2018

Aspects of The Preoperative Pathway in Pancreatic Head Malignancy

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ASPECTS OF THE PREOPERATIVE PATHWAY IN PANCREATIC HEAD MALIGNANCY

By

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A thesis submitted to Plymouth University in partial fulfillment for the degree of

DOCTOR OF MEDICINE

Peninsula College of Medicine and Dentistry

July 2018

Acknowledgement

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Dr. Simon Jackson

Consultant Radiology, Plymouth Hospitals NHS Trust

Role: Third opinion reporting areas of scan discrepancy

Dr. Helen Neilens

Research Advisor/Innovation Lead, Plymouth Hospitals NHS Trust

Role: Expert advice for research ethics

Dr. Christopher Rollinson

Research Governance Manager, Plymouth Hospitals NHS Trust

Role: Research governance training and online study registration

Dr. Golnaz Shahtahmassebi

Lecturer in statistics, School of Science and Technology, Nottingham Trent University

Role: Research supervisor, statistical advice and performance of inferential statistical tests

Professor Carl Roboottom

Professor of Radiology, PU PSMD

Role: Research supervisor, Re-reporting scan images

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Author declaration

At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award without prior agreement of the Graduate Sub-Committee.

Work submitted for this research degree at the Plymouth University has not formed part of any other degree either at Plymouth University or at another establishment. This is an original research project. I undertook data collection and descriptive statistical analyses. This project was self-funded. This research has been conducted under a formal agreement with Plymouth Hospitals NHS Trust.

- **Regional presentations**

- **Delay to surgery influences survival in patients with ampullary carcinoma**

  Oral and Poster presentation at the annual post-graduate PUPSMD research event, 22nd Oct. 2014 Cornwall, UK

- **The pre-operative pathway in pancreatic head malignancy-Assessment of interval to surgery on oncological outcome and survival**

  Oral presentation at Postgraduate Society Conference, 19th March 2014. Plymouth University, UK (Best Oral presentation Prize)

- **National presentations**

- **Impact of interval to surgery on resectability and histological outcome of peri-ampullary carcinoma**

  Poster presentation at the 2nd Scientific Meeting of GBIHPBA, 12th -13th March 2014, Warwickshire, UK (P05)

➢ **<u>International presentations</u>**

- **Effect of patient travel distance on resection rate and outcome in pancreatic head malignancy**

  Poster presentation at the First World Pancreatic Forum 18th-19th June 2015, Bern, Switzerland (Best Poster Travel Grant Prize)

- **Longer interval to surgery improves outcome in surgery for ampullary cancer**

  Poster presentation at the First World Pancreatic Forum 18th-19th June 2015, Bern, Switzerland

- **Correlation of CT with histopathological outcome in the assessment of tumour origin in pancreatic head malignancy**

  Poster presentation at European Society of Gastrointestinal and Abdominal Radiology Conference (ESGAR) 2015, 9th-12th June 2015, Paris, France

➢ **<u>Publications</u>**

- Amr B et al, Systematic evaluation of radiological findings in the assessment of resectability of peri-ampullary cancer by CT using different contrast phase protocols. Clin Radiol. 2017 Mar 11. pii: S0009-9260(17)30077-6. doi:10.1016/j.crad.2017.02.012. [Epub ahead of print].
- Amr B et al, Variation in survival after surgery for peri-ampullary cancer in a regional cancer network. BMC surgery. 2017;17 (1):23.
- Amr B et al, Assessment of the effect of interval from presentation to surgery on outcome in patients with peri-ampullary malignancy. HPB, Vol. 18, (4), 354 – 359.

Word count of main body of thesis: 30,670

Signed

Date:

Abstract

ASPECTS OF THE PREOPERATIVE PATHWAY IN PANCREATIC HEAD MALIGNANCY

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Malignancy within the pancreatic head can arise from pancreatic duct, distal bile duct, ampulla or duodenum. Since September 2000, surgery for all pancreatic head malignancy (PHM) has been centralised into regional pancreatic centres where assessment of preoperative imaging and subsequent surgery is undertaken. As part of this guidance, surgery must be performed within 62-days of referral.

This project will assess four aspects of the pre-operative pathway in PHM:

1) Potential variation in outcome of patients referred from different sites within a Cancer Network
2) Potential variation in outcome associated with different intervals to surgery within the 62 day guideline
3) The ability of interpretation of heterogeneous pre-operative CT scans from different hospitals to determine the resectability of PHM
4) The ability of CT scan to distinguish the different tumour types of PHM

Images of a consecutive series of patients were re-reported and compared with final pathology reports. Good agreement was noted in determining the tumour origin of PHM (observed agreement = 0.758, Kappa= 0.6 (0.51-0.68)).

In the assessment surgical outcomes, geographical isolation from the regional centre was not associated with delay to surgery. Variation in outcome between referral centres was however noted but this was not associated with travel distance. Although little association was noted between delay to surgery and outcome overall, a paradoxical improvement in survival was noted however for the small group of patients with ampullary tumours who waited longer than the median interval to surgery.

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1 Introduction

Pancreatic head malignancy (PHM) includes a group of malignant tumours arising from the Ampulla of Vater or from the nearby organs. The terms pancreatic head malignancy and periampullary cancer (PC) are used interchangeably in this thesis. These include carcinoma of the head of pancreas, ampullary carcinoma, distal bile duct cancer and duodenal cancer. Cancers arising from these origins often cause obstruction of the distal common bile duct within the pancreatic head leading to a similar presentation with obstructive jaundice. Identification of the exact site of the tumour origin could be difficult due to the close anatomical proximity of these sites.

Pancreatic ductal adenocarcinoma (PDA) is a cancer arising from the exocrine glandular cells of the pancreas, and carries a poor prognosis. It is one of the most aggressive fatal malignant neoplasms being the fifth most common cause of cancer related deaths in the USA and Europe. In USA, PDA accounts for about 3% of all cancers and about 7% of all cancer related mortality with an estimated increased mortality figures to rank 4th among cancer related deaths (1). In Europe, it is expected that deaths from pancreatic cancer to overtake breast cancer related deaths (2). Less than 20% of patients have a resectable tumour at the time of diagnosis with 5-year survival rate of 3-5% that would increase to about 6.5%-20% in patients with successful surgical resection (3-10).

While there is an approximate delay of 18 and 12 months for the data collection regarding the incidence and mortality rates respectively, it is estimated that pancreatic cancer is the eleventh most common diagnosed cancer in the UK in 2015 (11, 12) with a peak age between 65 and 80 years old at the time of diagnosis with slight female gender predominance (13, 14). Most recent published data in 2016 showed that there was an overall increase in the incidence with 4,364 males and 4,091 females registered in the UK

(15), with total deaths of 4,7520 and 4,538 males and females patients respectively in 2016 with pancreatic cancer remained the fifth most common cause of cancer mortality (Figure 1-1& Figure 1-2)(16).

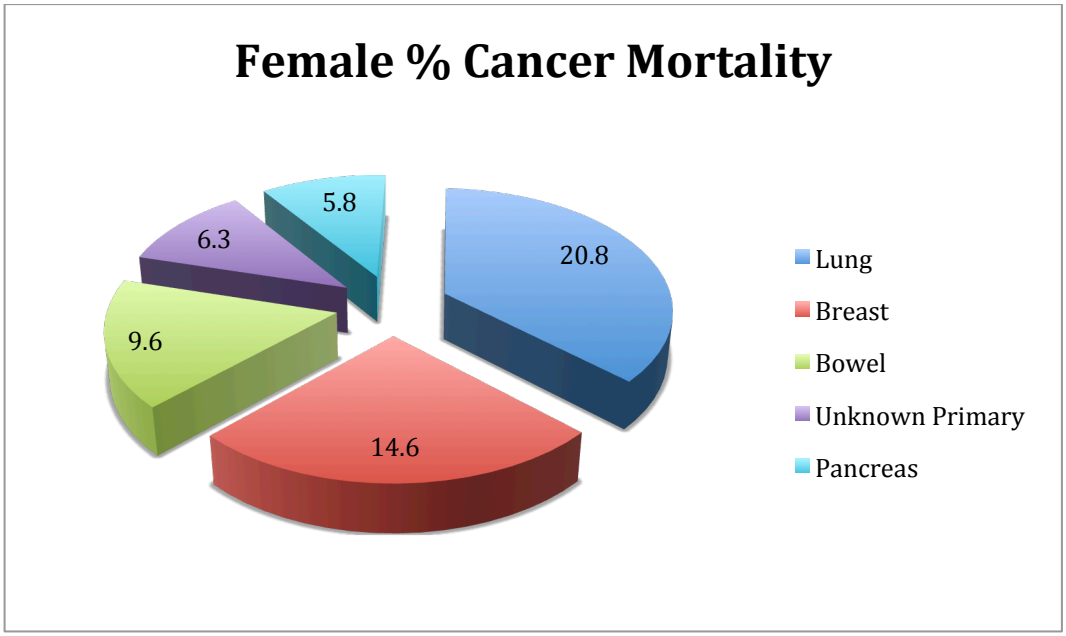

Figure 1-1 Female cancer mortality (% all malignant mortality) in the United Kingdom, 2016

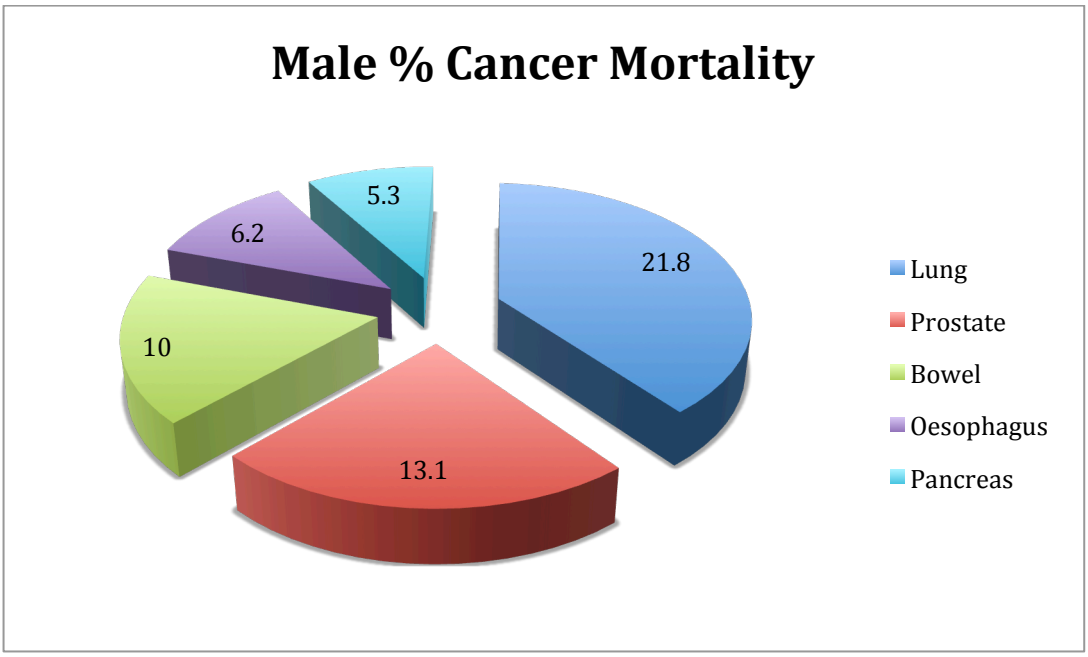

Figure 1-2 Male cancer mortality (% all malignant mortality) in the United Kingdom, 2016

Ampullary cancer arises from the epithelium of the Ampulla of Vater, into which the common bile duct drains. Ampullary tumours are usually diagnosed at an earlier stage than PDA and generally have a less aggressive clinical course.

Bile duct cancer or cholangiocarcinoma arises from the bile duct epithelium. These tumours may occur within the intra-pancreatic portion of the distal common bile duct and mimic PDA. These tumours are characterised by an infiltrative growth pattern, often along adjacent nerves.

Surgery is indicated for the treatment of this group of malignant tumours and evidence shows that the five-year survival following surgical resection for PDA varies from 6.5%-20% (3-9), for bile duct cancer 19.2%-30% (3, 5, 7, 8, 17, 18) and 33%-45% for ampullary cancer (3, 5, 7, 8).

Distinguishing between the main causes of periampullary cancers by histological examination can be difficult and is reflected in the wide range at which the lesions are reported in published series of pancreatic head resections. Histological examination of the resected malignant pancreaticoduodenectomy specimens revealed pancreatic head ductal adenocarcinoma (PDA) in 33-89%, being the most common histological type of these malignant tumours, ampullary carcinoma in 5-42%, distal bile duct cancer in 15-38% and duodenal carcinoma in about 10% (19-22).

