	12	5
	+ ve	1	5

Table 5.3.3

Diagnostic accuracy of LapUS in the N staging of 27 evaluable patients with pancreatic or periampullary carcinoma

		LapUS	
		- ve	+ ve
Outcome	- ve	16	4
	+ ve	2	5

Table 5.3.4

Diagnostic accuracy of SVA in the N staging of 21 evaluable patients with pancreatic or periampullary carcinoma

		SVA	
		- ve	+ ve
Outcome	- ve	16	0
	+ ve	4	1

TABLE 5.4

Diagnostic accuracy of staging investigations in predicting tumour unresectability according to N stage in 27 patients with pancreatic or periampullary carcinoma

	Sensitivity	Specificity	PPV	NPV
USS	0.67	0.85	0.61	0.88
CT	0.83	0.71*	0.50	0.92
LapUS	0.71	0.80	0.56	0.89
SVA	0.20	1.00	1.00	0.78

* $P \leq 0.05$ (SVA versus CT)

5.3.5 Evaluation of M stage

M stage was evaluable in 43 patients, of whom 16 were shown to have liver and / or peritoneal metastases following biopsy at laparoscopy (15 patients) or laparotomy (one patient) (prevalence of M_1 stage 37%). Metastatic lesions were visible during laparoscopy in 15 patients. A small malignant lesion on the edge of hepatic segment IV which, inexplicably, had not been detected during laparoscopy was discovered at laparotomy in one patient. Laparoscopic ultrasonography was the only modality to have detected small intraparenchymal liver metastases in seven out of 15 patients, although laparoscopically visible surface lesions were also present in all these cases. In 10 patients, both USS and CT failed to detect intraabdominal metastatic lesions which were frequently very small (range 1-15mm diameter). There was one 'false positive' CT examination in which a patient with intrahepatic duct dilatation was interpreted as having liver metastases. The validated results of the various staging investigations in predicting tumour resectability by M stage are shown as 2 x 2 contingency matrices in Tables 5.5.1 - 5.5.4. The derived summary measures of diagnostic accuracy for M staging are summarised in Table 5.6.

The sensitivity and predictive value of a negative result were significantly superior for laparoscopic staging of metastatic disease compared with either USS or CT (Table 5.6). Of the four patients with metastases who underwent SVA, none were identified, and there were no false positive results.

Table 5.5.1

Diagnostic accuracy of USS in the M staging of 32 evaluable patients with pancreatic or periampullary carcinoma

		USS	
		- ve	+ ve
Outcome	- ve	18	0
	+ ve	10	4

Table 5.5.2

Diagnostic accuracy of CT in the M staging of 39 evaluable patients with pancreatic or periampullary carcinoma

		CT	
		- ve	+ ve
Outcome	- ve	23	1
	+ ve	10	5

Table 5.5.3

Diagnostic accuracy of LapUS in the M staging of 43 evaluable patients with pancreatic or periampullary carcinoma

		LapUS	
		- ve	+ ve
Outcome	- ve	27	0
	+ ve	1	15

Table 5.5.4

Diagnostic accuracy of SVA in the M staging of 27 evaluable patients with pancreatic or periampullary carcinoma

		SVA	
		- ve	+ ve
Outcome	- ve	23	0
	+ ve	4	0

TABLE 5.6

Diagnostic accuracy of staging investigations in predicting tumour unresectability according to M stage in 43 patients with pancreatic or periampullary carcinoma

	Sensitivity	Specificity	PPV	NPV
USS	0.29§	1.00	1.00	0.71†
CT	0.33‡	0.96	0.83	0.59*
LapUS	0.94	1.00	1.00	0.96
SVA	0.00§	1.00	-	-

* $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.005$; § $P \leq 0.001$ (USS / CT / SVA versus LapUS)

5.3.6 Evaluation of overall tumour resectability

Fourteen patients were considered to have resectable tumours (i.e. 72% prevalence of unresectability). Laparoscopy with LapUS was the most reliable modality in determining overall tumour unresectability (Table 5.8), with overall positive and negative predictive values of 97% and 68%. Laparoscopic ultrasonography correctly upstaged disease following a 'negative' laparoscopy in patients with unresectable tumours due to nodal metastases or local invasion in 14 patients (28%). One patient

was staged overall as 'false positive' by LapUS on account of enlarged hilar lymph nodes (12 mm maximum diameter) which were incorrectly interpreted as metastatic.

There were six instances where LapUS failed to identify factors precluding curative resection when all factors were taken into consideration. Invasion of the portal vein had not been predicted in three patients (see Section 5.3.3). Infiltration of the posterior wall of the stomach was undetected in one patient, retropancreatic fat invasion was discovered in the distal pancreatectomy specimen of one patient and malignant peripancreatic lymphadenopathy (14 mm maximum node diameter) was demonstrated in the pancreaticoduodenectomy specimen of the remaining patient.

The validated results of the various staging investigations in predicting overall tumour resectability are shown as 2 x 2 contingency matrices in Tables 5.7.1 - 5.7.4. The derived summary measures of diagnostic accuracy for overall staging are summarised in Table 5.8.

Table 5.7.1
Diagnostic accuracy of USS in the overall staging of 39 evaluable patients with pancreatic or periampullary carcinoma

		USS	
		- ve	+ ve
Outcome	- ve	5	4
	+ ve	10	20

Table 5.7.2

Diagnostic accuracy of CT in the overall staging of 45 evaluable patients with pancreatic or periampullary carcinoma

		CT	
		- ve	+ ve
Outcome	- ve	7	6
	+ ve	11	21

Table 5.7.3

Diagnostic accuracy of LapUS in the overall staging of 50 evaluable patients with pancreatic or periampullary carcinoma

		LapUS	
		- ve	+ ve
Outcome	- ve	13	1
	+ ve	6	30

Table 5.7.4

Diagnostic accuracy of SVA in the overall staging of 32 evaluable patients with pancreatic or periampullary carcinoma

		SVA	
		- ve	+ ve
Outcome	- ve	7	4
	+ ve	8	13

TABLE 5.8

Diagnostic accuracy of staging investigations in predicting overall tumour unresectability in 50 patients with pancreatic or periampullary carcinoma

	Sensitivity	Specificity	PPV	NPV
USS	0.67	0.56	0.80	0.40
CT	0.66	0.54‡	0.79*	0.38
LapUS	0.83	0.93	0.97	0.68
SVA	0.62	0.64	0.82	0.40

* $P \leq 0.05$; ‡ $P \leq 0.005$ (CT versus LapUS)

5.4 Discussion

Staging laparoscopy with LapUS under general anaesthesia was shown to be a safe and effective means of assessing patients with pancreatic and periampullary carcinoma under consideration for definitive surgical intervention. The post operative deaths of two patients at six days and two weeks was considered to reflect their poor general health and advanced malignancy rather than any specific complication of the laparoscopic procedure. Although their rapid decline might be construed as reflecting injudicious selection for such an invasive procedure, the diagnosis was uncertain in each case, and both had expressed a wish for further investigation to clarify the prognosis. The two instances of malignant port site seeding are a cause for concern. The implications of this complication are considered more fully in Section of 6.4 of Study 4[301, 302].

5.4.1 Detection of the primary lesion

In this study, the high sensitivity of LapUS in revealing focal pancreatic or periampullary tumour masses in 96% of cases reflects the utility of high resolution contact sonography. This finding is similar to that reported from studies of EUS (see Section 1.2.10) in which reported diagnostic sensitivities of 98-100% were obtained in patients with established diagnoses of pancreatic or periampullary cancer[134, 136, 140]. However, such study designs inevitably overestimate the efficacy of such

diagnostic tests, as was illustrated by two other studies of EUS in which patients with non-neoplastic lesions (e.g. chronic pancreatitis) comprised 30% and 23% of the study populations respectively[138, 263]. Diagnostic sensitivities of 85% and 96%, and specificities of 80% and 73% were reported, highlighting the problem in differentiating malignant and benign focal pancreatic lesions in the wider patient population, and reflecting the need for reliable tissue sampling techniques. Thus, while it was not possible to investigate these wider issues in the present study, the observation that LapUS was able to image the underlying abnormality in nearly all cases underscores its utility in high-resolution imaging of the pancreas and periampullary region.

The improvement in the diagnostic sensitivity of LapUS from 82% in Study 2 to 96% in the present study presumably reflects increasing experience with the technique (*i.e.* "the learning curve"), as well as improvements in LapUS equipment. Nevertheless, the failure in two cases to identify pancreatic cancers, which in retrospect appeared echographically diffuse and isoechoic, has identified a diagnostic pitfall. Interestingly, periampullary cancers were readily identified despite their isoechoity and relatively small dimensions, due to dilatation of the pancreatic and bile ducts which could be traced to their abrupt termination at the site of obstruction.

It was also noteworthy that USS, CT and SVA were less performant than LapUS in establishing a diagnosis. The 82% sensitivity of USS, and the 93% sensitivity of CT should be considered in the context of previous studies which cite corresponding figures in the range 51-98% (Table 1.1), and 69-99% (Table 1.3) respectively. The 66% diagnostic sensitivity of SVA obtained in the present study compared favourably with the experience of others (range 33-72%[137, 172-175]) as discussed in Section 1.2.6. Nevertheless, the deficiencies of SVA as a diagnostic tool have again been emphasised, and these observations have reinforced the generalisation that normal visceral angiograms and portal phase venograms are not able to exclude pancreatic or periampullary tumours.

5.4.2 Detection of intraabdominal metastases

This study verified the findings of Study 2 that staging laparoscopy is highly sensitive (94%) in detecting 'occult' intraabdominal metastases in patients with pancreatic or periampullary cancer. Furthermore, the significant advantage of laparoscopy in this role was demonstrated conclusively by prospective blind

comparison with USS, CT and SVA. In common with Study 2, most other reports of staging laparoscopy in the staging of pancreatic cancer were comprised of patients selected retrospectively by USS and / or CT on the basis that they were free of metastatic disease[83-85, 251, 295, 298, 299]. In the present study, prospective standardisation of the methods of scanning and reporting had little impact on the failure of USS and CT to detect metastases in approximately two-thirds of cases examined. This demonstrates beyond doubt the limitations of these conventional imaging modalities in the detection of "occult" intraabdominal metastases.

The advent of more refined CT scanning techniques, in particular helical CT scanning (see Section 1.2.4), raises the question of whether this technology would have been more succesful in identifying metastatic disease than the conventional intravenous contrast enhanced CT utilised herein. A further study comparing helical CT with laparoscopy with or without LapUS would be required to determine this issue. Neverthless, of the two patients examined using helical CT scanning in the present study, a laparoscopically detected liver metastasis of the left hepatic lobe was missed in one patient. To date there has been only one published study of helical CT in the staging of pancreatic cancer[303]. Liver metastases were proven in 13 out of the 35 patients studied (37%), in five of whom (38%) helical CT failed to detect such lesions "...owing to their small size (between 1-3 mm) and only proved intraoperatively or laparoscopically"[303]. Based upon this limited available evidence it seems unlikely that helical CT will diminish the role of staging laparoscopy in detecting such small lesions in patients with pancreatic cancer.

The investigative algorithm employed in the present study necessitated the avoidance of SVA in most patients with detected metastases, and was thus a source of bias against its ability to fulfill this role. Neverthless, SVA failed to identify metastases in all four such patients examined. This is not at variance with the findings of other studies in which SVA was also shown to have been ineffective in detecting hepatic metastases, with reported sensitivities of 33-47%[174, 175, 180]. However, the tendency of SVA, in a previous report from this department[180], to over-diagnose hepatic metastases was not observed in the present study, in which there were no such false positives.

The principle that LapUS may identify intrahepatic metastases which are imperceptible to USS, CT and laparoscopy was illustrated in seven out of the 16 patients with M_1 stage disease on a 'lesion-by-lesion' basis. However, in agreement with the results of Study 2, the impact of LapUS as the only means of diagnosing

metastatic disease on a 'patient by patient' basis was once again marginal. As discussed in Section 4.4, these findings differ from those of Bemelman and colleagues for whom LapUS was the sole means of detecting intrahepatic metastases in approximately a third of such cases[298]. While the overall incidence of liver metastases in the present series was similar to that reported by Bemelman et al, the relatively higher sensitivity of laparoscopy observed in our experience, as opposed to that of laparoscopy *and* LapUS in the Dutch study, could have been the result of our rigorous laparoscopic technique. This included the use of a 30° telescope to scrutinise the subphrenic spaces and inferior aspects of the left and right hepatic lobes (as described in Section 2.3). Unfortunately, details of the laparoscopic technique employed in their study were not provided[298], although the authors did allude to difficulty in the laparoscopic diagnosis of metastases "on top of the dome or upper border of the liver". An alternative possibility is that LapUS failed to identify "occult" metastases in additional patients in our study. As discussed in Section 4.4, the ultimate arbiter of false negativity would require detailed long-term follow-up and study of patterns of tumour recurrence. Such measures were not available in any of these studies, although our routine use of high-resolution IOUS to examine the liver for metastases during laparotomy (*c.f.* Bemelman et al[298]) makes this a less likely explanation.