Recent attempts have been made to standardise and improve the histology reporting of pancreatic and periampullary cancer specimens according to Royal College of Pathologists guidelines (23). This has generally led to a higher rate of diagnosis of ampullary and bile duct cancer compared to pancreatic cancer (24). These techniques have been adopted by the Pathology Department at Derriford Hospital including axial slicing of resection specimens (in transverse section rather than longitudinal along ducts) with careful macroscopic examination of the tumour centre in relation to peri-ampullary

structures, rather than a reliance on histological staining which has low specificity in determining precise tumour phenotype (25). In addition identification of associated epithelial dysplasia can be helpful, particularly for ampullary lesions (26).

Precise identification of the tumour origin is of clinical significance as the adjuvant treatment is different for this group of malignant tumours. The prognosis also varies widely after surgical resection of these lesions from the high chance of cure following resection of localised ampullary cancer to the dismal prognosis following resection of PDA with evidence of local and nodal spread. This has major implications for patients' counseling. Also historical confusion of these diagnoses has reduced the reliability of earlier studies of adjuvant chemotherapy, where inclusion of ampullary cancers may have increased the overall survival of patients groups and potentially reduced the treatment effect of drugs targeting pancreatic cancer.

Because of the historical tendency to over-diagnose pancreatic cancer histologically, radiologists have not made rigorous efforts to distinguish the lesions on pre-operative imaging. Previously, this has not been clinically important as the surgical treatment of the lesions is identical and decisions regarding adjuvant chemotherapy can be made after the final histology report is available. This situation is changing with the recent advent of neo-adjuvant treatment that may be recommended without a precise diagnosis in patients with borderline resectable or locally advanced periampullary cancer based on pre-operative imaging. The rationale for this approach is that in a proportion of patients the disease will be downsized by this treatment, which may facilitate future resection (27). Some patients however will suffer tumour progression during the treatment phase and the relative benefits of the technique are unknown. Therefore, it is likely to be important in the future that the organ of origin of periampullary cancers to be identified prior to commencing therapy and hence correct tumour characterization becomes very important.

A further aspect of preoperative staging periampullary cancers is the ability of imaging to predict resectability that has been generally classified as 'resectable', 'border-line resectable' or 'unresectable'. The radiological criteria determining the surgical resectability are subjective and relate to assessment of the involvement of pancreatic vascular structures and have not been validated in a UK series and there is a risk that patients may be over-staged in terms of their resectability and be denied effective treatment. This issue has also become more important recently due to the era of neoadjuvant treatment.

The policy of the Peninsula HPB unit has been to offer surgical exploration to patients with borderline resectable periampullary cancers if they are medically fit, as this is the most effective treatment.

The publication of the "Improving Outcomes Document" in 2000 has led to restructuring the pancreatic cancer services into regionalized centres with introduction of new referral pathways. This aimed at developing high standard National Healthcare Services by achieving higher resection rates and improving the overall survival rates.

1.1 Study objectives

This project will address four aspects of the current practice within the Southwest of England HPB Cancer Network regarding the pre-operative pathway in patients with potentially resectable pancreatic head malignancy.

1.1.1 Study one

Research hypothesis: Regionalisation of pancreatic cancer services into major regional cancer centres does not disadvantage patients who live at a distance from the cancer centre.

The aim is to study the effect of patient travel distance to the regional Peninsula HPB Cancer Centre in an era of centralisation of pancreatic cancer services on patients' outcomes including tumour resectability and long-term survival.

1.1.2 *Study two*

Research hypothesis: Delay to surgery does not adversely affect the resectability, tumour histological stage and long-term survival in patients with pancreatic head malignancy treated at the regional cancer centre.

The aim of this study is to examine the effect of the interval to surgery from the time of symptomatic presentation at the referring hospitals to the time of surgery at the regional HPB cancer centre on the tumour resectability, histopathological outcomes and overall survival of patients undergoing Kausch-Whipple procedure for presumed PHM at the Peninsula HPB cancer centre.

1.1.3 Study three

Research hypothesis: Arterial phase preoperative staging in addition to standard abdominal CT scan is unnecessary in the assessment of tumour resectability in patients with pancreatic head malignancy.

The aim of this study is to assess the relative ability of preoperative dual and triple-phase CT scan to determine the presence of radiological indicators of resectability in suspected pancreatic head malignancy.

1.1.4 Study four

Hypothesis: Preoperative abdominal CT scan is unable to differentiate tumour organ of origin in patients with presumed pancreatic head malignancy.

The aim of this study is to assess the ability of the pre-operative CT scan to distinguish the exact site of tumour origin in patients with pancreatic head malignancy by comparing consensus radiological opinion against final histological diagnosis.

2 Centralization of pancreatic cancer services

2.1 Introduction of centralisation and the structure of the Hepato-Pancreaticobiliary (HPB) cancer services

In 1995 the Calman-Hine report (28) outlined the requirements for revolutionary changes within the British health system through centralisation of the NHS cancer services. These recommendations were aiming to improve cancer services outcome by concentrating the workload within regional areas with MDT expertise. However it was the publication of the "Improving Outcomes Document" in September 2000 (29), that has reinforced these significant changes in the provision of the cancer services. As part of these changes, the provision of HPB and Upper gastrointestinal cancer services has undergone regionalisation with increasing emphasis on delivery of high quality services. Currently there are 34 tertiary HPB centres (including liver transplant) in the UK working within designated cancer networks, each serving a population of approximately two to four million (30).

This shift towards centralisation was driven by the volume-outcome relationship (31-33). There is a current strong evidence of positive relationship between the hospital volumes and improved outcomes in cancer care indicated by higher pancreatic resection rates (34, 35), lower operative mortality (36, 37) and improved long-term survival (38-40) in units with higher treatment volumes.

Several factors have contributed to this positive volume-outcome relationship. Firstly, pancreatic surgery involves complex procedures and it has been proven that the surgeon's technical skills will improve with years of practice and experience (41). Secondly, the role of medical oncologists using multimodality treatment protocols with concentrated numbers of patients with pancreatic cancer treated at high volume centres

has beneficial impact on survival (42). Thirdly, immediate postoperative care is an essential part of the patients' journey. Medical, nursing and other healthcare personnel acquire great experience by dealing with postoperative patients. This will enable prevention and early detection of immediate postoperative complications, therefore reducing postoperative mortality (43). Furthermore, the availability of on site interventional radiology expertise dealing with postoperative complications has led to reduction in re surgery rates and mortality (44). Their influential role is essential part of the regional cancer centre structure. Other health care systems in the USA and Netherlands have shown a similar reduction in postoperative mortality and better survival rates by concentrating the service into large volume centres (33, 34, 45, 46).

2.2 Structure of HPB cancer services

The NHS executive evidence in 2001 " Improving outcomes in upper gastrointestinal cancers" (47) has highlighted the key recommendations necessary for creating a new service model for the cancer services (Figure 2-1). Establishment of inter-linked cancer units and cancer centres within appropriate cancer networks is part of the reconfiguration process of cancer services in the NHS in order to provide effective treatment and to reduce treatment associated morbidity and mortality.

2.2.1 Cancer Units

The following are the minimum requirements to set up a pancreatic cancer unit are:

I. Multidisciplinary team (MDT) formed of medical and surgical gastroenterology, radiology, pathology, cancer nurse specialist and oncology.
II. Radiological facilities include ultrasound scan, MDCT, MRI, endoscopic or laparoscopic guided biopsy especially for patients deemed non resectable.

These facilities should establish a diagnosis and assess the tumour resectability.

III. Therapeutic facilities including resources for radiological or endoscopic biliary stent application and at least surgical palliation. It is anticipated that the cancer unit is able to provide effective palliation for 70-80% of patients.

IV. Ancillary services include intensive care unit, high dependency unit, pain team able to provide acute and chronic pain service, and dedicated nutrition team.

2.2.2 Cancer centre

The designated HPB cancer centres are usually based in either university teaching hospitals or large regional hospitals where full radiology, endoscopy and oncology services are available. In addition to the basic requirements to provide the service at the pancreatic cancer units level, the HPB cancer centres must have at least weekly MDT meetings where patients are jointly assessed by relevant MDT members including: physicians, surgeons, oncologists, cancer nurse specialists, radiologists, histopathologists, palliative care specialists, nutritionists and research personnel. The referring units should have access to these MDT meetings and to the final decision made by the specialist HPB team in order to start treatment for referred patients. This link between the referring hospital and the regional centre could be established by means of electronic image transfer system and through virtual video-link meeting.

2.2.3 Numbers of surgeons and surgeon volume

It is recommended that the specialised HPB units should have at least 5 surgeons, with each surgeon required for approximately 0.5 million of population in order to provide continuous elective and emergency services. All surgeons should be able to deal with acute HPB referrals regardless of the subspecialisation interest.

The number of resections is expected to be about 60-70 pancreatic resections per year for every 2 million population served. As the workload is currently shared between consultants within the unit, there is no current recommendations regarding the individual surgeon's volume; however it is expected to be equally shared between the members of the surgical team. The practice of two-consultant operation should be encouraged within the unit especially for high-risk complex cases.

2.2.4 Specialist radiologist

The HPB cancer centre is expected to have consultant radiologists with special interest and expertise in HPB radiology including Ultrasound scans, CT scan, MRI, PET scan and EUS. It is recommended that the unit should have 24- hour interventional radiology service to support the emergency HPB services. It is also recommended that the cancer centre has expert interventional oncology for purpose of chemo and radio-embolization, however when this service is not available on site, there should be a link with a nearby centre to provide the service when required.

2.2.5 Specialist endoscopy

Endoscopy service is essential part of the regional HPB centre providing daily routine and emergency services. The service includes OGD, ERCP and EUS provided by expert surgeons, radiologists, gastroenterologists and hepatologists.

2.2.6 Specialist pathology

Consultant pathologist with a special interest in HPB malignancy is a crucial member of the regional MDT meeting. This service should be available onsite with regular involvement in the weekly MDT meeting.

2.2.7 Cancer nurse specialist

The role of the cancer nurse specialist is to support patients and their family from the time of the diagnosis and during their treatment journey and postoperative care.

2.2.8 Anaesthetist and critical care specialists

It is expected that HPB regional centre would have a team of anaesthetists and intensivists with special interest in HPB disease. Their role is to ensure optimal pre-, peri- and post-operative management of patients undergoing major HPB surgery. This include access to both level 2 and level 3 beds.

2.2.9 Non-surgical oncology specialist

It is required that the regional HPB centre would have medical and clinical oncology expertise to cover the range of HPB cancers including primary and metastatic cases. They are encouraged to take part of clinical trials when available.

2.2.10 Audit and monitoring

Each HPB centre should adopt regular monitoring with regular peer review assessment to be able to validate their data and to maintain their status as a tertiary regional centre. The process of data collection has become an integral part of the surgeon's portfolio as well as the appraisal and revalidation requirements. Furthermore there is an increasing public demand for information about the quality of the services indicated by volume of work and outcomes. Currently, the Association of Upper Gastrointestinal Surgeons (AUGIS) and the Great Britain and Ireland Hepato-Pancreaticobiliary Association (GBIHPBA) are developing the Surgical Workload Outcomes Audit Database (SWORD) (48), a national database to facilitate individual surgeons and cancer units to view their own data as well as their peers outcomes. Auditing process also includes examining the referral pathway, management protocols, outcomes including the resection rate, hospital mortality and the morbidity, and survival rate.

2.2.11 Education, training and research

The current training recommendation for surgeons to specialise in HPB surgery is to achieve successful completion of their training in General Surgery as well as spending a minimum of one and preferably two years at senior training years (ST7 and ST8) in a HPB unit. A Post-CCT senior fellowship is also recommended for one to two years in order to consolidate advanced surgical skills especially for complex procedures.

Clinical research and involvement in randomised trials is an essential part of the continuous professional development for doctors. It is therefore recommended that HPB surgeons should actively participate in research activities and clinical trials. Nominating a research lead that could co-ordinate and plan research projects locally or through a collaborative work could facilitate engagement in clinical research activities as well as recruiting patients into NIHR funded randomised trials. This could be a good opportunity for trainees who wish to pursue HPB research.

2.2.12 Early diagnosis and screening

In the UK, there are no current guidelines for pancreatic cancer screening. This is probably due to the fact that low disease incidence as well as there is no ideal screening tools. It is recommended however that high-risk patients such as patients with Familial Adenomatous Polyposis (FAP) should undergo 3-yearly duodenoscopy starting from age of 18 years old.

2.2.13 Outcome standards

The quality pancreatic cancer service is measured by certain criteria including a yearly pancreatic resection rate of 60-70 with postoperative mortality rates less than 5%, 10% and 20% for in–hospital, 90-day and 1-year mortality respectively. Whipple's procedure as well as Pylorus Preserving Pancreatico-Duodenectomy (PPPD) are the recommended surgical approaches with the aim to achieve a median number of at last 15

lymph nodes harvested. Postoperatively, all patients should follow Enhanced Recovery After Surgery (ERAS) protocols with expected length of stay to be less than 14 days. The long-term survival is determined by several factors; nevertheless the cancer unit survival rates should be consistent with published figures.

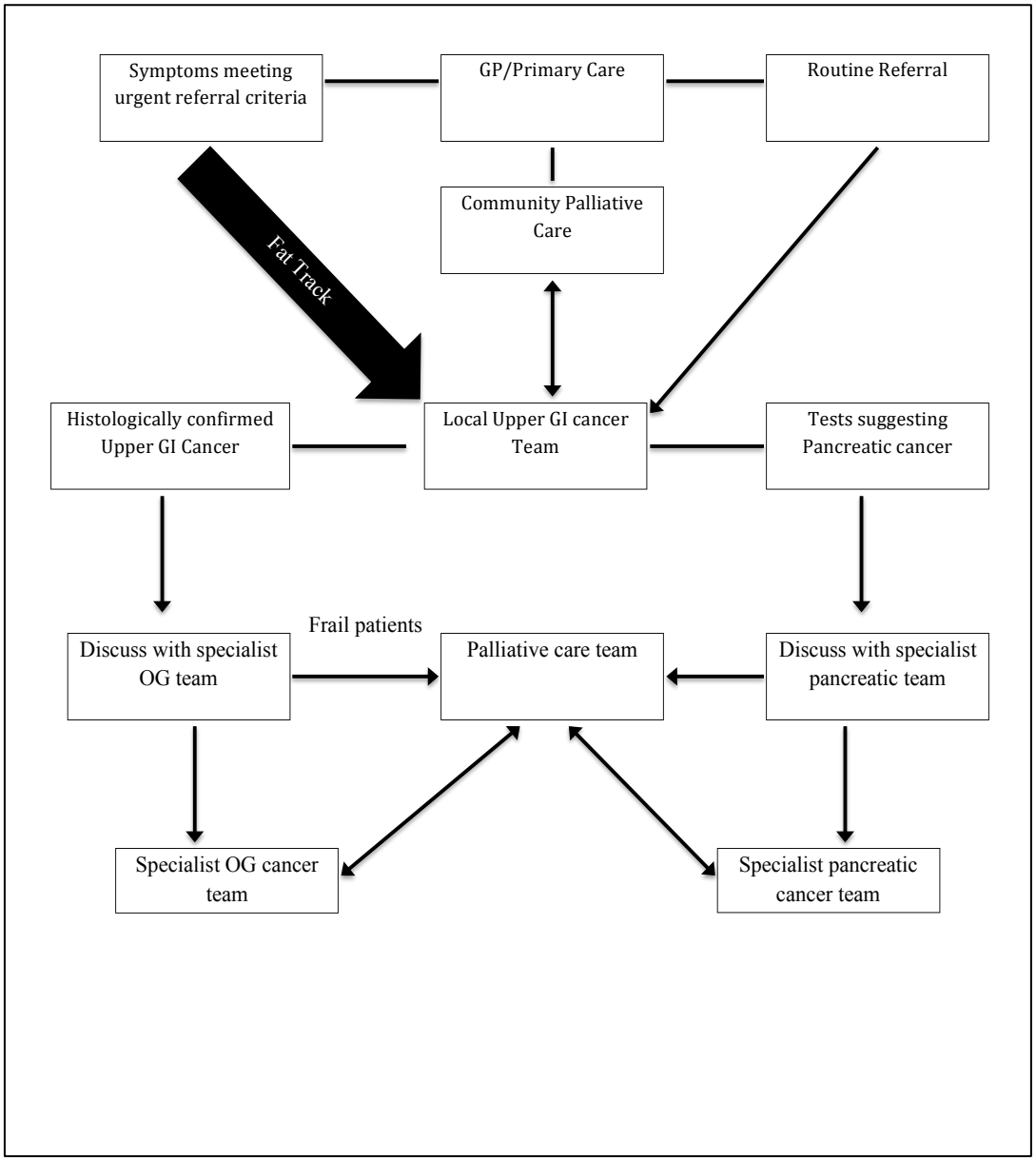

Figure 2-1 Service model for pancreatic and oesophagogastric cancer services " Improving outcomes in upper gastrointestinal cancers" (47).

2.3 Referral pathway into the tertiary HPB centre

In the UK, the current practice shows that gastroenterologists often investigate patients presented with jaundice who might be developing a pancreatic head malignancy. There are several steps in the referral pathway before surgery is undertaken which are summarised in (Figure 2-2). This current pathway commonly takes about 2-3 months before surgery is undertaken and is longer for patients referred from outside the regional centres. Although many of these patients do not suffer pain, they can suffer other symptoms due to biliary obstruction including pruritus, indigestion, loss of weight and diarrhoea. For this reason most patients undergo an ERCP and insertion of a stent to relieve biliary obstruction at the referring unit, although there is a strong evidence to support proceeding to pancreatic resection without preoperative biliary drainage on patients with bilirubin level less than 250umol (49, 50). Therefore, patients presenting with jaundice need to be discussed with the tertiary HPB centre with regard to the appropriate management protocol.

The current operational pressures relating to theatre capacity and ITU availability within the NHS might cause a further delay. Patient anxiety regarding delays to surgery is commonly experienced during consultations and the possible influence of these delays on the outcome is often raised.

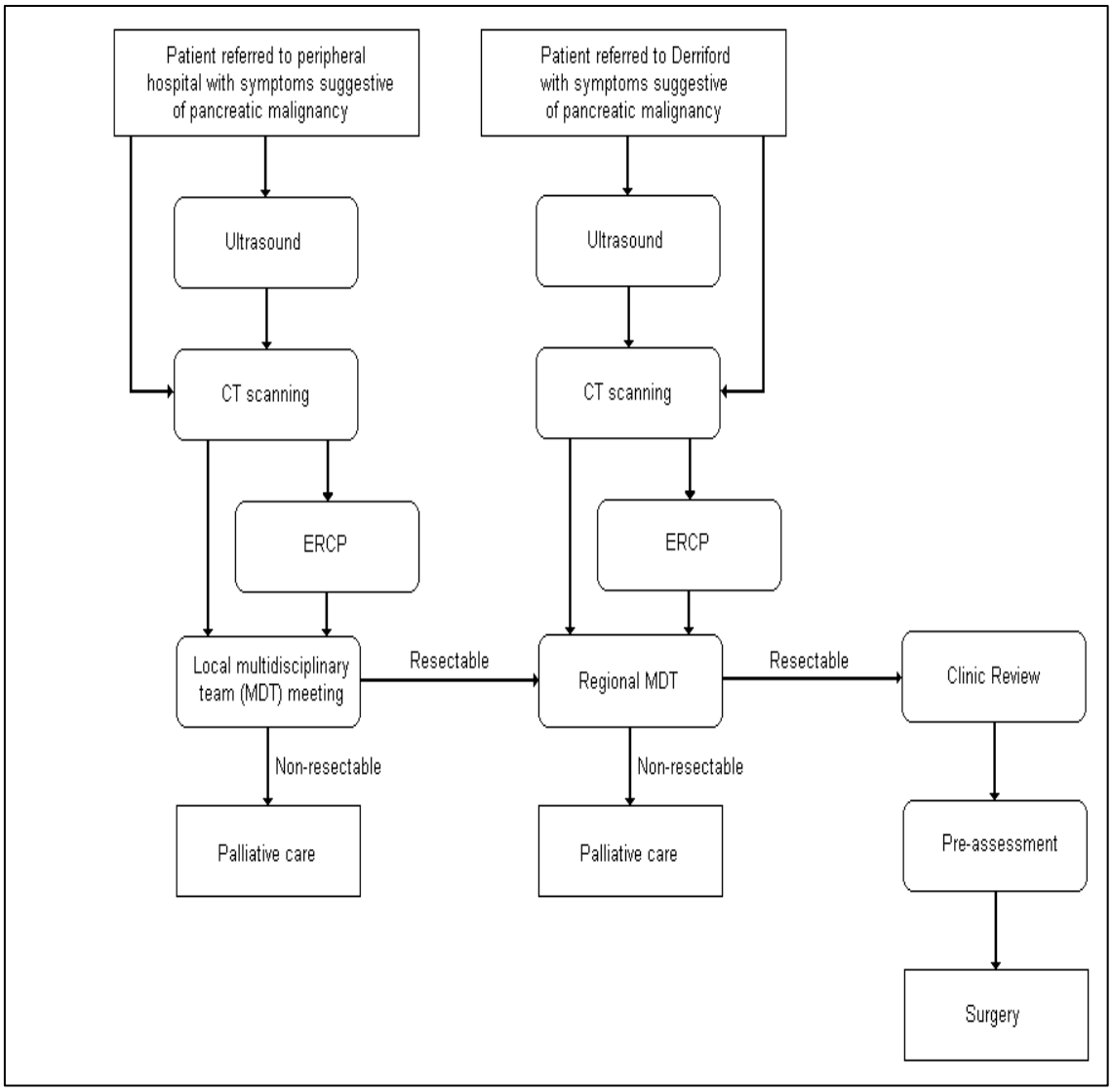

Figure 2-2 Patient pathways before surgery for periampullary cancer

It is recommended that patients with symptoms that might raise the suspicion of pancreatic cancer should be referred for investigations such as ultrasound scan, CT scan or MRI, which could be arranged at the DGH on an outpatient basis. Further specialised investigations such as EUS or ERCP should be carried out at the specialised HPB centre.

The following criteria should be referred to the cancer unit for further investigations:

I. Obstructive jaundice

II. Unexplained weight loss
III. Unexplained gastrointestinal bleeding or iron deficiency anaemia (in absence of an upper gastrointestinal or colorectal cause)
IV. Unexplained upper abdominal or back pain
V. Unexplained steatorrhoea.
VI. ''Idiopathic'' acute pancreatitis (no gall stones, no alcohol) in patients over 50 years of age.
VII. Unexplained diabetes in patients over 50 years of age (no family history, obesity, or steroids).

Patients' referral should follow an agreed documented referral policy between the general practitioner (GP) and the cancer unit and also between the local district general hospital (DGH) and the specialized HPB centre which expected to provide a 24-hour on call service by the regional HPB surgeon. This allows regional cover for HPB emergencies that might require immediate patient transfer to the centre or urgent transfer within 24 hours. The two-week waiting policy should be adopted by the cancer units receiving GP referrals and by the regional HPB centres responding to the cancer unit referrals.

2.4 Structure and current practice of the Peninsula HPB cancer centre

The Peninsula HPB unit, established in 2006, is the regional centre for liver, pancreatic and biliary cancer services as well as benign diseases within the South West of England. It is based in Derriford Hospital, Plymouth, UK. The current team consists of four consultant surgeons, six consultant hepatologists, four consultant radiologists with special interest in gastro-intestinal diseases, two consultant oncologists, two cancer nurse specialists and one consultant histopathologist. The unit acts as both local and tertiary referral centre that receives referrals from other hospitals across the South West Peninsula. The unit is

currently benefiting from having on site facilities such as CT scan, MRI, PET scan, EUS, Endoscopy, ERCP as well as interventional radiology to ensure continuous 24- hour service provision with on call consultant surgeon dealing with acute referrals and HPB emergencies. All patients referred to the unit are discussed at the regional HPB MDT before being offered surgery. Video-audio link with the referring hospitals have been used to ensure access to these meetings. The current practice is to offer surgery to all referred patients with resectable or borderline resectable disease. Surgical resection is performed by classic Whipple's procedure with pancreatico-gastrostomy reconstruction. In-patient care follows a standard Enhanced Recovery After Surgery (ERAS) protocol.

The unit is actively engaged in audit, research and publications within areas of HPB diseases. The unit offers opportunities for surgical trainees and clinical research fellows to enhance their knowledge in HPB related research projects. The unit offers higher training opportunities in HPB surgery via an established fellowship program for senior trainees with special interest in liver, pancreatic and biliary surgery.

3 Anatomy and physiology

3.1 Anatomic history

Eristoratos (310-250 BC) was the first to mention "Pancreas" in his writings (51). In 1543,Vesalius mentioned the word 'Pancreas' as derived from its Greek name 'pan' (all) and 'kreas' (flesh)(52, 53). In 1642, Wirsung described the main pancreatic duct (main pancreatic duct of Wirsung)(54). Santorini noticed the presence of the accessory pancreatic duct later in 1724 (55). He also described the main and the accessory duodenal papillae. In 1685, Gottfreid Bidloo was the first to illustrate the presence of the ampulla (the common duct dilatation) and the papilla (the projection into the postero-medial wall of the second part of the duodenum)(56). However it was named after Abraham Vater in 1720 who subsequently confirmed Bidloo's findings (57).