5.4.3 Evaluation of T stage

Having observed stringent criteria for defining T stage resectability, LapUS was found to be at least as predictive as USS, CT and SVA in determining resectability by T stage. However, the identification of six false negative results out of 19 cases (32%) of T_2-T_3 tumour unresectability (due to peripancreatic soft tissue invasion or portal vein involvement) has indicated the fallibility LapUS in this role. As regards the diagnosis of portal vein invasion, large (i.e. > 5 cm diameter) hypoechoic tumours and diffusely infiltrative, isoechoic tumours have been identified as pitfalls. It is pertinent to note the former scenario has also been identified as limiting EUS in the staging of vascular invasion[138, 264]. While such tumours are unlikely to be resectable for cure, their recognition and interpretation may improve with experience. Extrapancreatic soft tissue invasion also prove to be difficult to define reliably by LapUS. While loss of the hyperechoic serosal-tumour interface was apparent in retrospect following IOUS in the patient with a pancreatic body carcinoma infiltrating the posterior wall of the stomach, no sonographic features for the identification of diffuse retropancreatic infiltration were apparent. This is

probably because the sonographic interface between the pancreatic parenchyma and the retroperitoneal tissues is less well defined compared with those delineating vascular and ductal structures. This aspect of the LapUS examination remains, therefore, a potential weakness, although it was of clinical significance in a minority of patients.

Apart from obvious errors in the execution and interpretation of this operator dependent technique, other factors should also be considered regarding the failure of LapUS to define accurately local tumour invasion. Firstly, high-resolution contact ultrasonography does not always abolish the ill-defined global degradation of image quality discussed in the context of USS in Section 1.2.8[231-233]. This concept is largely subjective and difficult to quantify, and is usually indicated by the ultrasonographer experiencing a "difficult examination" in a patient who "does not scan well". This factor may be compounded by technical difficulties during LapUS such as those associated with the adhesions of previous surgery or the presence of a large fatty omentum overlying the pancreas. Several of the LapUS examinations which yielded false negative results fell into this category, although precise documentation of these effects had not been undertaken routinely during the study.

Secondly, the decision of an experienced pancreatic surgeon during exploratory laparotomy and trial pancreatic dissection was adopted as the arbiter of local tumour resectability, although this also must be regarded ultimately as an essentially subjective measure. Notwithstanding that this surgical decision is the endpoint which matters most to the patients' immediate fate in clinical practice, this concept has not been validated in more objective terms. Although other workers have been prepared to perform portal vein resections when confronted with apparent locally invasive tumour, and report having refuted venous invasion on histopathological examination[298], such instances are rare and the departmental policy remains one of avoidance of this aggressive approach for the reasons discussed in Sections 1.1.1 and 1.1.2. It is therefore highly unlikely that surgical overdiagnosis of vascular invasion was a factor in the work presented in this thesis. Alternatively, several surgeons have identified the fallibility of early trial pancreatic dissection in identifying tumour invasion of the lateral aspect of the spleno-porto-mesenteric venous junction, and cite the occasional need to perform portal vein resection when this is discovered unexpectedly following transection of the pancreatic neck (*i.e.* "the point of no return")[35, 285, 304]. However, there were no such instances where this scenario occured unexpectedly because of prior understaging, nor were positive resection margins documented in this site.

Reassuringly, LapUS did not overstage local tumour status in this study, as reflected by a specificity and PPV of 100%. Features of portal-superior mesenteric vein invasion such as occlusion, stenosis, loss of the hyperechoic vein-parenchymal interface, luminal invasion and vessel encasement prove to be reliable in this respect. This high specificity for LapUS was supported by the findings of Bemelman and colleagues who correctly identify locally unresectable tumours in 13 out of 14 cases, their one false positive result occuring in a patient with retroperitoneal radiation fibrosis[298].

In addition to these encouraging results, the rationale for LapUS in the local staging of pancreatic and periampullary cancer appears to have been strengthened by the parallel experience of those working with EUS, inasmuch as the two techniques share the fundamental principle of high-resolution contact sonography. The observations of the present study concur with the findings of Snady and colleagues who simultaneously investigated EUS criteria for vascular invasion in 38 patients with pancreatic tumours[305]. They defined three such criteria (vessel obliteration with venous collaterals, luminal tumour invasion and abnormal vessel contour with loss of vessel-parenchyma sonographic interface), and reported having observed at least one of them in the 21 patients subsequently shown to have vascular invasion. Conversely, none of these defined criteria were said to have been present in the 17 patients with resectable tumours[305].

Other studies of EUS in the evaluation of portal vein invasion[134, 136, 138, 140] also indicate few false negatives (sensitivity 88-100%, NPV 89-100%; see Table 1.8), although false positives were sometimes a problem with this technique (specificity 65-97%, PPV 83-100%; see Table 1.8). In Palazzo's series of 49 patients with pancreatic cancer, five false positive EUS examinations were attributed to large pancreatic tumours and duodenal infiltration, resulting in failure of duodenal intubation and a reliance on oblique sonograms, with consequent failure to image the tumour periphery[138]. Notwithstanding the occasional problem with upper abdominal adhesions, LapUS should in theory be less prone to such limitations since the transducer is not limited to the duodenal lumen and has a far greater range of manoeuvre. Thus, in the hands of experienced operators, high resolution contact sonography appears an appropriate method for defining local tumour stage whether applied during laparoscopy or endoscopy.

No evidence was provided in this study to support a definitive role for USS in the locoregional staging of patients with pancreatic or periampullary cancer. Although

Campbell and Wilsons' retrospective study concluded that USS was an effective staging tool in their institution, having correctly identified vascular invasion in 12 out of 16 patients (75%) with no false positives[131], the results of the present study did not reproduce these findings. Both under- and overestimation of T stage was observed, giving respective positive and negative predictive values of 66% and 58%, and a specificity which was significantly inferior to that of LapUS (Table 5.2). Operator dependency and technical considerations were not an issue. All USS examinations were performed by a defined consultant radiologist, who is a recognised by his peers as an expert sonographer, using "state of the art" equipment including Doppler and colour Doppler techniques to evaluate the peripancreatic vasculature. This experience reflects more closely the experience with USS reported in a Norwegian multi-centre review[137], and in several prospective comparative studies investigating USS alongside EUS in the staging of pancreatic and periampullary cancer[136, 138, 140] (see Table 1.2). Nevertheless, this experience does not detract from the utility of USS as a first-line method for confirming the diagnosis and defining the level of extrahepatic biliary obstruction, and for screening the liver for overt metastases. Convincing evidence supporting this primary role for USS already exists as discussed in Section 1.2.3, and was not evaluated further in this thesis.

While the performance of CT in predicting tumour *resectability* was shown to have been similar to that of LapUS, and in this respect was not at variance with the results reported by Freeny and colleagues[150, 154], the present study also identified a tendency for CT to overstage local tumour status, particularly with regard to peripancreatic fat invasion of (six patients) and portal vein invasion (three patients). This was manifested by a specificity (47%) and PPV (61%) which were significantly worse compared with the performance of LapUS (100%). Although other workers have expressed similar concerns regading the specificity of CT in the staging of pancreatic cancer[135, 152, 155], these studies were retrospective, and confounded by suboptimal scanning techniques such as the use of non-enhanced CT. Nevertheless, these flaws were avoided in the present study, which observed a similar technique to that described by Freeny et al[150, 154], while other workers utilising updated CT protocols have also documented false positive CT examinations in the locoregional staging of pancreatic and periampullary cancer[86, 136, 138, 156] (see Table 1.4).

These facts should be viewed with some concern as CT is widely regarded as the staging investigation of choice, particularly in the United States. A national survey of patterns of care for pancreatic cancer comprising 16 942 patients in 978 American

institutions reported that abdominal CT was performed in 79% of patients during 1983-1985, increasing to 88% of patients during 1990[294]. As discussed in Section 1.2.4, the main proponents of CT as a reliable means of staging of pancreatic cancer have claimed a high specificity for the technique[150, 154]. Although no false positives were reported amongst the 53 patients who did undergo surgical evaluation, final validation of tumour unresectability by exploratory laparotomy was performed in less than a third of Freeny's patients despite the incidence of local tumour invasion having been deemed to be 68%[150]. The results of the present study highlight the importance of prospective validation, by surgical exploration if necessary, of tumour unresectability when evaluating staging modalities. A relatively low resectability rate of 28% reflects this policy.

As discussed above, more advanced CT techniques have now superseded the methods used in this study, which nevertheless remain the mainstay of cross sectional imaging in many hospitals. Thin-section CT of the pancreas using 1.5 mm slice thickness at 5 mm intervals was recently reported by Fuhrman et al[306] to have correctly identified patients with resectable pancreatic carcinomas in 88% of cases. However, their contention that thin-section CT "represents the only accurate method" for the preoperative evaluation of vascular invasion can be criticised for several reasons. Their study should be regarded in the context of an aggressive surgical policy where portal vein resection was not necessarily considered a contraindication to curative resection, and mere *patency* of the superior mesenteric-portal vein was accepted as being indicative of resectability. Furthermore, having deemed it "inappropriate to surgically confirm unresectability", exploratory laparotomy was performed in only 42 out of 145 patients[306]. Their consequent resectability rate of 88% reflected this failure to validate positive CT findings[307, 308]. Certainly, the results of the present study refute Fuhrman's contention that "the accuracy of CT to predict unresectability is well established and does not need further confirmation"[306]. Gmeinwieser and colleagues recently reported their experience with "state of the art" helical CT in the evaluation of vascular invasion in 38 patients with pancreatic cancer[303]. Although the technique performed well in its assessment of portal vein involvement (sensitivity 91%, specificity 94%), complete avoidance of both false negative and false positive examinations proved elusive[303].

The present study has provided further evidence against the routine use of SVA in the preoperative assessment of patients with pancreatic and periampullary malignancy. False negative examinations were largely due to the inability of SVA to identify peripancreatic soft tissue invasion, whereas the diagnosis of vascular

encasement from the appearance of subtle narrowing in the vicinity of the superior mesenteric-portal venous junction yielded four false positives. This scenario has been documented previously[35, 159, 180], while Dooley and colleagues described "notching" in the vicinity of the portal-superior mesenteric venous junction as a "normal variant" of SVA which could be misconstrued as tumour encasement[160]. Therefore, while SVA contributed little additional useful information regarding T stage compared with less invasive investigations, serious concern has again been raised regarding its propensity to overestimate local tumour stage and so risk denying "curative" resections to patients with potentially resectable disease.

The utility of SVA in providing a "roadmap" of the peripancreatic vascular anatomy was discussed in Section 1.2.6 (see Table 1.6). In this regard, the contribution of SVA, and that of LapUS, in this role was investigated in Study 1, and discussed further in Section 3.4.2. Angiography provided clinically useful information in one other patient, in whom coeliac and superior mesenteric arterial occlusion was demonstrated. However, this diagnosis was also apparent during intraoperative inspection and palpation of the splanchnic vasculature, and its clinical benefit was therefore marginal.

5.4.4 Evaluation of lymph node status

The difficulty of accurately staging regional lymph node metastases in patients with pancreatic and periampullary cancer has again been demonstrated. Also, the relatively small number of patients defined as having positive regional nodes inhibits the formulation of definite conclusions regarding the diagnostic accuracies of the various investigations. The occurence of both false positive and false negative results for each of USS, CT and LapUS concurs with the experience of those evaluating EUS in confirming that malignant lymph node enlargement cannot be reliably identified on the basis of lymph node size alone[136, 138, 262, 265]. Nodal enlargement is frequently the result of reactive hyperplasia, and conversely, nodes of smaller size may harbour micrometastases. Consequently, patients with pancreatic or periampullary cancer should not be denied surgical assessment of resectability on the basis of regional lymphadenopathy alone in the absence of biopsy confirmation of nodal malignancy, and it is pertinent to note that this was not the case with any of the patients in this study.

5.4.5 Overall tumour staging

Critical evaluation of LapUS in comparison with USS, CT and SVA has broadly reproduced the results of Study 2, and those of Bemelman and colleagues[298] in the overall staging of patients with pancreatic and periampullary cancer. The sensitivity of laparoscopy and LapUS in identifying overall tumour unresectability was 83%, compared with 88% in the earlier study, probably reflecting the more stringent methods of validation in the present study. Nevertheless, high specificity was retained, the only significant errors in tumour overstaging occuring in the assessment of node status. Indeed, the specificity and PPV calculated for laparoscopy and LapUS (93% and 97%) were a statistically significant improvement over CT (54% and 79%) (Table 5.8).

The advantage of laparoscopy with LapUS over USS, CT and SVA in the overall staging of patients with pancreatic and periampullary carcinoma lies predominantly with the significantly superior sensitivity of laparoscopy in identifying intraabdominal metastases and facilitating their biopsy. The unique role of laparoscopy in this respect has been proven, and justifies its mandatory use prior to laparotomy in patients with potentially resectable lesions, irrespective of the results of USS and CT. While the sensitivity and NPV of LapUS in predicting tumour resectability are roughly comparable to those of USS and CT, its superior specificity and PPV in defining stigmata of unresectability support its adoption in the staging algorithm for such patients.