3.2 Morphological description, anatomical location and relationship

3.2.1 Pancreas

For morphological description, the pancreas is divided into the head representing about 30% of the gland while the neck, body and tail represents nearly 70% (51, 58).

It weighs about 80 g and lies transversely fixed in the retroperitoneal space between the duodenum on the right side and the spleen on the left side with the transverse mesocolon lying anteriorly. The omental bursa lies superiorly and the greater sac lies inferiorly (59, 60). The pancreatic head lies within the duodenal concavity opposite to the level of the second lumbar vertebra. Osler has described the relationship of the pancreatic head and the duodenal loop as "The abdominal area of romance, where the head of the pancreas lies folded in the arms of the duodenum"(61).

Coming off the head is the uncinate process, which lies in front of the aorta and the inferior vena cava (IVC) and relates anteriorly to the superior mesenteric vessels.

The pancreatic neck represents the junction between the head and the body and is related posteriorly to the superior mesenteric vessels and the junction between splenic vein and the superior mesenteric vein (SMV) forming the portal vein (PV).

The body is separated anteriorly from the posterior surface of the stomach by the lesser sac. The transverse mesocolon lies anteriorly. It is related posteriorly to the aorta, the origin of the superior mesenteric artery (SMA), left crus of the diaphragm, splenic vessels, left kidney along with the left renal vessels and the left suprarenal gland.

The tail extends to the left between the two layers of the lienorenal ligament. It is relatively mobile, compared to other parts, and reaches the splenic hilum in about 50% of individuals (51, 61).

3.2.2 Pancreatic ducts and Common bile duct

The pancreatic duct system classically consists of the main pancreatic duct of Wirsung and the accessory duct of Santorini.

The main pancreatic duct of Wirsung starts at the pancreatic tail by junction of multiple lobular ducts and runs through the tail and the body, midway between the upper and lower pancreatic margins closer to the posterior surface, towards the head. As it runs within the body it increases in diameter as it receives further lobular ducts that open into the main duct at right angles in alternate fashion (Herringbone pattern)(51, 60).

At the head it joins the common bile duct (CBD), formed by junction of the common hepatic duct and the cystic duct in the lateral portion of hepato-duodenal ligament, into a common pancreaticobiliary duct, which then opens into the papilla of Vater (major duodenal papilla) on the posteromedial wall of the second part of the duodenum (62, 63).

The accessory duct of Santorini starts at the pancreatic head closer to its anterior surface (opposed to the main duct) by junction of several lobular ducts. It drains the antero-superior part of the head and the uncinate process. It opens into the minor duodenal papilla, which lies cephalad to the major duodenal papilla, or into the main pancreatic duct in some cases (60, 62).

3.2.3 Ampulla of Vater

Ampulla is defined as a dilatation of the common pancreatico-biliary channel on the postero-medial wall of the second part of the duodenum adjacent to the major duodenal papilla. It lies approximately 7-10 cm from the pylorus (61) and has been classified into three types by Michels (64) based on the site of opening of the pancreatic and common bile ducts and colleagues have classified the ampulla into three types:

3.3 Arterial supply and venous drainage

The pancreatic vascular system (Figure 3.1) is a complex system with frequent normal variations. The arterial vascular network is derived from the coeliac axis and the superior mesenteric artery (SMA). The head of pancreas receives its arterial blood supply via branches derived from anterior and posterior arterial arcades. Arteries forming this complex arterial circulation arise from the gastro-duodenal artery (GDA), forming the superior component of the arcade, and the SMA forming the inferior component. This arterial arcade is almost always present and it supplies the head of the pancreas and the duodenal wall along its concave surface. The anterior arterial arcade is formed by junction of anterior superior pancreatico-duodenal artery from the GDA, branch of the celiac trunk, and the anterior inferior pancreatico-duodenal artery from the SMA. Junction of posterior superior pancreatico-duodenal artery, from the GDA, and the posterior inferior pancreatico-duodenal artery of the SMA forms the posterior arterial arcade.

The body and tail are supplied via numerous named and unnamed branches of the splenic and the left gastro-epiploic arteries (51, 58, 60, 65, 66). The ampulla of Vater receives arterial blood supply via the posterior superior pancreatico-duodenal artery, branches of the gastro-duodenal artery, which anastomose with the posterior inferior pancreatico-duodenal artery, and branches of the superior mesenteric artery. The retro-duodenal artery, branch of the GDA, gives origin to the ascending branches that anastomose with the descending branches of the cystic and right hepatic arteries at the lower part of the CBD (61).

The venous drainage of the pancreas (Figure 3.1) is through veins that run parallel and superficial to their arterial counterparts. The main venous drainage is into the portal, splenic, superior and inferior mesenteric veins while the pancreatic neck represents a site of confluence of the entire portal circulation where the splenic vein joins the SMV forming the portal vein posterior to the neck, which in turn receives the posterior superior pancreatico-duodenal vein (51, 58, 60).

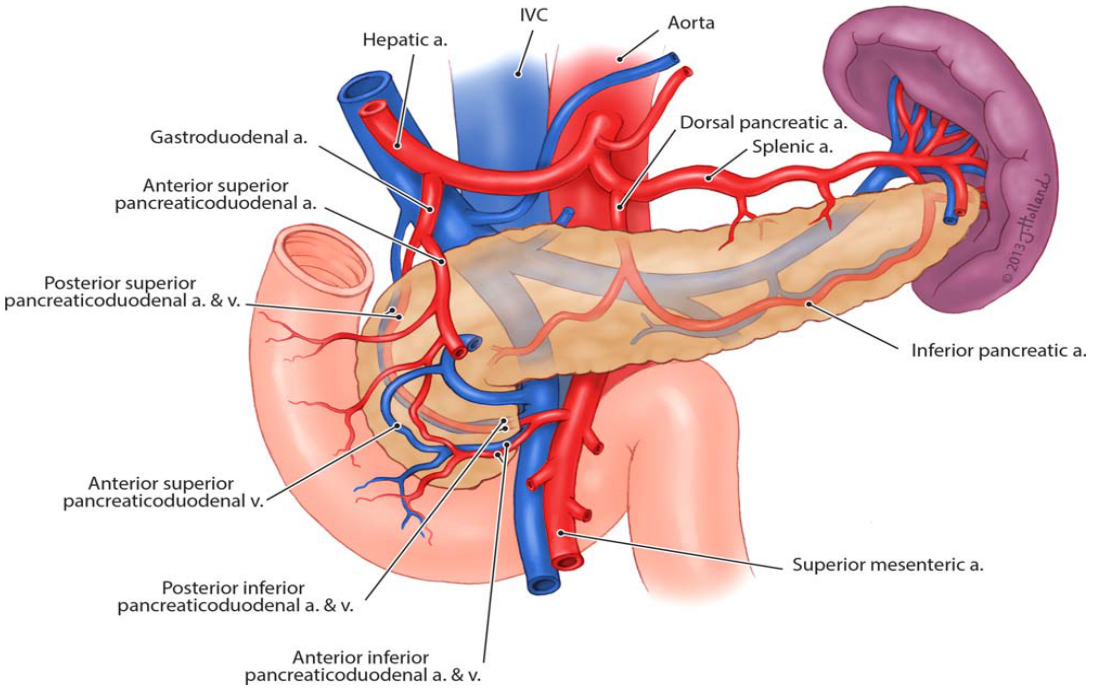

Figure 3-1 The arterial blood supply and the venous drainage of the pancreas (Cesmebasi A, et al.(67) With permission granted for thesis purpose).

3.4 Lymphatic drainage

The lymphatic drainage of the pancreas is formed of extensive tributaries followed by lymphatic channels, which accompany the blood vessels in the interlobular spaces and on the surface of the pancreas. They drain into five main collecting lymphatic trunks and lymph node groups namely superior, inferior, anterior, posterior and splenic as classified in 1978 by Cubilla (68) based on their anatomical location around the pancreas. The mapping system published by the Japanese Pancreas Society has assigned a station numerical code corresponding to the node anatomical location (Figure 3.2)(69). The following nodes should be included in standard Whipple's procedure: supra and infra-pyloric (station 5&6), along CHA (station 8a), along bile duct (station 12b), around cystic duct (station 12c), posterior aspect of the superior and inferior portions of pancreatic head (station 13a), right lateral side of SMA (station 14a&14b), on anterior surface of the superior and inferior portion of pancreatic head (station 17a&17b) (70).

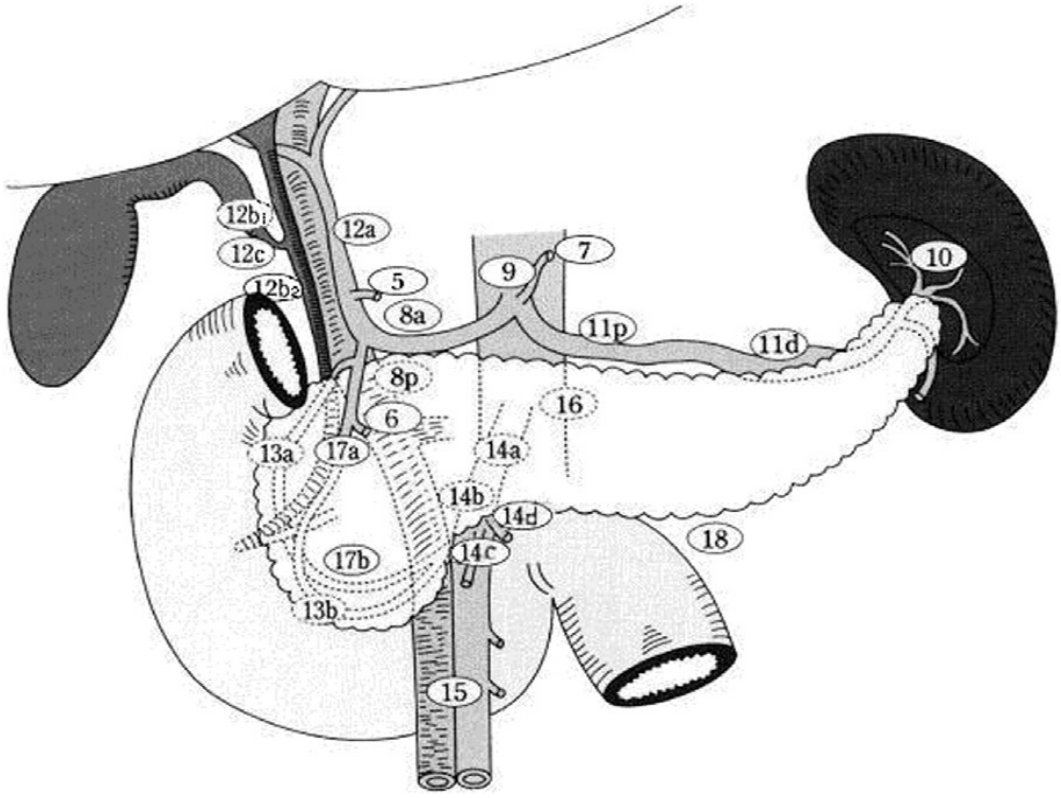

Figure 3-2 Japan Pancreas Society nomenclature of peri- pancreatic lymph nodes

3.5 Nerve supply

The sympathetic nerve supply is derived from the 6th to 10th thoracic spine segments. The parasympathetic fibers are through the coeliac division of the posterior vagal trunk. Sensory fibers and fibers carrying pain sensation from the pancreas, run through sympathetic and parasympathetic systems (60, 71).

3.6 Physiology

The pancreas functions as a mixed gland with endocrine and exocrine properties with the endocrine cells embedded into exocrine part. The main function of the endocrine pancreas is to regulate blood glucose level through production of several hormones involved in glucose metabolism including Glucagon, Insulin, Somatostatin, Gastrin and Pancreatic Polypeptide hormones secreted by Alpha, Beta, Delta and Gamma (F) cells of the islets of Langerhans respectively (72). The control of the endocrine pancreas is exclusively under the parasympathetic nervous system (73). Acetylcholine stimulates the secretion of insulin and glucagon while noradrenaline suppress insulin release in response to high glucose levels. It also inhibits the release of somatostatin and PP hormones (71, 72, 74, 75).

The main function of the exocrine pancreas is secretion of clear watery alkaline (pH 8.0-8.3) juice that is rich in digestive enzymes. These include proteolytic enzymes (trypsin, chymotrypsin, elastase, ribonuclease and deoxyribonuclease), lipolytic enzymes (lipase, colipase and phospholipase A2) and amylolytic enzymes (amylase). It is regulated by a complex neuro-hormonal mechanism. In addition to the vagal cholinergic fibers, the ductal and centro-acinar cells (bicarbonate ions and water transport) are under the control of the hormone Secretin (produced by duodenum and jejenum) while the exocrine acini (pancreatic digestive enzymes release) are under control of the duodenal cholecystokinin hormone (71, 72).

3.7 Periampullary cancers

Periampullary cancers include malignant tumours arising from Ampulla of Vater and other organs within 1 cm as these tumours tend to have a similar clinical presentation. These tumours include carcinoma of the head of pancreas, ampullary carcinoma, distal bile duct cancer and duodenal cancer (76). Identification of the exact site of the tumour origin could be difficult due to the close anatomical proximity of these sites histological similarity. The clinical distinction between non-pancreatic periampullary cancers from pancreatic cancer found in the region of pancreatic head is challenging however, For staging purposes, this distinction between these sites is purely based on anatomical origin of the tumours (TNM7)

3.8 Presentation

Patients with pancreatic head or periampullary cancer can often present with similar symptoms due to the close anatomical proximity of the organs involved. The presenting symptoms include manifestations of biliary obstruction in form of jaundice, dark urine, pruritus and acholic stool. Patients might experience intermittent vague abdominal pain, which become constant and severe that radiates to the back in advanced cases. Some patients might present with nausea and vomiting, which might indicate locally advanced disease with gastric outlet obstruction or duodenal involvement. General manifestations include anorexia, unexplained iron deficiency anaemia, fatigue, unexplained weight loss and malaise.

Pancreatic cancer should be excluded in patients with new adult onset diabetes with no family history or predisposing factors and in patients with unexplained episode of acute pancreatitis (76). Patients with duodenal cancer usually present with vague symptoms, which include intermittent abdominal discomfort, vague abdominal pain, GIT bleeding,

3.9 Blood tests and tumour markers

Full blood count may reveal anaemia or reactive thrombocytosis. Patients with biliary obstruction may show evidence of abnormal liver function tests with raised bilirubin, alkaline phosphatase, Gamma Glutamyltransferase (GGT), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST).

Cancer Antigen 19-9 (CA19-9) is the most widely used tumour marker in association with pancreatic cancer diagnosis and surveillance and it is elevated in nearly 75% of cases. However it is a non-specific marker as it may be elevated in benign hepatobiliary conditions like acute and chronic pancreatitis or in some cases of obstructive jaundice.

Other tumour markers not widely used in clinical settings include carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1) (77), SPan-1 (78), PAM4 (79), macrophage inhibitory cytokine-1 (MIC-1) (80), faecal KRAS mutation (81), DUPAN-2 (82), alpha1,4-N-Acetylglucosaminyltransferase (alpha4GnT) (83) and DNA methylation in pancreatic juice (84).

3.10 Histopathological diagnosis

Histopathological examination of the resected malignant pancreaticoduodenectomy specimens have shown that pancreatic head ductal adenocarcinoma (PDA) is the most common histological type in this group of malignant tumours being found in 33-76% (5, 24, 85-87) of the specimens, followed by ampullary carcinoma in11.5%-36% (7, 88), distal bile duct cancer in nearly 5-28% (5, 24, 85-87), and duodenal carcinoma in about 5-14% (5, 24, 85-87).

The Royal College of Pathologists guidelines highlights the standardised reporting of pancreatic and periampullary cancer specimens including axial slicing of resection specimens i.e. slicing perpendicular to the long axis of the duodenum (Figure 3.3)(23).

This has led to a higher rate of diagnosis of ampullary and bile duct cancer compared to pancreatic cancer (24).

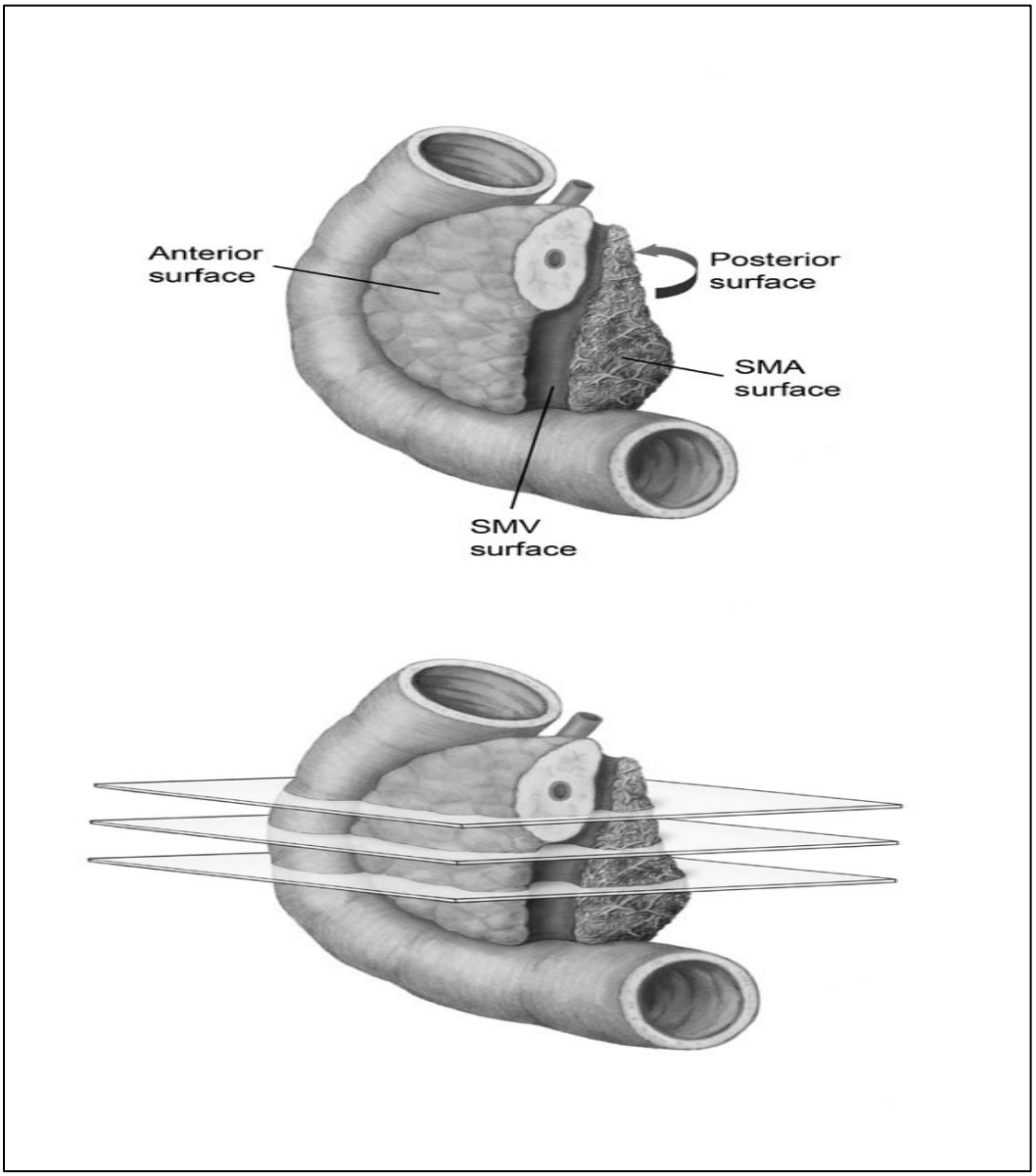

Figure 3-3 Head of the pancreas and the axial dissection

3.11 Pancreatic cancer

The term pancreatic cancer usually refers to PDA, which represents about 85-90% of primary exocrine pancreatic neoplasms with about two-third of cases are found in the pancreatic head (89).

3.11.1 Incidence, epidemiology and mortality of PDA

PDA is one of the most aggressive fatal malignant neoplasms that accounts for about 3% of all cancers and about 7% of all cancer related mortality with an estimated increased mortality figures to rank 4th among cancer related deaths in the USA (1). In the UK, it is the eleventh most common diagnosed cancer in the UK (12).

Less than 20% of patients have a resectable tumour at the time of diagnosis with 5-year survival rate of 3-5% that would increase to about 6.5%-20% in patients with successful surgical resection (3-10).

Pancreatic ductal adenocarcinoma, which accounts for more than 90% of all pancreatic tumours, is a devastating malignancy with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease and 5 year survival of less than 7% (90). Survival rates for patients with PDA are extremely poor, primarily due to the majority of tumours being at an advanced stage at diagnosis (91, 92).

3.11.2 Aetiology and risk factors for pancreatic cancer

Several risk factors have been identified as predisposing factors in the pathogenesis of pancreatic adenocarcinoma.

3.11.2.1 Smoking

Smoking has been universally identified as a well-established, major modifiable risk factor accounting for 25-30% of the causes (93). Current smokers carry a significant 75%

increased risk of developing pancreatic cancer compared to non-smokers with a positive dose response effect, depending on the number of cigarettes smoked and the duration of smoking, which might persist for a minimum of ten years after smoking cessation (93). Several epidemiological studies have confirmed the role of smoking in the pathogenesis of pancreatic cancer (94-119). Moreover smoking has been identified as a risk factor for familial pancreatic cancer (120). Tobacco carcinogens can reach the pancreatic gland via blood stream or directly through passage of the ingested tobacco from duodenum into the pancreatic duct. Smokeless tobacco such as chewing tobacco, snuffs and pipes has been identified as a risk factor (121-123). Pancreatic cancer mortality is increased among current smokers with risk increased as high as 60% (124-126).

Smoking cessation has been associated with potential risk reduction, however the exact duration of smoking cessation required to reduce the risk to non-smoker levels is debatable and ranges from 5 to 20 years (94, 97, 98, 125). On the other hand, a hospital based case-control study in Italy by Talmini (99) and a population based Canadian study by Anderson (127), concluded that no association existed between quitting smoking and pancreatic cancer risk reduction.

Implementing smoking cessation programs have shown risk reduction in pancreatic cancer mortality (128).

3.11.2.2 Alcohol

The role of alcohol consumption in the development of pancreatic cancer is controversial with inconsistent results. Several epidemiological studies revealed an association between alcohol intake and the risk of pancreatic cancer especially among heavy drinkers with increased years of drinking (96, 99, 129-133). On the other hand, some studies concluded no link between alcohol consumption and development of pancreatic cancer (95, 134).

3.11.2.3 Body weight and physical activity

Increased body weight, high body mass index (BMI ≥30) and the lack of physical activity have been identified as potential risk factors for pancreatic cancer. Several epidemiological studies demonstrated the association between increased BMI and the risk of developing pancreatic cancer (96, 124, 127, 135-138). On the contrary reduced risk was linked to regular physical activity but with inconsistent results (139-141).

3.11.2.4 Pancreatitis

The relation between pancreatitis and development of pancreatic cancer is well established with increased relative and absolute risk especially with age. The latent period between the attack of pancreatitis and the development of the pancreatic cancer is variable with each type of pancreatitis including chronic, acute and hereditary pancreatitis (100, 127, 142-149).

3.11.2.5 Diabetes

Diabetes is linked to increased risk of pancreatic cancer development (127, 132, 150, 151). Insulin dependent diabetic patients are at a higher risk when compared to other diabetic patients (100, 149).

Clinical presentation of recent onset (less than two years) adult diabetes should raise the suspicious of pancreatic cancer, which should be excluded especially if no associated family history of diabetes or predisposing factors like obesity or steroid therapy (76) are present.

3.11.2.6 Diet

The association between pancreatic cancer risk and certain food ingredients is controversial while food could play a two-way risk associated factor. The risk increases with certain food products with high glycemic index (GI) or with high sugar contents such

as sweets, refined carbohydrates and candy (152-154). Consumers of food containing high saturated fatty acids, lamb and beef products, high energy fat, saturated and polyunsaturated fat are at increased risk of pancreatic cancer (155-157); while food rich in vegetables, fruits, fibers, high content of omega-3 fatty acids, vitamins C and E are associated with risk reduction (127, 155-157).

3.11.2.7 Genetics

Acquired genetic alteration has been identified as an associated risk factor for pancreatic cancer. Several genetic syndromes with an autosomal dominant inheritance have been associated with increased risk of pancreatic cancer including hereditary breast cancer syndrome (BRCA2), familial atypical multiple mole melanoma syndrome (FAMMM), Peutz-Jeghers syndrome, Von Hippel-Lindau disease, and hereditary nonpolyposis colorectal cancer (HNPCC)(158-164).

Individuals with family history of pancreatic cancer carry a risk of increased pancreatic cancer incidence (127, 165, 166).

3.11.2.8 Other risk factors

Other factors have been identified as associated with increased risk but with inconsistent results.

Allergic conditions such as asthma and hay fever found to have an associated risk reduction effect (100, 167). ABO- blood group found to be linked to pancreatic cancer risk where individuals with non-O blood type carry a high risk (168-171). The relationship between coffee consumption and increased risk of pancreatic cancer is debated with variable results (127, 172-174).