Chapter 6 Study 4

Laparoscopic peritoneal cytology in the evaluation of patients with carcinoma of the pancreas and periampullary region

6.1 INTRODUCTION

As discussed in Section 1.2.9, it has been suggested that peritoneal cytology may have an important role in the preoperative assessment of patients with pancreatic cancer, both as an index of tumour resectability, and as a determinant of prognosis[256, 257]. Furthermore, an association between positive peritoneal cytology and preceding operative tumour manipulation[256] or needle biopsy[257] has been hypothesised, implicating these manoeuvres in the dissemination of malignant cells. However, in previous studies of peritoneal cytology in patients with pancreatic cancer, peritoneal washings were either obtained during laparotomy[309], or during laparoscopy in only a subset of patients[257]. If cytological analysis of peritoneal washings is to be useful in the preoperative staging of patients with pancreatic and periampullary cancer, the reproducibility of the aforementioned results must be demonstrated in the context of staging laparoscopy.

A prospective study was performed in parallel with Study 3 to evaluate the contribution of peritoneal cytology performed exclusively during staging laparoscopy. The aims of the study were to evaluate the incidence of positive peritoneal cytology in this group of patients, to investigate patterns of tumour spread associated with positive peritoneal cytology and to assess the impact of positive peritoneal cytology on short term survival. Also, the reproducibility of the results of the routine hospital cytopathology service was assessed.

6.2 PATIENTS AND METHODS

6.2.1 Patient details

Forty six patients of the 50 patients with carcinoma of the pancreas or periampullary region in Study 3 who underwent staging laparoscopy with LapUS between March 1993 and April 1995 were evaluated. There were 29 men; median age 61 years;

range 42-78 years. Eight patients were classified as having periampullary tumours where endoscopic, operative and pathological findings indicated the carcinoma to be arising predominantly within the papillary region.

A histological diagnosis of pancreatic or periampullary carcinoma was obtained in 38 patients by percutaneous (four patients) or operative (n=10) needle biopsy of the pancreas, laparoscopic (n=13) or operative (one patient) biopsy of metastatic lesions in the liver, serosal surfaces or regional lymph nodes, histopathological examination of the pancreatic resection specimen (n=13) and / or endoluminal biopsy of periampullary lesions (n=10). As discussed in Section 5.2.1, no histological diagnosis was obtained in the other six patients, although a pancreatic mass lesion was documented by imaging investigations, and death from carcinomatosis was observed in each case (crude mean survival 34 weeks (range 12 - 67 weeks)). The primary tumour was situated in the pancreatic head (32 patients), pancreatic body (five patients), pancreatic head and body (one patient) and periampullary region (eight patients). A biliary stent had been inserted in thirty patients by the endoscopic (22 patients) or percutaneous route (eight patients), and a cholecystjejunostomy had previously been performed in one patient at the referring hospital.

6.2.2 Laparoscopic peritoneal cytology

Laparoscopic peritoneal cytology was not performed in four of the 50 consecutive patients studied in Study 3 due to breaches of protocol.

Laparoscopy with LapUS was performed as described in Section 2.3. Peritoneal washings, or samples of ascitic fluid, were retrieved during laparoscopy for cytological anlysis as described in Section 2.4 (see Figure 33B). Ascites was defined as being present when > 100 ml of free intraperitoneal fluid was discovered during laparoscopy. The samples were prepared, and interpretation of the slides was performed, as described in Section 2.4.

All cytological examinations were performed initially as part of the routine hospital service by a number of cytopathologists, and were later reviewed independently by a defined cytologist (EMcG) who was both experienced in the technique and blinded to patient details.

6.2.3 Validation of tumour resectability

As in Study 3, the end-point of overall tumour resectability was determined according to the adopted staging convention defined in Table 2.1 / Section 2.1.1[272]. Validation of tumour resectability was by laparoscopic biopsy of intraabdominal metastases to distant sites (n=13) or regional lymph nodes (n=2), by surgical assessment of resectability (27 patients), by histopathological examination of the resection specimen with regard to involvement of the planes of transection and lymph nodes with tumour (13 patients), and by the corroborating findings of USS / CT / LapUS and SVA (five patients).

Summary measures of diagnostic accuracy were calculated and compared as described in Section 2.1.2 (Table 2.2). Actuarial survival was calculated for patients with positive and negative peritoneal cytology by life table analysis and Kaplan Meier plotting.

6.3 RESULTS

6.3.1 Patient outcome

The decision regarding tumour resectability, and the treatment received by the 46 patients in whom laparoscopic peritoneal cytology was performed, is summarised in Table 6.1. For the purposes of this study, 13 patients (28%) were deemed to have resectable disease as confirmed at laparotomy and histopathological examination of resection specimens. As discussed in Section 5.3.1 of Study 3, three patients were considered during exploratory laparotomy to have potentially resectable tumours, although pancreatoduodenectomy was considered inappropriate for reasons not related to tumour extent. Also, three patients who underwent pancreatic resection were subsequently reclassified as having unresectable disease due to histopathological evidence for retroperitoneal tumour invasion (one patient), and overt regional lymph node metastases (n=2).

Thirty three patients were considered unresectable (72%). Laparoscopic biopsy demonstrated distant metastases to the liver and / or peritoneum in 13 patients, and malignant regional lymphadenopathy in two patients. Sixteen patients were shown to have locally unresectable tumour, of whom nine underwent palliative biliary and / or duodenal bypass surgery. One patient with previously unsuspected malignant

Table 6.1

Outcome for 46 patients with pancreatic or periampullary carcinoma in whom laparoscopic peritoneal cytology was performed

Outcome	Number
"Resectable"	13
Whipple operation	7
Transduodenal local resection	3
Biliary bypass ± gastroenterostomy	3
"Unresectable" - M_1 / N_1	17
No operation	14
Whipple operation	1
Total pancreatectomy	1
Biliary bypass and gastroenterostomy	1
"Unresectable" - T_{2-3}	16
No operation	5
Distal Pancreatectomy	1
Laparotomy and biopsy	1
Biliary bypass and gastroenterostomy	5
Gastroenterostomy alone	2
Biliary bypass alone	2

infiltration of the posterior stomach wall from carcinoma of the pancreatic body underwent laparotomy and biopsy.

6.3.2 Peritoneal Cytology

The results of independent review of the cytology specimens concurred with those reported by the routine hospital service in all cases. Laparoscopic peritoneal cytology was positive for the presence of malignant cells in seven patients (15%) (Figure 44). Review of the laparoscopic peritoneal cytology preparations revealed the following additional observations: a bloodstained sample was reported in 36 cases (78%), the preparations contained scanty mesothelial cells making satisfactory

interpretation difficult in six cases (13%), and degenerative mesothelial cells were present in 11 cases (24%). Large amounts of an amorphous material which was presumed to represent a fibrinous or mucoid exudate was present in 23 patients (50%) (Figure 45). In 27 patients (59%), inflammatory or reactive mesothelial cells were observed in large numbers (Figure 45), the interpretation of which required particular care to avoid confusion with malignant cells. However, there was no instance where a false positive result was identified under these circumstances.

All seven patients with positive peritoneal cytology had laparoscopic evidence of tumour unresectability due to extrapancreatic dissemination of malignancy (lymph node metastases in one patient; peritoneal metastases in four and / or liver metastases in four. *i.e.* stage III-IV disease). Negative peritoneal cytology results were obtained in 39 patients, 13 of whom were deemed to have resectable tumours (i.e. predictive value 33%). These results are expressed in terms of summary measures of diagnostic accuracy in Table 6.2.

Table 6.2
Diagnostic accuracy of laparoscopic peritoneal cytology in the staging of 46 patients with pancreatic or periampullary carcinoma

		Laparoscopic peritoneal cytology	
		Negative	Positive
Outcome	Resectable	13	-
	Unresectable	26	7

Sensitivity = 7 / 33 = 21% Specificity = 13 / 13 = 100%

PPV = 7 / 7 = 100% NPV = 13 / 39 = 33%

Positive peritoneal cytology was observed more frequently in patients with carcinoma involving the pancreatic body (three out of six patients (50%)) compared with those with tumour in the pancreatic head (four out of 28 patients (14%)), or periampullary region (none) (see Table 6.3). Malignant peritoneal cytology was also observed in three of the four patients (75%) in whom previous percutaneous pancreatic needle biopsy had been performed (*c.f.* four out of 38 patients with no

biopsy (11%)) (see Table 6.3). Twelve patients were found to have clinically undetectable free ascitic fluid during laparoscopy. Positive peritoneal cytology was

Table 6.3

Results of laparoscopic peritoneal cytology in 46 patients with pancreatic or periampullary carcinoma in relation to the tumour site and stage, and the presence of ascitic fluid and preceding percutaneous needle biopsy

	Result	
	Positive	Negative
Number of patients	7	39
Tumour site		
Periampullary	-	8
Pancreatic head	4	28
Pancreatic head & body	-	1
Pancreatic body	3	2
Previous biopsy		
Yes	3	1
No	4	38
Ascites		
Yes	6	6
No	1	33
Intraabdominal metastases *	7	10
Liver	4	7
Serosal	4	4
Nodes	1	3
Cancer stage grouping[272]		
I / II	-	30
III	1	3
IV	6	7

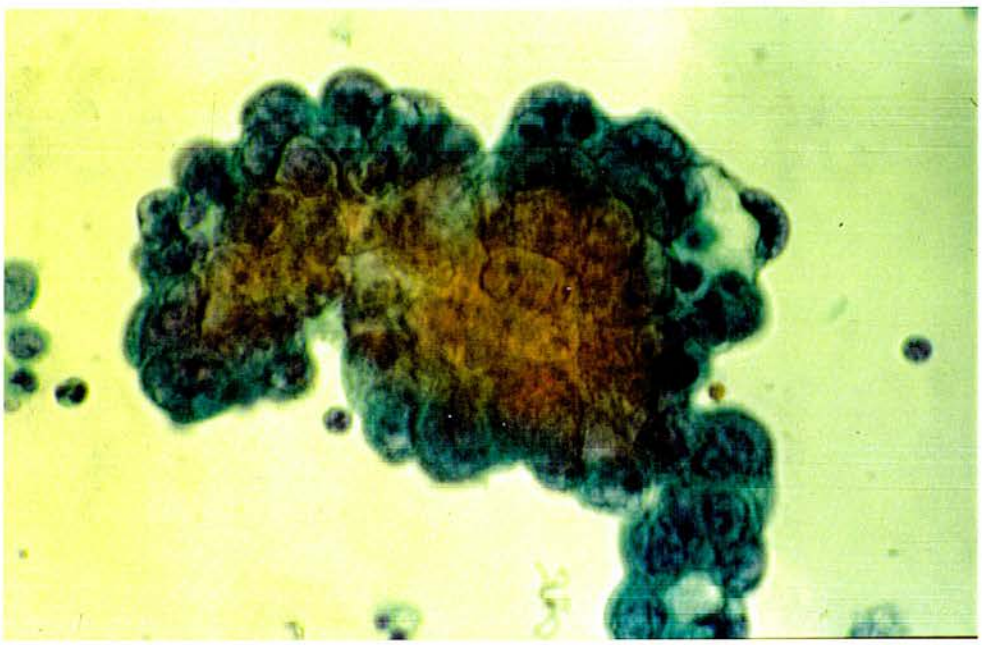
* six patients had intraabdominal metastases in more than one site

recorded in six (50%) of these patients, compared with one out of 34 patients without ascites (3%) (see Table 6.3). One patient with a periampullary carcinoma underwent pancreaticoduodenectomy with curative intent and with histologically negative resection margins following the discovery of cytology negative ascites at laparoscopy. This patient was alive and well one year later with no clinical or radiological evidence of tumour recurrence. Of the 13 patients with proven distant metastases to the liver (11 patients) and / or serosal surfaces (eight patients), peritoneal cytology was negative in seven (54%) and positive in six (46%) (see Table 6.3). Negative peritoneal cytology was obtained in all 16 patients in whom local tumour invasion (*i.e.* stage T_{2-3} unresectable) was the sole contraindication to tumour resection.

The cumulative survival of patients found to have positive laparoscopic peritoneal cytology was less than that of patients with negative peritoneal cytology (Figure 46). The median cumulative survival at three and six months was 17% and 8% for patients with positive cytology, compared with 87% and 71% respectively for those with negative cytology. All patients with positive peritoneal cytology had died by nine months, whereas 45% of those with negative cytology were still alive.