3.11.3 Histopathological features of Pancreatic Ductal Adenocarcinoma

PDA is a gland-forming tumour where the glands tend to be rounded in shape or slightly angulated giving the tumour its indolent appearance. The extent and the quality of the glands decide the degree of tumour differentiation, which correlates with the patient's outcome (175).

The characteristic anisonucleosis (more than four-one nuclear size variation within a single gland) helps in the histological confirmation of the diagnosis (176, 177). The tumour characteristically elicits a hard desmoplastic stromal reaction, which is almost always present. The shield-like property of the stroma prevents the penetration of the chemotherapy agents into the cancer tissues (178).

Rare cystic changes secondary to tumour necrosis may develop indicating aggressiveness of the tumour which can infiltrate into the mesenteric vessels, lymphatic vessels and nodes, nerves (peri-neural invasion), distal CBD, duodenum, ampulla of Vater and extra pancreatic soft tissue (179).

3.11.4 Morphological and genetic precursors to the PDA

Several morphological and genetic mechanisms are involved in the development of PDA which has been summarised into the pancreatic cancer progression model (Figure 3-4) (180). The precursors of the PDA believed to be the intraepithelial lesions include pancreatic intraepithelial neoplasia (PanIN 1A, 1B, 2 and 3), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), and solid pseudopapillary tumours (181).

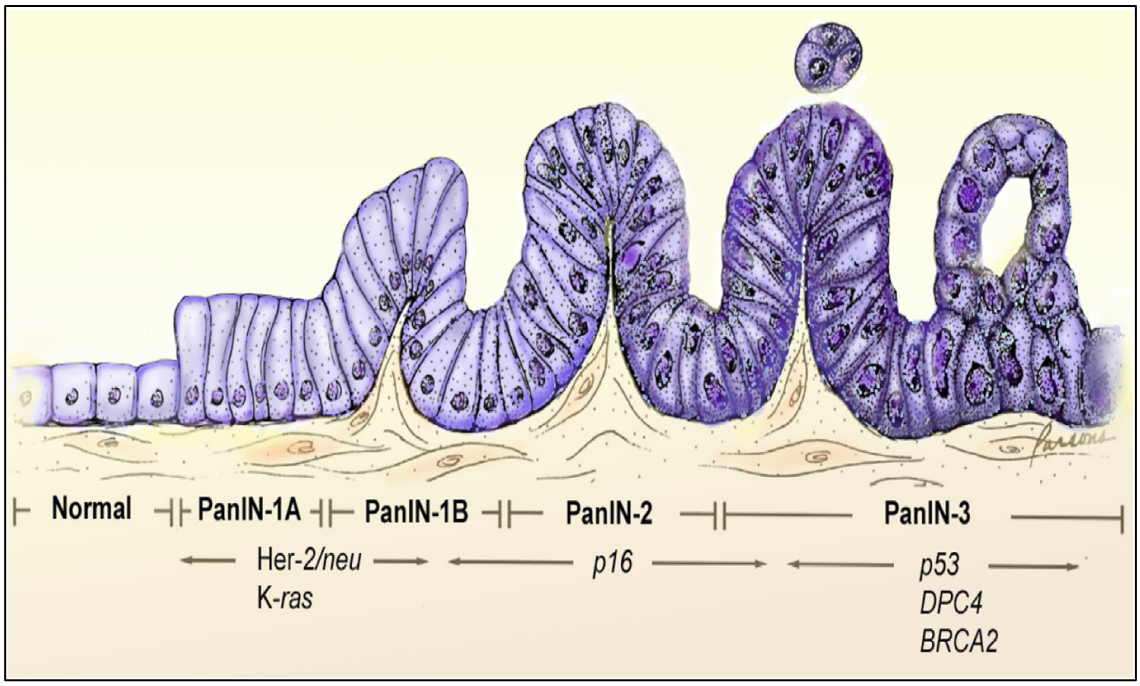

Figure 3-4 Pancreatic Cancer Progression Model (with permission for thesis purpose from Hruban et al.(180)

3.12 Ampullary cancer

It represents about 11.5-36% (7, 88) of all resected periampullary cancers and about 75% of the ampullary tumours (182). It carries a favorable outcome that is better than PDA and the bile duct cancer. In the UK, it is a rare disease with a stable incidence rate between 1998 and 2007 with 3,258 (52.7% males) newly diagnosed cases. The incidence is associated age. It was noticed that incidence is slightly higher in more deprived areas (183, 184). The five-year survival following surgical resection varies from 33%-45% (3, 5, 7, 8). Smoking has been identified as a strong contributing risk factor for cancer ampulla of Vater (185). Ampullary cancer is also associated with familial adenomatous polyposis (FAP) (162, 186). The adenoma-carcinoma sequence has been reported as a risk factor (187, 188).

3.12.1 Histopathological features of ampullary cancer

Ampullary carcinoma could be histologically classified into two categories based on the epithelial origin:

I. The intestinal type: as the name suggests, it originates from the intestinal epithelium overlying the ampulla.

II. The pancreaticobiliary type: arises from the endothelium lining of the distal CBD, the distal pancreatic duct or the common pancreaticobiliary channel.

Patients with the pancreaticobiliary type carry poor prognosis, as this type is an aggressive tumour that behaves like PDA, while patients with the intestinal type carry better prognosis as the tumour behaves like duodenal cancer (182, 187, 189-193).

3.13 Bile duct cancer

Bile duct cancer is the commonest biliary malignant neoplasm. It accounts for 3% of all gastrointestinal tract (G.I.T) cancers (194) with five-year survival of about 10% (195) that improves with surgical resection to 19.2%-30% (3, 5, 7, 8, 17, 18). The overall incidence is rising in the UK with a slightly higher incidence among males with male to female ration is 1.2: 1 (183, 196). The incidence is rare before the 4th decade of life and there is an associated risk with increased age where 65% of cases are diagnosed above the age of 65 years (195). Most case are sporadic, however primary sclerosing cholangitis is the commonest identified risk factor with absolute lifetime risk of 5-35% (197). Other risk factors include chronic intraductal gallstones, bile duct adenoma and biliary papillomatosis (198, 199). Congenital anomalies including choledochal cysts and Caroli's disease are associated with increased risk (194, 195). Increased risk is also associated with chronic viral hepatitis including hepatitis B virus (HBV) or hepatitis C virus (HCV) and other causes of liver cirrhosis (195, 198, 200, 201). In South-east Asia, liver flukes (Opisthorcis viverrini and Clonorchis sinensis) are responsible for increased risk (195,

199). Thorotrast, a previously used contrast agent, was found to be associated with 300 fold increased risk (202).

3.13.1 Histopathological features of bile duct cancer

Adenocarcinoma of the bile duct is the commonest histological type of bile duct cancers representing about 90% of biliary cancers (203). It arises from the intraductal epithelium of the biliary tree either within the liver (Intra-hepatic Cholangiocarcinoma) or more commonly outside the liver (Extra-hepatic Cholangiocarcinoma) which is further subdivided into types I to IV (Bismuth classification) (204) according to the tumour site and hepatic duct system involvement. Among histological types, sclerosing differentiation is the most common and it is characterised by annular bile duct thickening (199, 205).

3.14 Duodenal cancer

Duodenal cancer is rare representing 0.3% of all gastrointestinal cancers. Duodenal adenocarcinoma represents over 50% of all malignant tumours affecting the duodenum. It can arise from any part of the duodenum, however the second part is the most common site (206, 207). The global peak incidence is the 7th decade of life, with men being affected more than women (71, 208, 209). In the UK, 2684 patients with median age of 72 were diagnosed between 1998-2007. The male to female ratio is about 1.4:1 (183, 184). The five-year survival is 16.1% following diagnosis (183).

Polyps found in patients with familial adenomatous polyposis (FAP), Gardner's syndrome and Celiac disease carry a malignant transformation risk. Patients with FAP carry lifetime risk of nearly 100% for developing precancerous adenomatous polyps that might progress to adenocarcinoma or might arise in the adenoma (186, 210-213), with a median interval of 22 years between a colectomy for FAP and the development of duodenal cancer (212).

3.14.1 Histopathological features of duodenal cancer

Adenocarcinoma of the duodenum is the commonest type among other malignant neoplasms affecting the duodenum. Three histological types have been identified including polypoid, schirrous, and sessile differentiation (214).

3.15 Surveillance of high risk populations

Due to the unavailability of a simple screening test as well as low disease incidence in the general population and there is no current pancreatic cancer screening program(215).

The Pancreatic section of the British Society of Gastroenterology has defined the at-risk patients group to include patients with chronic pancreatitis, adult onset diabetes with no family history or predisposing factors, patients with hereditary pancreatitis, familial pancreatic cancer syndrome, familial ovarian or breast cancer syndrome, familial multiple mole melanoma syndrome and familial adenomatous polyposis (76).

The National Institute for Health and Care Excellence (NICE)(216) has recommended surveillance for people with any of the following criteria:

- Hereditary pancreatitis and a PRSS1 mutation
- BRCA1, BRCA2, PALB2, or CDKN2A (p16) mutations, with one or more first-degree relatives diagnosed with pancreatic cancer
- Peutz-Jeghers syndrome
- Two or more first-degree relatives with pancreatic cancer, across two or more generations
- Lynch syndrome and any first-degree relatives with pancreatic cancer.

NICE has recommended MRI/MRCP for pancreatic cancer surveillance for people without hereditary pancreatitis while CT scan (pancreatic protocol) for people with hereditary pancreatitis without offering EUS

Patients with long standing FAP should be offered an examination with endoscopic biopsy of the periampullary region; the frequency of which is determined by the severity of the duodenal polyposis, however in stage-4 duodenal polyposis, surgically fit patients should be offered a pylorus preserving pancreaticoduodenectomy (Grade III evidence) (217).

The Consensus guidelines published by the International Association of Pancreatology (218) recommended that all patients at increased inherited risk of pancreatic cancer should be referred to a dedicated multidisciplinary specialist centres for a specialist opinion with expert clinical assessment, genetic counseling and advice on secondary screening investigational program.

3.16 Treatment options

3.17 Surgical resection

Surgical resection is the only curative treatment for patients with pancreatic and periampullary cancer. Nevertheless, the resection rate for pancreatic head adenocarcinoma is less than 20% at the time of diagnosis (6, 219), and about one-third of patients with distal cholangiocarcinoma deemed resectable at the time of the diagnosis (205, 220, 221). Inconsistent results were noted regarding the resection rate for patients with ampullary cancer (222-224).

These figures vary significantly between high volume centres and low volume centres including higher resection rates (34, 35), lower operative mortality (36, 37) and improved long-term survival (38) in units with higher treatment volumes.

The contraindications to surgical intervention include

- Metastatic deposits involving lung, liver, lymph nodes and peritoneal metastasis
- Vascular encasement of portal vein, superior mesenteric vein, superior mesenteric artery, coeliac trunk and hepatic artery
- Liver cirrhosis and portal hypertension
- Surgically unfit patients

The prognostic markers for survival following surgical resection include tumour size, tumour grade, resection margin status, degree of vascular invasion and the lymph node status.

3.17.1 Historical background

In 1898, Alessandro Codivilla (1861-1912) performed the first pancreatic head resection (225). The patient died at 18 days postoperatively from cachexia and steatorrhoea.

In 1898, Halsted performed the first successful resection of a ampullary cancer (226).

In 1912, Walther Kausch (1867-1928) reported the first successful two stage pancreaticoduodenectomy for carcinoma of the papilla (227). The operation took four hours.

In 1914, Hirschel performed the first successful one stage pancreaticoduodenectomy (228). Patient died one year after surgery.

In 1918, Lester Reynold Dragstedt (1893-1975) demonstrated the feasibility of total duodenectomy in dogs and pigs and its compatibility with survival(229).

In 1922, Tenani (230) performed a successful two-stage partial pancreaticoduodenectomy.

In 1935, Whipple and colleagues (231) reported successful en-block resection of pancreatic head and the duodenum in two stage procedure in three patients. First patient died 30 hours postoperative while second and third patients died 9 and 24 months post resection.

In 1940, Whipple published the first one stage complete excision of the head of the pancreas and the entire duodenum (229).

3.17.2 Types of surgical resections

For pancreatic head malignancy and periampullary cancers, Kausch-Whipple pancreaticoduodenectomy or pylorus preserving pancreaticoduodenectomy is the standard surgical management. It involves three main classic operative steps:

I. Assessment of resectability: this involves careful examination of the liver, peritoneum and periampullary area to rule out occult metastatic deposits.
II. Resection: this involves resection of the head of the pancreas, duodenum, distal common bile duct and gallbladder. In a standard pancreaticoduodenectomy the stomach is divided proximal to the antrum, while in a pylorus preserving pancreaticoduodenectomy the first part of the duodenum is transected distal to the pylorus. In case of SMV, PV invasion, the vein could be transected en-block with the tumour specimen and reconstructed afterwards.
III. Reconstruction: this involves reestablishing the biliary, pancreatic and the enteric continuity by means of triple anastomoses namely hepaticojejunostomy, pancreaticojujenostomy and gastrojejunostomy (for classic Kausch-Whipple pancreaticoduodenectomy) or duodenojejunostomy (for pylorus preserving pancreaticoduodenectomy).

The pylorus preserving pancreaticoduodenectomy has the advantage of reducing post gastrectomy complications including enterogastric reflux when compared with the standard Kausch-Whipple operation. It is also associated with improved postoperative nutritional status and weight gain (232-235), and it does not compromise the long term survival (236). Nevertheless, its drawbacks include incomplete lymph node clearance and failure to achieve a clear resection margin especially when the tumour is close to the pylorus or if there is a proximal duodenal involvement (237, 238).

The radical extended resections proposed first in 1977 (239) involving en-bloc pancreatic, portal vein and lymph node resection failed to achieve any survival benefits when compared with the classic Kausch-Whipple operation (240).

3.18 Adjuvant therapy

Precise identification of the tumour origin is of clinical significance as the adjuvant treatment and prognosis is different for this group of malignant neoplasms. Adjuvant chemotherapy has a clearly defined role starting 1-2 months following potentially curative surgical resection for pancreatic cancer. Gemcitabine is now prescribed as the standard of care (241) with better long-term disease free survival compared to observation group as been studied in the CONKO-001 (242, 243). The ESPAC-3 trial has shown significant improvement in survival following surgical resection in patients receiving 6 months of 5-Fluorouracil and leucovorin as adjuvant therapy (244). The more recent ESPAC-4 study has shown long-term survival benefits of the addition of Capecitabine to Gemcitabine (245).

The role of adjuvant chemotherapy has been less well assessed in cases of ampullary cancer, although the large ESPAC-3 study had a limb for these patients also using Gemcitabine (246).

For patients with distal cholangiocarcinoma, there is no current evidence to support the use of adjuvant chemotherapy or radiotherapy. Appropriate trials are needed to address this issue. The largest trial currently happening is the BILCAP trial looking at capecitabine following surgical intervention (247).

The role of chemoradiotherapy has been also explored as an adjuvant treatment in several trials namely the Gastrointestinal Tumor Study Group (GITSG) trial (248), the European Organization for Research and Treatment of Cancer (EORTC) trial (249), and the European Study Group for Pancreatic Cancer (ESPAC-1) trial (250), which did not reveal enough supporting evidence for the routine use of chemoradiotherapy as a standard adjuvant therapy. The combined non-randomised results however reported from Johns Hopkins University and the Mayo Clinic revealed significant improvement in survival in chemoradiotherapy group compared to surgery only group with median survival of 21.1 months vs. 15.5 months ($P < 0.001$) (251, 252).

3.19 Neoadjuvant therapy

Because of the historical tendency of pathologists to over-diagnose pancreatic adenocarcinoma radiologists have not made rigorous efforts to distinguish the organ of origin on pre-operative imaging. This has not previously been clinically important as the surgical treatment of the lesions is identical and decisions regarding adjuvant chemotherapy can be made after the final histology report is available. This situation is changing with the recent advent of neo-adjuvant treatment, which may be recommended without a precise diagnosis in patients with borderline resectable or locally advanced pancreatic head malignancy based on pre-operative imaging. The advantage of neoadjuvant therapy is that it allows tumour down staging and locoregional control thus allowing curative surgical resection in patients with borderline resectable tumours, however without significant survival improvement (253-255). This issue has been addressed in a Phase II study (SCALOP)(256) and Phase II/III study (ESPAC-5)(257).

Other studies have shown survival improvement by intention to treat following neoadjuvant treatment for patients with resectable or borderline resectable pancreatic cancer (258).

Although these studies have confirmed that neoadjuvant therapy has been shown to be effective in treating pancreatic cancer there is a possibility that these series have included patients with other diagnoses. Although there is a general agreement that neoadjuvant treatment should be offered to patients with locally advanced disease and those with a high risk of R1-resection in order to increase the chance of a complete resection, patients with primarily resectable cancer potentially benefit the most from neoadjuvant therapy. On the other hand, some patients however might suffer tumour progression into a metastatic state during treatment, therefore becoming unresectable and hence avoiding unnecessary exposure to a stressful major operation (259).

The role of added radiotherapy as neoadjuvant treatment is debatable. Currently, many studies are being performed in order to test new treatment concepts and to evaluate the true role of neoadjuvant therapy e.g. ESPAC-5F (260) NEOPA(261), PREOPANC trial (262)and NEOPAC (263). The oncological benefits of neoadjuvant chemo-radiotherapy with Gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer have been studied in a multicenter, phase 2/3, prospective randomized trial. Results have shown that neoadjuvant chemo-radiation provides significant oncological benefits in terms of 2-year survival rates and R0 resection rates compared to upfront surgery (264). Other trials proved improved outcome in terms of survival benefits and R0 resectability with chemoradiotherapy such as GTS-GX/RT: GTX (gemcitabine, docetaxel, and capecitabine) plus GX (gemcitabine and capecitabine) combined with radiation therapy (RT) (265).

There is no standardized neoadjuvant regimen; however there have been several trials using different regimens including FOLFIRINOX (5-flurouracil, leucovorin, irinotecan, and oxaliplatin) (266) and GTX (gemcitabine, docetaxel, and capecitabine) (267).

The current practice at the Peninsula HPB cancer unit is to offer neoadjuvant chemo-radiotherapy for patients with non-metastatic borderline resectability following regional MDT discussion and clinical outpatient assessment including biochemical testing of CA19-9.

3.20 Biliary decompression and stent

3.20.1 Preoperative stent

The role of biliary stents reducing jaundice related morbidity and mortality prior to surgical resection is controversial (268-272).

Stent could be inserted by endoscopic route or via percutaneous transhepatic method.

The use of biliary stents is associated with complications include perforation, bleeding, fungal colonization, sepsis, obstruction, migration and disease progression (273, 274).

3.20.2 Palliative stent

Compared to the preoperative biliary stent insertion, palliative biliary stenting represents the procedure of choice for patients with unresectable disease, severe comorbidity and metastatic disease (275-277).

Biliary stents are available in plastic, metal, covered and uncovered varieties. The metal stents are superior to plastic stents in terms of greater patency rate (12 months vs. 3 months), fewer complications, shorter hospital stay and possibly cost effectiveness (199, 278, 279).

The use of plastic stents is associated with stent replacement at least once and it could be reasonable to be used in patients with less than six months life expectancy.

The use of covered metal stents has been introduced to reduce the tumour ingrowth (280). The preference of covered stent over the uncovered stents has been explored and results are debatable including stent patency, cost effective, stent dysfunction and survival benefits (280, 281).

3.21 Palliative treatment

3.21.1 Bypass surgery

Bypass surgery is indicated in surgically fit patients with advanced unresectable disease. The aim is to relieve the biliary and the gastric outflow obstruction.

The use of the bile duct for the biliary bypass surgery (i.e. choledochoenterostomy) is more reliable relieving the jaundice than the use of the gall bladder (i.e. cholecystoenterostomy) (282).

To relief gastric outflow obstruction, a gastroenterostomy is performed either as a single procedure or combined with the biliary bypass surgery (i.e. Roux-en-Y). A prophylactic retrocolic gastrojejunostomy, performed at the time of initial surgical intervention, significantly decreases the incidence of a late onset gastric outlet obstruction without increasing the postoperative hospital stay or postoperative complications (283).

In patients with distal cholangiocarcinoma, placement of a plastic duodenal stent could be an alternative option to gastroenterostomy, which has a minimal role in relieving the gastric outflow obstruction.

3.21.2 Chemotherapy

The potential role of chemotherapy as a palliative therapy in patients with metastatic disease should be weighted against its toxic side effects. The use of 5-FU and Mitomycine was used as first line therapy for advanced metastatic disease, however a randomized trial concluded that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms (pain, performance status and weight) in patients with advanced, symptomatic pancreas cancer. Treatment with gemcitabine was associated with a survival advantage at 1 year (18%) compared with fluorouracil (2%) and median survival of 5.6 vs. 4.4 months (284).

3.21.3 Relief of pain

Abdominal pain experienced in patients with pancreatic and periampullary cancer could be intolerable and represents a challenge facing the treating physician. Pathophysiology of pancreatic pain includes increasing parenchymal pressure secondary to ductal destruction, perineural infiltration, perineural neuropathy secondary to chemo or radiotherapy, pancreatic inflammation and biliary stenosis (285, 286).

Management of pancreatic pain follows the analgesic ladder for pain treatment including non-opioid analgesia for mild pain, opioids for mild to moderate pain and opioids for moderate to severe pain. Other methods include decompression of pancreatic duct either endoscopically or surgically (287). Coeliac ganglion ablation via percutaneous, laparoscopic or open surgical technique using phenol 5% or ethanol 50% or cryoablation have shown good results (287-293). Thoracoscopic division of splanchnic nerves has been also implemented in the alleviation of pancreatic pain (294). External beam radiotherapy and radio-chemotherapy have been also prescribed (295).

4 Pre-operative radiological assessment of pancreatic head malignancy

4.1 Introduction

Patients with pancreatic and periampullary cancer often present with features of biliary obstruction, however they might have non-specific symptoms that largely depends on the anatomical location of the tumour and its biological behaviour. In the absence of other specific diagnostic parameters e.g. blood tests, imaging modalities play an important role in detection of the tumour mass, tumour extension and its resultant effects. Furthermore, it helps identifying the relationship between the tumour mass and the vascular structures in nearby organs. Imaging enables identification of the tumour's local invasion and distant metastases, which affect the choice of treatment. There has been significant development in imaging technology and computer software over the past two decades resulting in improvement in imaging acquisition and reconstruction techniques, which has reshaped the management of patients with pancreatic head malignancy. Precise pre-operative identification of the tumour mass followed by accurate assessment and staging is a crucial tool in the management of patients with periampullary cancers to identify the group of patients who would benefit from surgical intervention and to avoid unnecessary surgical exploration.

Transabdominal ultrasound scan is usually the first imaging modality for the majority of patients presenting with symptoms of jaundice, weight loss or vague abdominal pain. Further imaging adjuncts include multi-detector row computed tomography (MDCT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), positron emission tomography (PET), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and laparoscopic staging. The choice of the imaging modality depends on availability,

experience and individual patient circumstances. Other new modalities in early detection include including cyst fluid biomarkers, genomic profiling, nano-particle imaging, spectroscopy, and circulating pancreatic cells (296).

4.2 Ultrasound scan

It is the most widely used primary investigation tool in the diagnosis of pancreatic and periampullary cancers. It is non-invasive, inexpensive, readily available with reported sensitivity as high as 88.6-95% (297) and specificity of 98.8% (297). The use of ultrasound in the preoperative staging is limited by the retroperitoneal position of the pancreas, which sometimes might be obscured by the bowel gas. Additionally, the examination is operator dependent with inter-observer variation (297-299). Advances in ultrasound technology and the introduction of Doppler ultrasound could lead to improvement in assessing tumour-vessel relationship (300, 301).

4.3 Magnetic resonance imaging (MRI)

The use of MRI could be a comparable alternative to the use of MDCT in the preoperative diagnosis and staging of pancreatic and periampullary cancers. MRI has superior soft tissue contrast when compared with MDCT but with less spatial resolution. The non-contrast MRI is a good alternative diagnostic modality to the MDCT in patients with renal insufficiency or patients with known contrast allergy (302).

With advances in MRI imaging techniques, the use of magnetic resonance cholangiopancreatography (MRCP) has improved the visualization of the pancreaticobiliary area resulting in better evaluation of the relationship of pancreatic lesions to the pancreaticobiliary structures. Moreover, the use of the magnetic resonance angiography (MRA) has advantages in evaluating the relationship of pancreatic lesions to the peri-pancreatic vasculatures (303).

4.4 Endoscopic ultrasound (EUS)

EUS is an important tool in the pre-operative assessment and staging of pancreatic and periampullary neoplasms especially when no masses identified or with inconclusive MDCT or MRI findings (304, 305). It uses high frequency ultrasonic waves (5-10 MHz) with special radial or linear echo-endoscope, which bypasses the bowel gas interface (compared to limited view of the trans-abdominal US) by placing the transducer within the gastrointestinal tract (306, 307). When compared to MDCT, EUS has a higher sensitivity for tumour detection (308, 309) especially for detecting small solid lesions less than 20 mm in comparison with MDCT or MRI (309, 310). When combined with fine needle aspiration cytology (FNAC), the use of the EUS became a powerful diagnostic modality by adding cytological or histological confirmation of the suspected lesions. A metanalysis by Hewitt (311) confirmed pooled sensitivity for malignant cytology of 85% (95% CI, 84-86), and pooled specificity of 98% (95% CI, 0.97-0.99). This tissue diagnostic advantage supports the choice of adjuvant therapy especially for non-resectable tumours. Furthermore, it is extremely useful tool confirming the presence of metastatic deposits (e.g. metastatic lymph node) (312, 313) and differentiating pancreatic malignancy from other non-neoplastic lesions including pancreatitis or pancreatic cystic lesions (314).