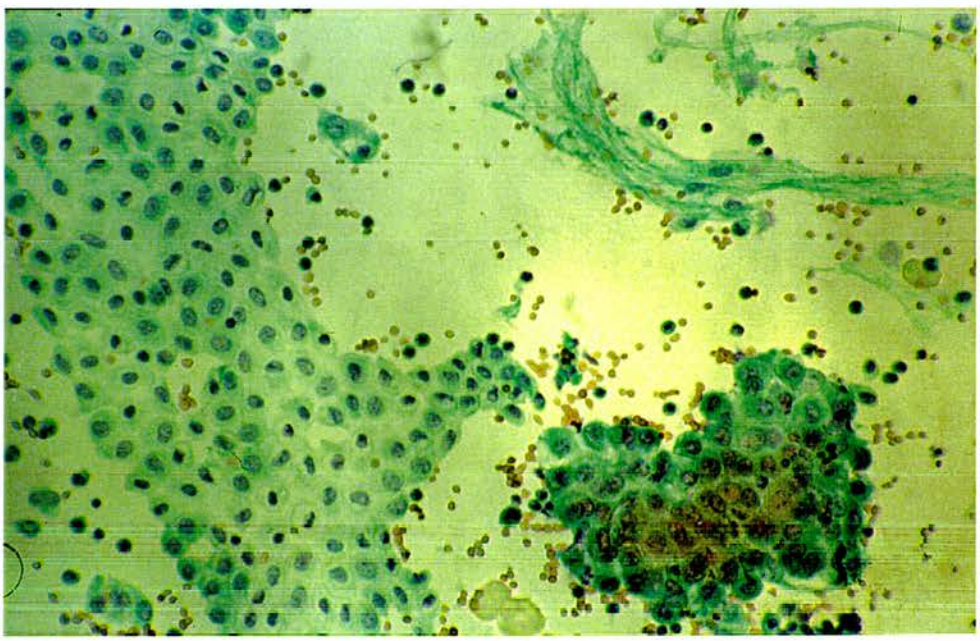
As described in Section 5.3.1, malignant port site seeding at the umbilicus was diagnosed in one patient six weeks after laparoscopy. This patient had carcinoma of the pancreatic body, and had undergone CT-guided percutaneous needle biopsy of the pancreas two weeks prior to laparoscopy with a negative yield. Peritoneal carcinomatosis, multifocal superficial liver metastases and positive peritoneal cytology had been revealed at laparoscopy. Otherwise, there were no instances of post operative morbidity attributable to the laparoscopic peritoneal cytology procedure.

Figure 44



Malignant peritoneal cytology specimen (magnified x250: Papanicalou stain). A clump of large epithelial cells of bizarre appearance showing hyperchromatic staining, nuclei with visible nucleoli of varying sizes and with visible mitotic bodies indicating an underlying adenocarcinoma.

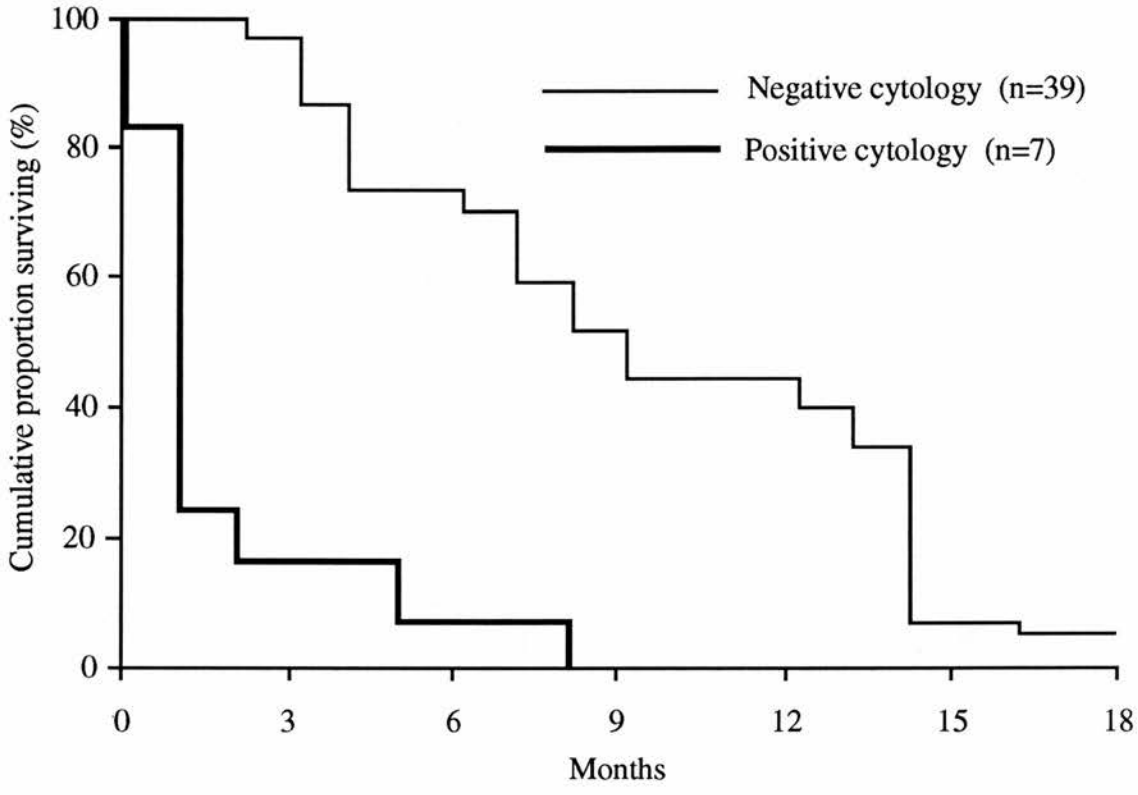
Figure 45



"Negative" peritoneal cytology specimen (magnified x1000: Papanicalou stain). A sheet of normal mesothelial cells with uniform staining and cellular morphology is situated along the left side of the photograph. Scattered erythrocytes indicate a degree of contamination with blood. There is a cluster of abnormally large cells (bottom right) exhibiting polychromasia and enlarged nuclei, although with no cellular atypia or features of malignancy. These features indicate benign reactive mesothelial cells. A strand of homogenous material and interpreted as mucoid or fibrinous exudate is also shown (top right).

Figure 46

Cumulative survival of 46 patients with pancreatic or periampullary carcinoma following laparoscopic peritoneal cytology



6.4 DISCUSSION

The incidence of positive peritoneal cytology in the present study (15%) was less than that recorded previously (25-30%) by Martin and Goellner[256] and Warshaw[257]. This difference could be due to the inclusion in the present study of eight patients with periampullary cancer, none of which were associated with malignant peritoneal cytology. However, the apparent rarity of positive peritoneal cytology in patients with pancreatic malignancy has been supported by the findings of similar work published more recently from other centres (see Table 6.4). Studies performed in Toledo, Ohio[310], the University of Milan, Italy[311] and MD Anderson Cancer Center, Houston, Texas[312] have reported positive peritoneal cytology in 8%, 13% and 7% of cases, although their resectability rates of 33-70% may reflect a high degree of patient selection. Furthermore, Warshaw's group's recent update of their experience indicated that the incidence of positive peritoneal cytology had fallen to 17%[295], compared with 30% in their earlier report[257], while their overall

resectability rate of 32% was not disimilar to that reported herein (28%). It is also pertinent to note that both these studies differ from others in that fluid samples for peritoneal cytology were obtained exclusively at laparoscopy (see Table 6.4), thus facilitating an evaluation of its specific contribution to the preoperative staging process. However, there is no obvious reason why the incidence of positive peritoneal cytology should be influenced by the method of retrieval of peritoneal washings providing that the sample is removed before the tumour is mobilised or traumatised in any way.

As with any staging investigation, the avoidance of 'false positive' results is of paramount importance and accurate interpretation of the cytological samples is critical given that the majority of lavage samples contained many mesothelial cells showing inflammatory changes. Furthermore, as cytological interpretation is a highly observer-dependent techniqe and prone to inter-observer variation. It was reassuring that independent retrospective review of the specimens by a specialist cytologist appears to have validated the accuracy of the routine hospital cytology service. Despite having deferred laparoscopic biopsies until after retrieval of peritoneal washings, significant bloodstaining was present microscopically in 78% of samples. This may reflect minor bleeding associated with trocar and port insertion, minor trauma associated with the LapUS procedure and / or a direct effect of the underying malignancy. However, bloodstaining did not prevent cytological diagnosis in any case. Degenerative mesothelial cells were observed in 24% of samples, perhaps reflecting an imperfect choice of collecting fluid. Furthermore, the adequacy of the laparoscopic peritoneal cytology technique could be questioned in the six cases (13%) where scanty mesothelial cells were present in the sample. This highlights the importance of utilising the maximum 'dwell time' that is practicable, and supports the practice of altering the position of the operating table to ensure 'agitation' of the intraperitoneal fluid, manoeuvres which were not routinely performed in the present study. Neverthless, the failure of Leach and colleagues to retrieve peritoneal washings laparoscopically in 18% of patients due to the presence of adhesions was not experienced in the present study. The observation of large quantities of an amorphous substance in a half of the samples was a new finding which does not appear to have been reported before. Its exact significance is unclear.

Although laparoscopic peritoneal cytology was found to have been insensitive (23%) in identifying patients with unresectable tumours, the predictive value of a positive result was 100% and was associated with tumour unresectability due to metastatic

Table 6.4

Summary of studies of peritoneal cytology in assessment of patients with pancreatic or periampullary carcinoma

Author and year	Positive peritoneal cytology (mode of retrieval)	Resectability rate	Prior biopsy (PPC*)	Staging information
Martin et al[256] 1986	5 / 20 = 25% (all laparotomy)	2 / 20 = 10%	N/A	Sensitivity = 28% Specificity = 100% PPV = 100% NPV = 13%
Warshaw[257] 1991	12 / 40 = 30% (laparoscopy 27) (laparotomy 13)	14 / 35 = 40%§	n = 8 (6 / 8)	Sensitivity = 43%§ Specificity = 93% PPV = 90% NPV = 52%
Lei et al[310] 1994	3 / 36 = 8% (all laparotomy)	17 / 36 = 47%	N/A	Sensitivity = 18% Specificity = 100% PPV = 100% NPV = 48%
Zerbi et al[311] 1994	2 / 15 = 13% (all laparotomy)	5 / 15 = 33%	n = 2 N/A	N/A
Fernández-del Castillo[295] 1995	16 / 94 = 17% (all laparoscopy)	30 / 94 = 32%	n = 15 (4 / 15)	N/A
Leach et al[312] 1995	4 / 60 = 7% (laparoscopy 29) (laparotomy 31)	42 / 60 = 70%	n = 49 (3 / 49)	Sensitivity = 22% Specificity = 100% PPV = 100% NPV = 75%
Present study	7 / 46 = 15% (all laparoscopy)	13 / 46 = 28%	n = 4 (3 / 4)	Sensitivity = 21% Specificity = 100% PPV = 100% NPV = 33%

* PPC = number of patients with prior percutaneous needle biopsy / aspiration cytology who had positive peritoneal cytology

§ resectability in 35 patients with cancer of the *pancreatic head* only. Palliative resection in one patient with positive peritoneal cytology.

disease in all seven cases. However, laparoscopic peritoneal cytology contributed no additional staging information, all seven patients with positive results having been shown to have metastases within the peritoneal cavity by laparoscopy, LapUS and biopsy. These observations concur with those of Martin and Goellner[256] and Lei and co-workers[310] who also reported positive peritoneal cytology exclusively in the context of intraabdominal metastases, while Leach and colleagues documented distant metastatic disease at a median of 4.8 months after diagnosis in the four patients with positive cytology in their study[312]. These findings are at variance with those initially reported by Warshaw during 1985-1990[257], who observed that of 12 out of 40 patients with positive peritoneal cytology, only one was associated with a visible surface tumour implant. All 12 patients with positive cytology in the latter study were found to have locally advanced tumour, while all six patients with liver metastases had yielded negative peritoneal cytology[257]. These disparate results were not reproduced in subsequent work from the same group which showed a significant association between positive peritoneal cytology and visible intra-abdominal tumour spread (45%, *versus* 8% in patients without metastases)[295]. However, 31% of patients with positive peritoneal cytology were said to have been unresectable because of vascular invasion.

It is pertinent to note that none of the 49 patients found to have malignant peritoneal cytology in seven studies[256, 257, 295, 310-312] (including the seven patients in the present study) have undergone potentially curative pancreatoduodenectomy, although a palliative resection with grossly positive resection margins was performed in one patient in Warshaw's series[257].

If transcoelomic spread of exfoliated cancer cells is accepted as the likely mechanism whereby peritoneal tumour seedlings become established, then the failure to detect malignant cells in four out of eight patients with serosal dissemination was surprising and may indicate the need for better methods of retrieval, or more sensitive analytical methods such as immunocytology[313]. Nevertheless, peritoneal cytology must be readily undertaken utilising existing hospital resources if it is to become useful as a routine staging investigation, and it is within this context that these results should be interpreted. Alternatively, and based on an assumption that there were no false negative results in this, or other studies, the observation that peritoneal carcinomatosis is not always associated with cytologically demonstrable malignant cells within the peritoneal cavity supports an alternative hypothesis that peritoneal dissemination of malignancy is established by the haematogenous or lymphatic route.

As described in Section 1.2.9, it has been suggested that needle biopsy[257] or surgical mobilisation of the pancreas[82, 310] may be significant in the dissemination of cancer cells into the peritoneal cavity, and that such tumour disturbance might be implicated in establishing tumour unresectability as reflected by positive peritoneal cytology[257]. Such observations have stimulated recommendations that injudicious percutaneous or transduodenal biopsy of potentially resectable pancreatic tumours be avoided[257, 314]. Preoperative percutaneous needle biopsy of the pancreas was performed too infrequently in the present study to allow definite conclusions regarding its association with malignant peritoneal cytology or tumour dissemination. Nevertheless, three out of four such patients were found to be unresectable with cytologically malignant ascites, although all had presented with advanced tumours, three of which were situated in the pancreatic body. The possibility that such advanced and unresectable tumours were the source of positive peritoneal cytology, irrespective of subsequent biopsy, is a confounding factor which cannot be excluded. A similar criticism can be made of Warshaw's original report[257], and it is noteworthy that further work in the same institution subsequently revealed no significant difference between patients with positive laparoscopic peritoneal cytology who had undergone biopsy (27%) and those who had not (15%)[295]. Furthermore, the association between positive peritoneal cytology, unresectability and prior percutaneous FNA biopsy has since been refuted by Leach and colleagues[312] who reported a series of 60 patients with pancreatic cancer, of whom 49 (82%) had previously undergone biopsy. When these were compared with 11 patients in whom no biopsy had been attempted, they found no significant differences in the incidence of positive peritoneal cytology (6% *versus* 9%), "eventual peritoneal failure" (10% *versus* 18%) or disease-free survival[312].

Malignant peritoneal cytology has previously been detected in 9%[310] and 50%[257] of patients with pancreatic cancer associated ascites, while Garrison and colleagues reported positive cytology in 52 out of 92 patients (57%) with clinically evident malignant ascites associated with a variety of intraabdominal tumours[309]. The results of the present study suggest that patients who are found to have small quantities of ascitic fluid on laparoscopy should not necessarily be considered as having a poor prognosis, which concurs with the views of others[257, 310]. Indeed, five out of nine such patients proved to be peritoneal cytology negative, one of whom with a localised periampullary carcinoma was found to be suitable for tumour resection with curative intent.

The case of malignant port site seeding in the present study gives cause for concern. There have been two other case reports of malignant seeding to the parietes following laparoscopy in patients with pancreatic cancer[301, 302], and one instance of needle track seeding of pancreatic cancer following percutaneous FNA biopsy[315]. The patient reported herein had presented with malignant ascites and peritoneal carcinomatosis following a recent, albeit negative, percutaneous needle biopsy of a carcinoma of the pancreatic body, and was clearly at increased risk of such an occurrence. Although there has been increasing concern regarding the risks of port site seeding following laparoscopy in patients with a variety of intraabdominal malignancies, the majority of reported cases have been in the context of therapeutic laparoscopy in patients with gallbladder or colorectal cancers[316]. Although, as discussed in Studies 2 and 3, the benefits of staging laparoscopy in the evaluation of selected patients with pancreatic cancerappear to outweigh such potential risks, it would also seem prudent to recommend that laparoscopic biopsy or manipulation of potentially resectable tumours be avoided. The incidence and mechanisms of malignant seeding in the context of laparoscopy clearly require further attention.

The grave prognosis associated with positive laparoscopic peritoneal cytology in the present study concurs with the findings of other studies[256, 257, 310, 312] that positive peritoneal washings are an indicator of advanced disease, characterised by unresectability, early metastasis and short survival. Nevertheless, the results of the present study do not support the adoption of routine peritoneal cytology as a useful adjunct to staging laparoscopy in the detection of patients with unresectable tumours. However, the available information suggests that those patients with positive peritoneal cytology have an appalling prognosis irrespective of tumour stage. The identification of this subgroup of patients with a short life expectancy may therefore aid clinical decision making such as the appropriateness of adjuvant therapy or palliative surgical intervention.

Chapter 7 Summary and Conclusions

The results of the studies comprising this thesis have verified the feasibility and safety of laparoscopy with LapUS as an imaging investigation in a tertiary referral population of patients with suspected pancreatic and periampullary cancer.

Staging laparoscopy was shown to be highly sensitive (83-94%) in the detection and biopsy of distant intraabdominal metastases, and was significantly superior to USS, CT and / or SVA in this role. Its clinical impact was to prevent unnecessary laparotomy in 30-35% of patients studied, although laparoscopy was of limited utility as a diagnostic and staging modality in the absence of disseminated malignancy. Nevertheless, these findings support routine staging laparoscopy as a prelude to laparotomy in any patient considered to have potentially resectable pancreatic or periampullary cancer.

Having devised a systematic method for LapUS examination of the hepatobiliary and pancreatic region, the ability of LapUS to identify defined anatomical points of reference was demonstrated in the majority of patients. The technique is inherently operator dependent and a "learning curve" effect seemed likely. Most difficulty was experienced in identifying the superior mesenteric artery and coeliac axis (20-22%), and the distal reaches of the common bile duct and papilla (15-25% after the first 40 examinations).

Laparoscopic ultrasonography was highly sensitive (82-96%) in demonstrating the presence of a primary pancreatic or periampullary malignant lesion. The presence of pancreatic carcinomas with a diffusely infiltrative and isoechoic appearance was identified as a potential pitfall. Independent comparison with USS, CT and SVA showed these diagnostic modalities to be less sensitive (66-93%).

Laparoscopy with LapUS was shown to be superior to laparoscopy alone in the overall staging of patients with pancreatic or periampullary cancer, primarily because of its ability to identify tumour invasion of the portal-superior mesenteric vein. In this regard, there was minimal tendency to overstage the tumour (0-4%) as verified by surgical validation of positive findings. Understaging of local tumour invasion by LapUS was encountered more frequently, and LapUS was shown to be fallible in demonstrating peripancreatic soft tissue invasion. Although LapUS was as least as predictive of tumour resectability (73%) as USS, CT and SVA (58-64%), there were no significant differences in this respect. However, the tendency for the

latter "conventional" investigations to overstage local tumour stage in our study was a cause for concern. No patient should therefore be denied exploratory laparotomy with a view to 'curative' pancreatic resection on the sole basis of an USS, CT or SVA result.

All the techniques studied were ultimately unreliable in determining lymph node status on the conventional basis of node size alone. Better criteria must be devised for differentiating malignant from reactive lymph nodes, and no patient should be denied surgical intervention on this basis without biopsy confirmation of nodal metastases. This highlights a deficiency of the LapUS technique with regard to the accurate retrieval of tissue specimens, and further development of LapUS-targeted needle biopsy (or aspiration cytology) is required.

Laparoscopic peritoneal cytology was simple to perform and yielded results which were not affected by inter-observer variation. Positive results were relatively rare (15%), and always reflected overt intraabdominal metastatic disease which had been obvious during laparoscopy. However, the appalling survival of the sub-group of patients with positive laparoscopic peritoneal cytology suggested that this technique might be useful in identifying patients with a particularly poor prognosis.

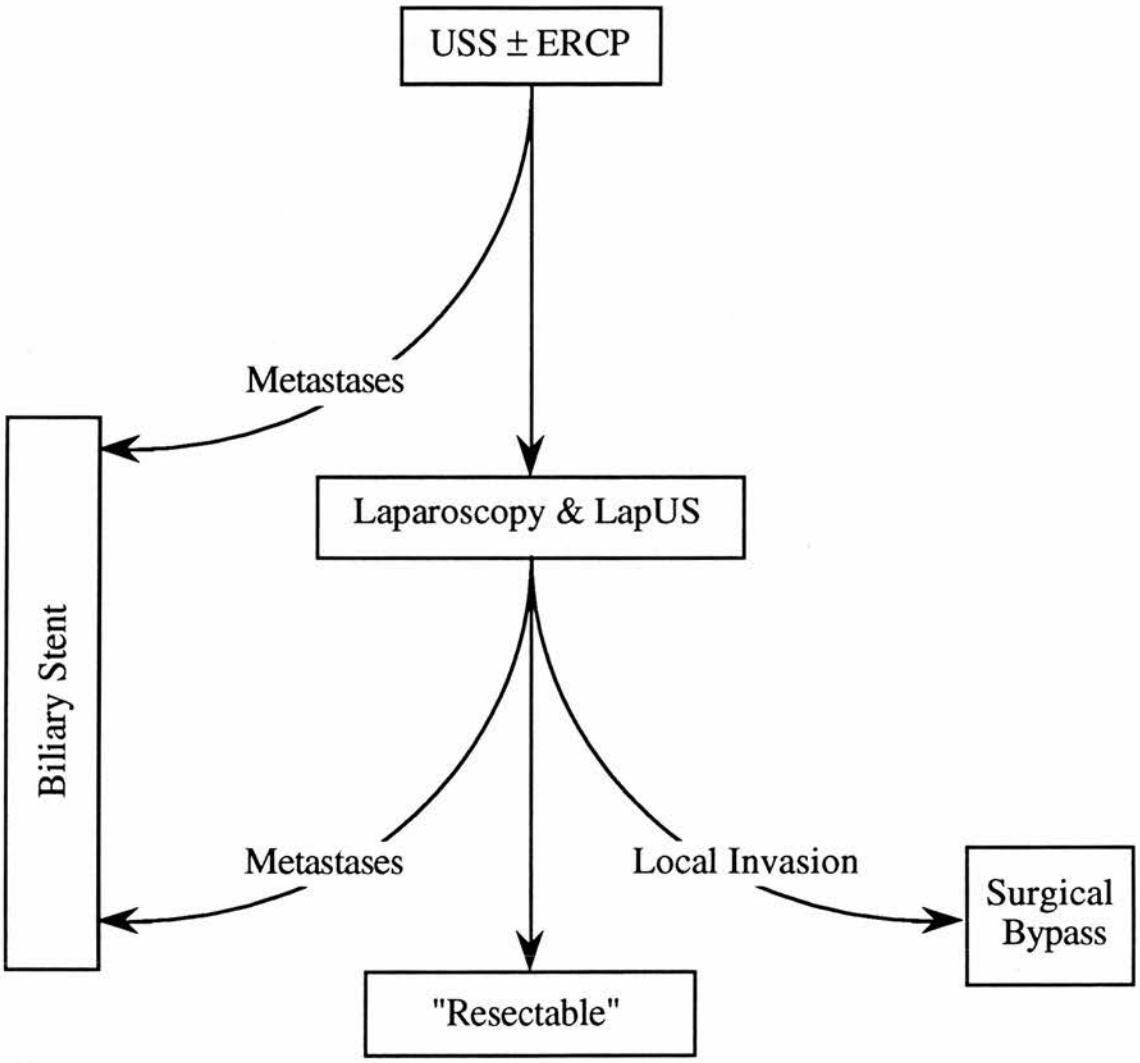
Concealed port-site bleeding and malignant seeding to the parietes were identified as potential complications. The former was of little clinical consequence and should be minimised by careful technique. Port-site tumour implantation remains a cause for concern although seems to be rare and occured in a patient with short life expectancy without influencing survival.

The work in this thesis permits the proposal of a rationalised staging algorithm for the investigation of patients with suspected pancreatic or periampullary cancer (Figure 47). Transabdominal USS remains the first-line treatment for establishing the diagnosis of extrahepatic biliary obstruction, and for excluding (or confirming by guided-biopsy) the presence of obvious liver metastases. Confirmation of biliary obstruction by ERCP (and treatment by biliary stent insertion where appropriate) also remains standard practice. The next stage of the algorithm might be addressed appropriately by laparoscopy with LapUS. The rationale for omitting Doppler USS and CT as staging investigations at this juncture rests with the relative insensitivity of these modalities in detecting "occult" intraabdominal metastases, a role where laparoscopy has been shown to be uniquely performant. Furthermore, compared with USS and CT, local tumour staging by LapUS is as least as sensitive and

predictive in determining tumour resectability, and much less likely to overestimate tumour stage. The abandonement of SVA in the routine investigation of patients with pancreatic or periampullary cancer is supported, both from the point of view of local tumour staging, and that of demonstrating the peripancreatic arterial anatomy.

Figure 47

Proposed staging algorithm for patients with potentially resectable pancreatic or periampullary carcinoma



However, these proposals should be considered in the context of the the prevailing expertise in radiological imaging and the philosophy of the clinicians practising in the Department of Surgery where this work was undertaken. These conclusions will not necessarily be applicable to all hospitals, and the reproducibility of these LapUS

findings in other institutions is required before it can be adopted as a routine staging modality by the wider surgical community. Clearly the pattern of patient referrals to a particular hospital would influence the feasibility of such an approach. Laparoscopy with LapUS is inherently operator dependent and a learning curve phenomenon was identified during the course of the work presented herein. While the general surgeon may acquire sufficient skill with LapUS to demonstrate the important hepatobiliary and peripancreatic anatomical structures during operations such as laparoscopic cholecystectomy, it does not necessarily follow that this will ensure accurate staging of patients with pancreatic and periampullary malignancy. It would seem appropriate thereforethat the inexperienced laparoscopic ultrasonographer validate his initial findings against a recognised "benchmark" (e.g surgical exploration).

Investigative algorithms may need to be revised as newer imaging techniques become available, while further evaluation and validation of future biotechnologies will be required prior to integration into clinical use. Already, comparison of laparoscopy and LapUS with alternatives such as EUS and spiral CT scanning is desirable to evaluate the relative merits of each in the staging of patients with pancreatic or periampullary cancer.

Finally, the advent of laparoscopic techniques for the minimal access palliation of patients with established or impending malignant biliary and / or duodenal obstruction will introduce a further treatment option into an already complex situation. Neverthless, the establishment of such an alternative management stategy for patients with unresectable tumours would clearly benefit from accurate methods of laparoscopic staging such as that provided by LapUS. Such issues should be addressed by further clinical studies, and ideally these would incorporate measures of endpoints such as quality of life and health economic factors.

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Appendix A

Ex vivo examinations were performed using an Aloka UST-5521-7.5 laparoscopic ultrasound probe connected to an Aloka SSD 500 portable scanner. A tissue mimicking test was used to objectively assess a number of single image parameters[317]. The test object ('Cardiff test object', Diagnostic Sonar Ltd, Livingstone, Scotland, UK) contained a gelatin base loaded with graphite particles and an array of 0.15mm stainless steel wires as specified in British Standards BS5724[317]. The gelatin / graphite mixture gives the speckled appearance of tissue parenchyma and has an attenuation of 0.86 dB cm^{-1} MHz^{-1} and a speed of sound of 1539 ms^{-1}. The probe was coupled to the test object using a shallow water bath. With the time gain compensation controls set to give a uniform speckle pattern to as great a depth as possible, the speckle pattern could be imaged to a depth of 27 mm using low contrast penetration, and to greater than 50 mm in depth using high contrast penetration. The transducer "dead zone" was estimated to be < 1 mm. Optimum lateral resolution of 2.0 - 3.0 mm was obtained between 3 and 27 mm from the transducer face. Over the same depth range the axial resolution was estimated to be 0.8 ± 0.1 mm.

Appendix B

Pancreatic and Ampullary Cancer Staging Study: Laparoscopy

Name: Date: Surgeon:

Tumour seen? *Yes / No* Ascites: *Yes / No*

Secondary signs of biliary obstruction:

Unresectability	Details	
Local factors:	Local invasion	*Yes / No*
	Regional lymphadenopathy	*Yes / No*
Distant mets:	Liver	*Yes / No*
	Peritoneal	*Yes / No*

Peritoneal Cytology: *+ve / -ve / equivocal / not done*

Biopsy: *Yes / No* Site: Result: *+ve / -ve*

Laparoscopic Ultrasonography

Tumour seen? *Yes / No / Possibly* Biliary stent: *Yes / No*

Unresectability	Details	
Local factors:	Local invasion	*Yes / No*
	Regional lymphadenopathy (>5mm):	*Yes / No*
	Vascular involvement:	*Yes / No*
Distant mets:	Liver	*Yes / No*

Guided Biopsy: *Yes / No* *+ve / -ve* Details:

Additional Information: *Yes / No* Details:

Appendix B (continued)

Primary tumour (T)

[ ] T_X Cannot be assessed

[ ] T_0 No evidence of primary tumour

[ ] T_1 Tumour limited to the pancreas (or ampulla)

[ ] T_2 Tumour extends directly to duodenum, bile duct or peripancreatic tissues

[ ] T_3 Tumour extends directly to major vessels, stomach, spleen or colon

Lymph Nodes (N)

[ ] N_X Cannot be assessed

[ ] N_0 No lymph node metastases

[ ] N_1 Regional lymph node metastases

Distant Metastases (M)

[ ] M_X Cannot be assessed

[ ] M_0 No distant metastases

[ ] M_1 Distant metastases

Lap US Findings:

Intrahepatic duct dilatation *Yes / No*

CBD *Yes / No* Size: mm

PD *Yes / No* Size: mm

Tumour *Yes / No* Size: mm

Coeliac Axis *Yes / No*

SMA *Yes / No*

PV / SMV *Yes / No*

SpV *Yes / No*

Decision: ***Resectable / Unresectable***

Appendix C

Pancreatic and Ampullary Cancer Staging Study: USS Examination

Name: Date:

Tumour seen: *Yes / No / Possibly* Biliary endoprosthesis: *Yes / No*

Site: *Head / Body / Tail / Diffuse* Maximum tumour diameter: mm

Unresectability	Details	
Local factors:	Local invasion	*Yes / No*
	Regional lymphadenopathy (>5mm):	*Yes / No*
	Vascular involvement:	*Yes / No*
Distant metastases:	Liver	*Yes / No*
	Peritoneal	*Yes / No*

Primary tumour (T)

[ ] T_X Cannot be assessed

[ ] T_0 No evidence of primary tumour

[ ] T_1 Tumour limited to the pancreas (ampulla)

[ ] T_2 Tumour extends directly to duodenum, bile duct or peripancreatic tissues

[ ] T_3 Tumour extends directly to major vessels, stomach, spleen or colon

Lymph Nodes (N)

[ ] N_X Cannot be assessed

[ ] N_0 No lymph node metastases

[ ] N_1 Regional lymph node metastases

Distant Metastases (M)

[ ] M_X Cannot be assessed

[ ] M_0 No distant metastases

[ ] M_1 Distant metastases

Decision: ***Resectable / Unresectable***

Appendix D

Pancreatic and Ampullary Cancer Staging Study: CT Examination

Name: Date:

Tumour seen? *Yes / No / Possibly* Biliary endoprosthesis: *Yes / No*

Site: *Head / Body / Tail / Diffuse* Maximum tumour diameter: mm

Unresectability	Details	
Local factors:	Local invasion	*Yes / No*
	Regional lymphadenopathy (>10 mm):	*Yes / No*
	Vascular involvement:	*Yes / No*
Distant metastases:	Liver	*Yes / No*
	Peritoneal	*Yes / No*

Primary tumour (T)

[ ] T_X Cannot be assessed

[ ] T_0 No evidence of primary tumour

[ ] T_1 Tumour limited to the pancreas (ampulla)

[ ] T_2 Tumour extends directly to duodenum, bile duct or peripancreatic tissues

[ ] T_3 Tumour extends directly to major vessels, stomach, spleen or colon

Lymph Nodes (N)

[ ] N_X Cannot be assessed

[ ] N_0 No lymph node metastases

[ ] N_1 Regional lymph node metastases

Distant Metastases (M)

[ ] M_X Cannot be assessed

[ ] M_0 No distant metastases

[ ] M_1 Distant metastases

Decision: ***Resectable / Unresectable***

Appendix E

Pancreatic and Ampullary Cancer Staging Study: Angiography

Name: Date:

Anatomy: *Normal / Variants* **Details:**

HA	*Norm*	*Displaced*	*Encased*	*Occluded*
SMA	*Norm*	*Displaced*	*Encased*	*Occluded*
SA	*Norm*	*Displaced*	*Encased*	*Occluded*
GDA	*Norm*	*Displaced*	*Encased*	*Occluded*
PDA	*Norm*	*Displaced*	*Encased*	*Occluded*
SMV	*Norm*	*Displaced*	*Encased*	*Occluded*
PV	*Norm*	*Displaced*	*Encased*	*Occluded*
SV	*Norm*	*Displaced*	*Encased*	*Occluded*

Liver metastases:

Comments:

Decision: ***Resectable / Unresectable***

Appendix F

Pancreatic and Ampullary Cancer Staging Study - Patient Details

Name: DOB: *Male / Female* Age: yrs

Presenting symptoms:

Mode of diagnosis prior to referral:

ERCP: *Yes / No* Date: Findings:

Biliary endoprosthesis: *Yes / No*

Preoperative biopsy: *Yes / No* *+ve / -ve / equivocal* Method:

Surgical Staging / Final Outcome

Operation: *Yes / No* Date:

Resectable: *Yes / No* Procedure:

Primary tumour (T)

[ ] T_X Cannot be assessed

[ ] T_0 No evidence of primary tumour

[ ] T_1 Tumour limited to the pancreas (ampulla)

[ ] T_2 Tumour extends directly to duodenum, bile duct or peripancreatic tissues

[ ] T_3 Tumour extends directly to major vessels, stomach, spleen or colon

Lymph Nodes (N)

[ ] N_X Cannot be assessed

[ ] N_0 No lymph node metastases

[ ] N_1 Regional lymph node metastases

Distant Metastases (M)

[ ] M_X Cannot be assessed

[ ] M_0 No distant metastases

[ ] M_1 Distant metastases

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Carcinoma of the Pancreatic Head and Periampullary Region

Tumor Staging with Laparoscopy and Laparoscopic Ultrasonography

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Objective
The authors performed a prospective evaluation of staging laparoscopy with laparoscopic ultrasonography in predicting surgical resectability in patients with carcinomas of the pancreatic head and periampullary region.

Summary Background Data
Pancreatic resection with curative intent is possible in a select minority of patients who have carcinomas of the pancreatic head and periampullary region. Patient selection is important to plan appropriate therapy and avoid unnecessary laparotomy in patients with unresectable disease. Laparoscopic ultrasonography is a novel technique that combines the proven benefits of staging laparoscopy with high resolution intraoperative ultrasound of the liver and pancreas, but which has yet to be evaluated critically in the staging of pancreatic malignancy.

Methods
A cohort of 40 consecutive patients referred to a tertiary referral center and with a diagnosis of potentially resectable pancreatic or periampullary cancer underwent staging laparoscopy with laparoscopic ultrasonography. The diagnostic accuracy of staging laparoscopy alone and in conjunction with laparoscopic ultrasonography was evaluated in predicting tumor resectability (absence of peritoneal or liver metastases; absence of malignant regional lymphadenopathy; tumor confined to pancreatic head or periampullary region).

Results
"Occult" metastatic lesions were demonstrated by staging laparoscopy in 14 patients (35%). Laparoscopic ultrasonography demonstrated factors confirming unresectable tumor in 23 patients (59%), provided staging information in addition to that of laparoscopy alone in 20 patients (53%), and changed the decision regarding tumor resectability in 10 patients (25%). Staging laparoscopy with laparoscopic ultrasonography was more specific and accurate in predicting tumor resectability than laparoscopy alone (88% and 89% *versus* 50% and 65%, respectively).

Conclusions
Staging laparoscopy is indispensable in the detection of "occult" intra-abdominal metastases. Laparoscopic ultrasonography improves the accuracy of laparoscopic staging in patients with potentially resectable pancreatic and periampullary carcinomas.

Accurate tumor staging is important for selecting patients with carcinoma of the head of the pancreas in whom it may be appropriate to attempt pancreatic resection with curative intent. Unfortunately, the natural history of ductal adenocarcinoma of the pancreas is such that only a minority of patients prove to be candidates for curative resection. Signs of advanced disease frequently are present at operation, leaving surgical palliation of established or impending duodenal or biliary obstruction the only surgical option. The availability of endoscopic[1] and percutaneous[2] biliary intubation and, more recently, the development of laparoscopic duodenal and biliary bypass,[3,4] has reinforced the need to identify patients with unresectable disease who might avoid unnecessary laparotomy. Ideally, the preoperative assessment of patients with malignant biliary obstruction should include investigations that are sensitive in detecting localized and potentially curable lesions, and at the same time, specific enough to identify factors that render the tumor unresectable.

The pancreas is a difficult organ to evaluate radiologically because of its anatomic location within the retroperitoneum and its intimate relationship with the adjacent viscera and major vascular structures. Although the continued development of modern radiologic techniques has been accompanied by an apparent decline in the incidence of "nontherapeutic" laparotomy for pancreatic carcinoma,[5] it also has been recognized increasingly that imaging modalities, such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and selective visceral angiography, may not always be sufficiently accurate in staging pancreatic cancer, even when used in combination.[6] Several authors have stressed the inability of these techniques to detect "occult" metastatic deposits within the peritoneal cavity and liver. Discovery of such lesions at the time of laparotomy will curtail the intended operative procedure, whereas their failure to detect them before resection surgery results in early tumor recurrence. These limitations of imaging techniques have supported recommendations for routine laparoscopy as a highly sensitive means of detecting lesions that cannot be resected.[7-10] Laparoscopic ultrasonography is a new technique that provides the surgeon with a sensitive means of detecting small metastases within the peritoneal cavity by direct inspection and allows assessment of local tumor invasion, regional nodal involvement, and distant metastatic spread to the liver using high resolution, real-time, B-mode ultrasound. We already have reported encouraging preliminary results with laparoscopy and laparoscopic ultrasonography in the assessment of patients with pancreatic tumors[11] and liver malignancy.[12,13] In this prospective study, we report the use of laparoscopy with laparoscopic ultrasonography in the evaluation of resectability in patients with carcinoma of the head of the pancreas and periampullary region.

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PATIENTS/METHODS

From January 1991 to September 1993, 40 patients diagnosed as having pancreatic or periampullary carcinoma were considered, at the time of referral to our department, as candidates for tumor resection with curative intent either by pancreatoduodenectomy or by transduodenal local resection. Patients considered unsuitable for surgical intervention for reasons of advanced age, infirmity, or previously recognized distant metastases were not evaluated laparoscopically or by angiography and have not been included in this study. Failure to achieve laparoscopic access to the peritoneal cavity occurred in one patient with adhesions from a previous laparotomy, and this patient has been excluded from further analysis. The diagnosis usually was made on endoscopic retrograde cholangiopancreatography (ERCP), transabdominal ultrasonography, or dynamic CT scanning, and histopathologic confirmation was obtained in each case. All patients were managed according to an algorithm in which staging laparoscopy with laparoscopic ultrasonography was followed by angiography before assessment of tumor resectability at exploratory laparotomy. Preoperative radiologic assessment typically comprised transabdominal ultrasonography and intravenous enhanced (dynamic) CT scanning. A variety of scanning techniques and equipment were employed by the various referring hospitals, and such investigations were repeated only if our unit radiologist considered them to be inadequate.

After laparoscopy with ultrasonography was performed, selective visceral angiography was undertaken in patients 1) with no evidence of metastatic tumor spread and disease that still was considered operable or 2) a tumor that was considered inoperable because of locoregional extension, but in whom further evaluation of these findings was considered appropriate before surgical exploration. The technique of selective visceral angiography employed in this study has been described previously.[14] Histopathologic confirmation always was obtained, either after examination of the surgically resected specimen, by needle biopsy of the primary tumor, by luminal biopsy of periampullary tumors during ERCP, or after biopsy of metastatic deposits during laparoscopy or laparotomy.

Laparoscopic ultrasonography was performed under

general anesthesia by a standardized technique that has been described previously.[13,15] Briefly, two disposable $^{10}/_{11}$-mm laparoscopic cannulae (Endopath, Ethicon Ltd., Edinburgh, United Kingdom) were inserted at the umbilicus and right flank, and a thorough inspection of the abdominal cavity was performed using a 30-degree telescope. Particular attention was paid to evidence of metastatic disease involving the liver, mesenteric and hilar lymph nodes, and all visible serosal surfaces. No attempt was made to enter the lesser sac to visualize the pancreas directly.

Laparoscopic ultrasonography was performed using a 9-mm diameter linear-array contact ultrasound probe (Aloka UST-5521-7.5, Keymed Ltd., Southend-on-Sea, United Kingdom), connected to an Aloka SSD-500 B-mode portable ultrasound machine. Both the ultrasound and laparoscopic images were viewed simultaneously using "picture-in-picture" visual mixing. The liver was examined for evidence of metastatic disease, and the hilar, peripancreatic, and para-aortic regions were examined for lymphadenopathy. Identification of regional lymph nodes larger than 10 mm in diameter was interpreted as evidence of tumor unresectability, and where possible, this was confirmed by biopsy during laparoscopy or subsequent laparotomy. The criteria used to define primary tumor advancement and locoregional irresectability were as follows: 1) tumor size of 5 cm or greater; 2) extrapancreatic invasion of adjacent tissues (i.e., duodenum, stomach, common bile duct, retroperitoneum); and 3) occlusion or stenosis of the portal or superior mesenteric veins, or major branches of the celiac trunk or superior mesenteric artery (with the exception of the gastroduodenal artery). Laparoscopic ultrasonography was performed and interpreted by members of the surgical team (OJG/TGJ) and was undertaken as a separate procedure from laparotomy. The entire laparoscopic examination always was completed within 30 minutes.

Locoregional resectability of tumor ultimately was determined by an experienced pancreatic surgeon (DCC or OJG) at the time of exploratory laparotomy. Palpation, mobilization, and trial dissection of the head and neck of the pancreas were performed to assess the extent of the tumor and its relationship with the adjacent vascular and visceral structures as described elsewhere.[16,17] Intraoperative ultrasound scanning of the liver was performed to detect nonvisible liver metastases and guide needle biopsies (5-MHz linear-array contact ultrasound probe, Aloka UST-587T-5, Keymed Ltd.). In patients whose earlier laparoscopic findings had contraindicated further assessment of resectability at open operation, tumor unresectability always was confirmed by biopsy of intra-abdominal metastases or by selective visceral angiography when vascular invasion was suspected. Data were tabulated using a standard 2×2 matrix analysis,[18] whereby the actual tumor resectability (negative) or "irresectability" (positive) was correlated with that predicted by the operator (true or false) after laparoscopy/laparoscopic ultrasonography. The sensitivity, specificity, and overall accuracy of the prediction regarding resectability was expressed for laparoscopy alone, and in combination with laparoscopic ultrasonography. These staging parameters were not assigned to laparoscopic ultrasonography independent of the findings on prior laparoscopic examination.

RESULTS

Forty consecutive patients underwent staging laparoscopy (22 women, 18 men; median age 59 years [range 36–78 years]), 38 of whom also underwent laparoscopic ultrasonography. Endoscopic insertion of a biliary stent had been performed previously in 21 patients (53%). Procedure-related complications were encountered in one patient in whom an asymptomatic port-site hemorrhage had occurred with the discovery of intraperitoneal blood at laparotomy 6 days later (2.5% complication rate).

Laparoscopy (n = 40)

It was not possible to directly inspect the primary tumor in any patient during the laparoscopic examination, although it was occasionally possible to palpate a retrogastric mass with the tip of the ultrasound probe. Tumor resectability was inferred correctly from the absence of signs of dissemination within the abdominal cavity in all 12 patients considered resectable (i.e., 100% sensitivity). Previously unsuspected metastatic tumor spread to the liver (ten patients), peritoneal surfaces (eight patients) (Fig. 1), and hilar lymph nodes (two patients) were identified during laparoscopy in a total of 14 patients (35%). Biopsy material was obtained and metastatic carcinoma was confirmed in each case. Exploratory laparotomy was, therefore, withheld from these patients, who in terms of predicting resectability, were regarded as having undergone "true positive" laparoscopic staging examinations (Table 1).

Laparoscopy failed to detect malignant dissemination to distant sites within the abdominal cavity in three patients (i.e., "false-negative" procedures). In one patient, a cluster of tiny peritoneal tumor deposits were concealed by adhesions in the right subhepatic space and were not recognized by the laparoscopist. Liver metastases were not demonstrated laparoscopically in three patients. In one case, laparoscopic biopsy of a suspicious subcapsular lesion indicated biliary ectasia, although bi-

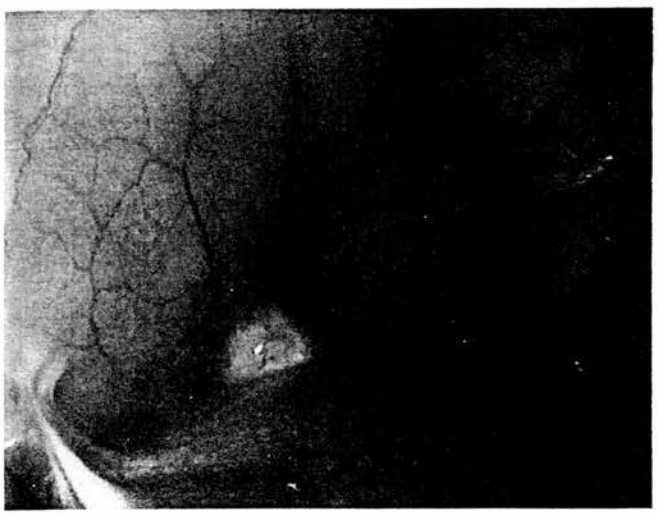

Figure 1. Preoperative staging laparoscopy performed in a patient thought to have a resectable periampullary carcinoma revealed a small white nodule situated at the junction of the falciform ligament and capsule of the left hepatic lobe. Laparoscopic biopsy confirmed metastatic adenocarcinoma. There was no other evidence for extrapancreatic spread of tumor.

opsy at open operation confirmed metastatic carcinoma. A 10-mm metastasis within the caudate lobe, a region not always readily accessible to laparoscopic inspection, was demonstrated by laparoscopic ultrasonography in another patient. A small tumor deposit on the free edge of the right lobe of the liver was discovered during laparotomy after an unremarkable laparoscopy in a third patient. A delay of 2 months had ensued between laparoscopy and laparotomy in this deeply jaundiced patient. Ultimately, unsuspected small liver and peritoneal tumor deposits were demonstrated after laparoscopy, laparoscopic ultrasonography, or laparotomy in 17 of the 40 patients (43%).

Laparoscopy alone failed to identify the 12 patients (30%) with locoregional tumor unresectability, which subsequently was demonstrated by laparoscopic ultrasonography, angiography, or operative assessment. Overall, there were 14 false-negative laparoscopic examinations, including those where distant metastases were overlooked, resulting in a specificity of only 50% in predicting resectability and an overall accuracy of 65% for staging laparoscopy (Table 1).

Laparoscopic Ultrasonography (n = 38)

Satisfactory images of the primary pancreatic/periampullary lesion were obtained using laparoscopic ultrasonography in 31 patients (82%) (Figs. 2 and 3). The pancreatic duct was identified proximal to the obstructing mass lesion in 31 cases, in 23 (74%) of whom duct dilatation >3 mm was observed. In each case, the sonographic appearance of the primary tumor was of a predominantly heterogeneous hypoechoic mass (Fig. 3). Factors indicating tumor unresectability were identified correctly by laparoscopic ultrasonography in 23 cases (61%), namely the following: liver metastases (10 patients); locally invasive tumor measuring >5 cm (12 patients); and vascular involvement with tumor (12 patients) (Fig. 3). In addition, regional lymph node enlargement >10 mm was identified in 14 patients (Fig. 4), and biopsies were obtained to confirm malignant infiltration in three cases. In those patients without biopsy proof of malignant lymphadenopathy, tumor unresectability always was confirmed by the other criteria outlined above. In 20 patients (53%), information relevant to the assessment of tumor stage—and not apparent after laparoscopy—was derived from the laparoscopic ultrasound examination. This new staging information altered the decision concerning tumor resectability based on laparoscopy alone in 10 patients (25%). Six of these ten patients had locally advanced tumors >5 cm in diameter, eight had invasions of the adjacent superior mesenteric and portal venous trunk (Fig. 3), and, as detailed above, one patient had metastatic liver disease, which had remained undetected during laparoscopy. Enlarged regional lymph nodes also were demonstrated in six of these patients, although biopsies were not obtained. Having correctly predicted tumor unresectability in 23 of 26 patients, these factors were responsible for increasing the specificity and accuracy to 88% and 89%, respectively (Table 2).

Failure of the surgeon performing laparoscopic ultrasonography to recognize tumor invasion of the superior mesenteric and main portal vein in one patient and tumor infiltration of the common bile duct and pylorus in another yielded false-negative results for laparoscopic ultrasound. In another patient, laparoscopic ultrasonog-

Table 1. PREDICTION OF RESECTABILITY BY STAGING LAPAROSCOPY IN 40 PATIENTS WITH PANCREATIC AND PERIAMPULLARY CARCINOMA

	Laparoscopy	
	Resectable	Nonresectable
Outcome		
Resectable	12	0
Nonirresectable	14	14

Sensitivity = 12/12 = 100%; specificity = 14/28 = 50%; accuracy = 26/40 = 65%.

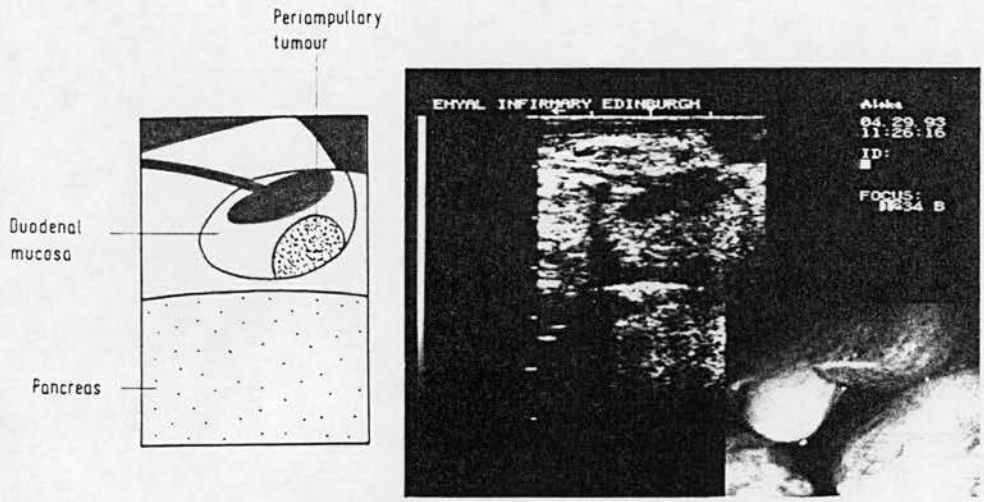

Figure 2. Laparoscopic ultrasonography was performed in a patient suspected of having a periampullary tumor, causing obstructive jaundice, although no mass lesion was identified by other investigations. The linear-array probe has been placed on the duodenum (insert), and the rectilinear sonogram obtained defined a 10-mm periampullary carcinoma. This tumor was deemed to be resectable and subsequently was excised by transduodenal local resection.

raphy suggested local infiltration of the duodenum with tumor, but this finding was not confirmed at laparotomy, and the patient underwent a Whipple operation. This represents the only false-positive laparoscopic ultrasound examination, accounting for the sensitivity of 92% observed for laparoscopic ultrasonography in recognizing resectable disease (Table 2).

Outcome

Twenty-two patients (55%) progressed to laparotomy and operative assessment of resectability; 12 were considered to have resectable tumors (30% overall resectability). Pancreatoduodenectomies were performed in ten patients, and one patient underwent transduodenal resection of a periampullary adenocarcinoma. Another patient, in whom resectability of a periampullary carcinoma was confirmed at laparotomy, became profoundly hypotensive, and it was considered appropriate to perform a biliary bypass rather than attempt pancreatic resection on this occasion. This patient is alive and well at 8 months, with no evidence of disease progression. The patient has refused further surgery and for the purposes of this study, has been classified as having resectable disease. Palliative biliary and duodenal bypass procedures were performed in ten patients in whom tumor unresectability was confirmed at laparotomy.

DISCUSSION

For the majority of patients with ductal adenocarcinoma of the exocrine pancreas, the outlook is bleak.[19] It

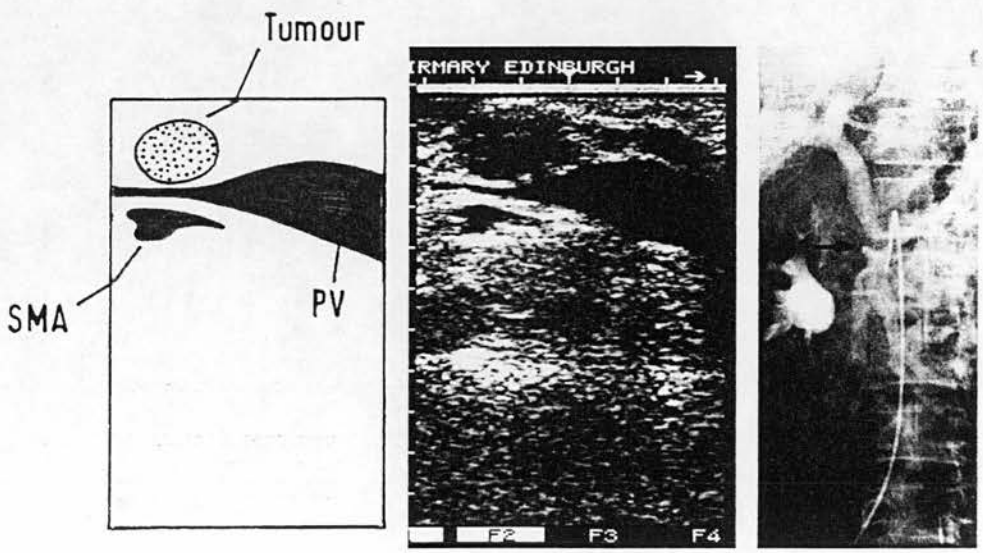

Figure 3. A laparoscopic sonogram in the region of the neck of the pancreas (parasagittal cut) has defined a 20-mm diameter hypoechoic carcinoma within the head of the pancreas, causing a stenosis of the adjacent superior mesenteric—portal vein. The constant appearance of a venous stenosis during real-time scanning in several planes was interpreted as "irresectable" vascular involvement. Selective visceral angiography with portography (right) corroborated the appearances of tumor invasion at the confluence of the portal, superior mesenteric and splenic veins (arrow). PV = portal vein; SMA = superior mesenteric artery

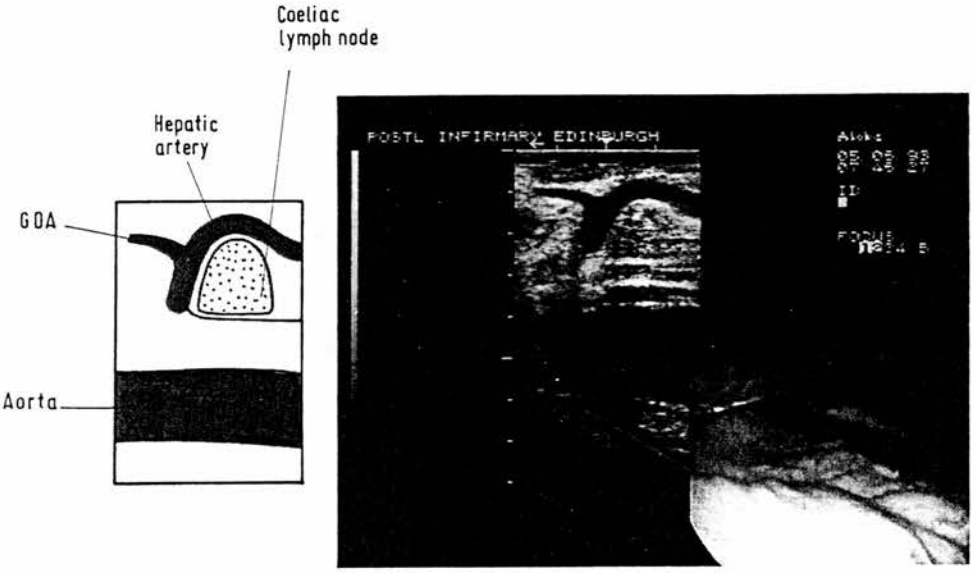

Figure 4. With the laparoscopic ultrasound probe placed on the stomach (inset), a sagitally orientated sonogram defining the origin of the celiac axis from the aorta has been obtained. A cluster of enlarged paraaortic lymph nodes were identified; their malignant infiltration was confirmed after laparotomy and biopsy. The node depicted measures 15 mm and has a hypoechoic and well-circumscribed appearance, typical of malignant lymphadenopathy.

is one of the causes of death from cancer encountered most commonly in surgical practice, its incidence appears to be rising,[20] and most patients exhibit local invasion of tumors and distant metastatic spread by the time symptoms occur. Nevertheless, recent reports indicate that in experienced hands, potentially curative pancreaticoduodenectomy (Whipple operation) can be undertaken with negligible perioperative morbidity and mortality[16,21-23] and a prospect of prolonged survival if it is discovered an early stage.[24]

Of those investigations traditionally employed in the selection of patients with pancreatic and periampullary carcinoma for resection surgery, ultrasonography is noninvasive, repeatable, and relatively inexpensive, although it is highly operator dependent. Its usefulness as a first-line test in confirming extrahepatic biliary obstruction and for screening the liver for metastatic disease is widely recognized, and it can be at least as accurate as CT scanning in determining local resectability of pancreatic cancer.[25,26] However, these results have not been reproduced widely, and in practice, suboptimal imaging of the retroperitoneal structures caused by overlying bowel gas and body-wall tissues may limit the usefulness of this modality.[27] High-resolution dynamic CT scanning is regarded widely as the diagnostic and staging investigation of choice in the assessment of pancreatic cancer[28,29] and has been shown to be more accurate than transabdominal ultrasonography.[30] However, most studies of CT in the diagnosis and staging of pancreatic cancer have been subject to some degree of bias. In a blind analysis of dynamic CT scanning in a random population of patients with cancer of the pancreas or periampullary region, Bryde Anderson and colleagues showed that CT was too inaccurate to recommend its use alone as a staging investigation.[31] Similarly, Ross and co-workers concluded that predictions of tumor unresectability based solely on the CT diagnosis of locally advanced disease were unreliable,[32] although not all scans were enhanced with intravenous contrast. There is no evidence that magnetic resonance imaging currently confers any advantage over dynamic CT scanning in this context[10,28]

Although some surgeons have successfully resected segments of the superior mesenteric and portal vein to achieve extirpation of tumors in the head of the pancreas,[16,33-35] most would regard tumor invasion of these vascular structures as a contraindication to pancreatic resection with curative intent, and this philosophy was observed in selecting patients for resection in this study. Selective visceral angiography has been reported as an

Table 2. PREDICTION OF RESECTABILITY BY COMBINED STAGING LAPAROSCOPY/ LAPAROSCOPIC ULTRASONOGRAPHY IN 38 PATIENTS WITH PANCREATIC AND PERIAMPULLARY CARCINOMA

	Laparoscopy/Laparoscopic Sonography	
	Resectable	Nonresectable
Outcome		
Resectable	11	1
Nonresectable	3	23

Sensitivity = 11/12 = 92%; specificity = 23/26 = 88%; Accuracy = 34/38 = 89%.

accurate means of defining locally advanced tumor as demonstrated by encasement, stenosis, or occlusion of the extrapancreatic arteries and veins (Fig. 3).[36,37] Conversely, angiography can be potentially misleading in predicting tumor unresectability,[16,38] and has been shown to confer little additional benefit to dynamic CT scanning.[14,29] Nevertheless, it may be of value in confirming tumor unresectability in selected cases in which doubt persists.[16] In the current study, we used angiography primarily as a means of validating the findings of laparoscopic ultrasonography regarding vascular invasion. Selective visceral angiography also provides a vascular road map of the abdomen, but although recognizing that peripancreatic vascular anomalies may occur in 30% to 35% of patients with pancreatic and periampullary carcinoma,[14,39,40] not all surgeons would accept that this justifies routine preoperative arteriography.

Use of laparoscopic ultrasonography to assess pancreatic malignancy seems logical. The detailed view of the peritoneal cavity at laparoscopy is superior to that provided by any other contemporary investigation in detecting tiny peritoneal tumor deposits and liver metastases (especially subcapsular lesions measuring less than 10 mm in diameter) (Fig. 1).[11,31] Although abdominal ultrasound and CT scanning revealed no metastatic disease in those patients in the current study, this characteristic pattern of intra-abdominal tumor dissemination ultimately was demonstrated in 42% of patients. In 83% of these cases, laparoscopy had been confirmatory, a finding that supports previous observations.[7–10] Nevertheless, the laparoscopist is limited in his/her ability to assess the primary tumor directly. Although direct laparoscopic inspection of pancreatic tumors from within the lesser sac has been described well by both infragastric[41,42] and supragastric routes,[43–45] and although recognizing that this may be useful in the diagnosis and biopsy of tumors of the body and tail of the pancreas, it is not, in practice, a suitable means of assessing resectability of small inaccessible tumors within the head of the gland. However, we found that direct apposition of a high-resolution, linear-array ultrasound transducer at laparoscopy consistently provided highly detailed images of the pancreas and neighboring retroperitoneal structures (Figs. 2 and 3). Accordingly, it was possible to demonstrate the signs of local tumor invasion, peripancreatic lymphadenopathy (Fig. 4), and vascular invasion (Fig. 3) so that the combination of laparoscopy and laparoscopic ultrasonography gave a more reliable prediction of tumor unresectability than laparoscopy alone (specificity 88% *vs.* 50%). A tissue diagnosis was not always obtained in those cases in which the inability of tumor resection due to malignant lymphadenopathy was diagnosed, although this finding of its own always was supported by other features precluding resection with curative intent. Nevertheless, further evaluation is required to determine the reliability of a laparoscopic ultrasound diagnosis of lymph node metastases, and biopsy or fine-needle aspiration of enlarged nodes is recommended in cases of doubt.

Since Japanese workers described the combination of A-mode ultrasound scanning with laparoscopy 30 years ago,[46] laparoscopic ultrasonography has evolved to the extent that ultracompact linear-array B-mode ultrasound probes currently can be used laparoscopically to obtain high resolution images comparable to those obtained by intraoperative ultrasonography at laparotomy. Although intraoperative ultrasound has gained acceptance as the most sensitive method of detecting occult liver metastases at the time of resection of primary colorectal tumors[47,48] and as an indispensable tool in liver resection,[49–52] the technique has had limited application to the operative assessment of pancreatic carcinoma. It has been proven useful in the localization of neuroendocrine tumors within the pancreas,[53–57] and others have reported its use in the operative assessment of pancreatic cancer.[58,59] Machi and colleagues recently reported[60] that intraoperative ultrasound was significantly more specific (86.4% *vs.* 54.5%) and accurate (89.7% *vs.* 64.1%) than a combination of preoperative transabdominal ultrasound, dynamic CT scanning, and angiography in assessing portal vein invasion by pancreatic cancer, findings that reflect our current experience in this context. Several authors have reported the use of laparoscopic ultrasonography to confirm the presence of primary pancreatic tumors and accurately define hepatobiliary and pancreatic anatomy,[61–63] and our experience demonstrates its potential for accurate staging assessment of patients with pancreatic and periampullary cancer, both in relation to distant metastatic spread and locoregional invasion.

Endoscopic ultrasonography offers another impressive alternative to conventional imaging in evaluation of the pancreas. Rösch and colleagues assessed tumor size, lymph node status, and vascular invasion in defining local tumor stage in patients with pancreatic and periampullary carcinomas,[30] whereas Tio and colleagues report overall accuracies of 92% and 88%, respectively, in the assessment of local tumor infiltration from pancreatic and periampullary cancers.[64] However, endosonography cannot be expected to detect peritoneal and liver metastases, and this is reflected in its overall accuracy of 66% in TNM staging of pancreatic cancer.[64]

In this study, we examined the role of staging laparoscopy with laparoscopic ultrasonography in a cohort of patients who would otherwise have been regarded as suitable for operative assessment of tumor resectability. Although preceding patient selection increased the proportion of patients with resectable disease and introduced

an element of bias, we believe that this is representative of clinical practice if laparoscopic staging were to be introduced at this point in an investigative algorithm. Our results suggest that staging laparoscopy is a valuable routine undertaking before laparotomy and operative assessment of resectability in patients with pancreatic and periampullary cancer. Comparative studies between conventional investigations and this new technology are indicated to fully evaluate of the precise role of laparoscopic ultrasound.

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