In the assessment of vascular invasion, the following criteria can be identified (315):

1. Peri-pancreatic venous collaterals in an area of a mass that obliterates the normal anatomic location of a major portal confluence vessel.

2. Tumour within the vessel lumen.

3. Abnormal vessel contour with loss of the vessel-parenchymal plane.

The EUS diagnostic accuracy for vascular invasion has been assessed in several studies. In a metanalysis by Puli et al. (316), the pooled sensibility was 73% and the specificity 90%. The diagnostic accuracy of EUS for venous invasion (80-91%) is generally reported better than that for arterial invasion (17-67%) (317). EUS has reported increased sensitivity for portal vein assessment and 100% for the splenic artery and vein with decreased sensitivity for celiac axis and SMA and SMV (318).

Although it is considered a safe procedure, nevertheless EUS has a low incidence of complications including bleeding (1%-4%), pancreatitis (1%-2%) and (0.3%) perforation rate (319).

EUS is the most sensitive test in early detection of pancreatic cancer and it is used as a screening tool in high-risk individuals.

4.5 Positron emission tomography (PET)

The role of unenhanced PET/CT in the diagnosis and staging of pancreatic and periampullary neoplasms is limited due to the poor delineation of the tumour and its relationship to surrounding structures. On the other hand, it has a valuable role in detection of distant metastatic deposits (320).

The accuracy of staging and assessing the resectability may increase with the use contrast enhanced PET/CT scan (321).

4.6 Multi-detector computed tomography (MDCT)

With the rapid advances in scanning technology and imaging acquisition, the introduction of the MDCT has made a significant improvement in diagnosis of pancreatic and peri-ampullary cancers compared to single slice CT. According to the National Comprehensive Cancer Network guidelines (NCCN) (322), MDCT (also known as multidetector CT, multisection CT, and multislice CT) could be defined as multiphase high

quality dedicated imaging technique that is performed by acquiring thin, preferably sub-millimetre, axial sections using a dual-phase pancreatic protocol (pancreatic and liver portal venous). Multiplanar reconstruction is recommended as it allows precise visualization of the tumour-vessel relationship as well as detection of sub-centimetre metastatic deposits. Compared to the conventional and the helical CT scanners, MDCT has a two-dimensional array of detector elements that replace the linear array of detector elements used in the other types. This feature allows the MDCT scanners to acquire multiple slices simultaneously and to increase the speed of image acquisition significantly. MDCT has the advantage of providing high spatial resolution in all imaging planes with large volume coverage in a short scanning time typically 7-9 seconds for 64-slice MDCT of the abdomen and pelvis (323). The use of a dedicated pancreatic protocol as a routine investigating tool of patients presenting with suspicious diagnosis of pancreatic cancer has improved the preoperative assessment of pancreatic and periampullary tumours. Furthermore, it improves visualization of the periampullary duodenum, to assist in distinguishing ampullary neoplasms, with good prognosis, from other periampullary neoplasms.

. With a relatively uniform consensus, the overall accuracy of MDCT in detecting pancreatic tumour and predicting resectability ranges from 86 to 99% (324-328). The MDCT has a reported sensitivity in pancreatic cancer detection is as high as 86%-97% for tumours larger than 2 cm and 68- 77% for tumours less than 2 cm (306, 329-333). Legmann et al. (334) reported 100% sensitivity for detecting tumours greater in size than 15 mm. The reported specificity ranges between 88% and 100% in identification of pancreatic tumours (335, 336).

4.6.1 Indications

The use of a dedicated pancreatic CT scan protocol is indicated in patients with clinically suspected pancreatic or periampullary cancers, unexplained episode of acute

pancreatitis, chronic pancreatitis, adult onset diabetes in absence of family history or risk factors, evaluation of jaundice and in patients with unexplained wight loss (76).

4.6.2 Timing

It is extremely important to consider the timing of scanning during the suspected cancer pathway. Trans-abdominal ultrasound scan is the first imaging modality for the majority of patients presenting with jaundice. If biliary dilatation is detected, then ERCP will be considered possibly with biliary stent insertion. At this stage, pancreatic MDCT should be undertaken preceding the endoscopic biliary intervention as the use of ERCP, stent, brush cytology or endoscopic biopsy could result in local inflammatory changes that mimic the tumour. This could limit the ability to visualise the tumour on subsequent scanning which might lead to a delay in the accurate radiological staging and the assessment of the tumour-vessel relationship (331, 337).

4.6.3 Contraindications and precautions

The use of CT scan is contraindicated in patients with known allergy to the contrast medium (iodine-based), renal impairment and during pregnancy. Certain precautions should be taken when scanning diabetic patients on Metformin or related medications as it might result in metabolic acidosis. Patients with hyperthyroidism might develop thyrotoxic crisis. There is a theoretical risk of hypertensive crisis in patients with phaeochromocytoma. In patients with myasthenia gravis, there is slight risk of worsening the condition upon use of the contrast medium. There is an increased risk of bronchospasm in patients suffering from bronchial asthma (338).

Certain conditions might interfere with the accuracy of the imaging and hence the reporting. These include patients with metallic intra-abdominal objects from previous surgery or the presence of contrast in the gut especially barium following a previous contrast study.

4.6.4 Technique of MDCT Pancreatic protocol

A dedicated MDCT pancreatic protocol has four essential components (332):

I. Neutral oral contrast.
II. Rapid bolus of intravenous contrast.
III. Thin section biphasic scanning.
IV. Reconstruction with two-dimensional (2D) and 3D volumetric images combination.

Patient preparation requires fasting for at least 4 hours. On the day of the examination, an intravenous catheter (size 18-20 gauge) will be inserted under antiseptic precautions in the antecubital vein (preferred site allowing the power injection of the intravenous contrast agent at a rate of 4-5 ml/second). Patient is asked to drink 750 ml to 1 L of a neutral oral contrast (near water attenuation, in contrast to the positive and negative contrast medium with higher/lower attenuation than the surrounding structures). Several agents have been used such as water (339), barium suspension with low Hounsfield unit such as Volumen® (340), and whole milk (341).

The use of a neutral oral contrast just before the scheduled scanning time causes gastro-duodenal distension allowing delineation of the bowel loops adjacent to the pancreas. This facilitates identification of any invasion of these structures. When 3-D processing is incorporated, the discrimination between periampullary duodenal and ampullary tumours from the periampullary pancreatic head tumours is improved by better visualization of the ampullary region (342, 343). The use of a neutral oral contrast is superior to the use of positive oral contrasts with high attenuation, which might interfere with the assessment of the peri-pancreatic vasculature masking underlying radiological signs of an early carcinoma (332, 344).

An unenhanced pre-contrast scan of the liver, pancreas and kidneys should be obtained to allow detection of hepatic steatosis, subtle pancreatic ductal or parenchymal calcifications and subtle primary or metastatic lesions (345).

Following the pre-contrast scan, rapid intravenous bolus injections of 100-150 ml of iodinated low osmolality contrast at a rate of 4 to 5 ml/second are administered. The dose of the intravenous contrast should be calculated and adjusted according to the patient body weight (1.5-2.0 mg I/kg) and the contrast should be injected using a power injector (346, 347). The acquisition of images should be during the optimal pancreatic and hepatic parenchymal enhancement phases.

The pathophysiological explanation of the pancreatic protocol could be understood by considering the blood supply to the liver and pancreas. As the blood supply of the pancreas is through the splanchnic vessels, arising from coeliac axis and the superior mesenteric artery, while the blood supply of the liver is mainly through the portal vein, the peak pancreatic parenchymal enhancement occurs relatively earlier than the peak hepatic parenchymal enhancement. Following the same principle, the peri-pancreatic venous structures may not enhance homogenously during the peak of pancreatic enhancement and enhances late near the peak of the hepatic enhancement instead. Therefore a dual phase protocol is adopted incorporating pancreatic parenchymal phase and hepatic/portal venous phase (345, 348, 349).

In practical terms, for an ideal pancreatic imaging protocol based on 16-64 imaging detector, the acquisition of the images should ideally start 50 to 55 seconds following the injection of the intravenous contrast for creating the pancreatic phase, while for the hepatic phase, the imaging acquisition should start 65-75 seconds following the contrast injection (350). This timing of imaging acquisition is based on the use of 16-64 imaging detector, however the dose, injection rate and the imaging interval should be modified according to the patients and to comply with the local institutional guidelines

bearing in mind that the faster the scanner speed, the shorter the acquisition time for each phase (351).

The dual phase imaging acquisition allows simultaneous scanning of the pancreas at its optimal parenchymal enhancement allowing tumour detection along with identification of vascular invasion by homogenous opacification of the adjacent peri-pancreatic arteries and veins. In a similar way, the liver will be scanned during the peak hepatic parenchymal phase (324, 345, 350).

During the pancreatic phase, the intravenous contrast will cause intense enhancement of the normal pancreatic parenchyma, improving lesion conspicuity by illustrating the difference in the vascular perfusion between a typically hypovascular, hypodense pancreatic adenocarcinoma and the background of normal pancreatic parenchyma (332, 352). Assessment of the tumour-vascular relationship is facilitated by the enhancement of the coeliac axis, superior mesenteric artery and pancreatic arteries (296).

It is ideal to obtain the images of the whole abdomen and the pancreas in one breath-hold acquisition as it might demonstrate a thin peripheral enhancement surrounding subtle liver metastasis with perfusion abnormalities known as flow phenomena (332).

The hepatic-portal venous phase is optimum for visualizing liver metastases and assessing the peripancreatic venous status including the portal vein, superior mesenteric vein and splenic vein (331).

4.6.5 Post processing

Following image acquisition phase, routine reconstructions and reformations are performed as part of the dedicated pancreatic imaging protocol. This will create 2D and

3D high resolution curved planar images highly effective in visualizing the peripancreatic vascular structures allowing identification of vascular involvement. Furthermore it allows better demonstration of the fluid-filled pancreatic duct which will be extremely useful in determining sites of duct interruption or obstruction aiding in accurate localisation of the site of the primary tumour (10).

The process of reconstruction entails creation of 3-4 mm slice width images in both axial and coronal planes, which will be sent to the PACS system (Picture Archiving and Communication System). Another sets of images will be created as thin as 0.6 mm slice width as possible. These will be dealt with either directly at the CT console or will be sent to 3D workstation for multiplanar reformatting, 3D angiography, CT volume rendering, CT cholangiopancreatography (CTCP) (351).

4.6.6 Characteristic imaging findings of Pancreatic ductal adenocarcinoma (solid neoplasms)

Pancreatic adenocarcinoma is identified in 65% of cases in the head of pancreas, 15% body and tail while the remaining 20% diffusely affect the pancreas (353, 354). Pancreatic adenocarcinoma typically manifests in the pancreatic phase as focal ill-defined hypovascular, hypodense (hypoattenuating) poorly enhancing mass in 90-95% of cases when compared to the arterially enhancing normal pancreatic parenchyma (327, 332, 337, 355, 356). On average, there is a difference of 40 HU (Hounsfield Unit is definition for CT scanners which is calibrated with reference to water) between the hypoattenuating focal mass lesion and the background of normal pancreatic parenchyma (345). In the remaining 5-10% of pancreatic adenocarcinomas, tumours fail to demonstrate attenuation difference, especially if size is less than 2 cm, therefore tumour mass will be identified as isodense or isoattenuating. In such circumstances it is essential to pay attention to the indirect signs that might indicate the presence of malignancy including upstream duct dilatation

associated with pancreatic atrophy and double duct sign in the absence of calculus duct obstruction (333, 355-358).

Segmental dilatation of the pancreatic duct is highly suggestive of a neoplastic lesion. Dilatation of the main pancreatic duct is considered the earliest sign in pancreatic cancer (359). Gangi et al. reported dilatation of pancreatic duct 18 months before the diagnosis of pancreatic cancer (360).

The finding of a hyperattenuating lesion could be diagnostic for neuroendocrine tumour. The characteristic identification of these hypervascular tumours with or without hypervascular liver metastasis would be identified on images obtained during the pancreatic phase (361).

Metastases to the pancreas are rare, most commonly secondary to renal cell or bronchogenic carcinoma without any preference to any particular part of the pancreas. Vascular involvement is uncommon. Tissue diagnosis with percutaneous core biopsy may be necessary to confirm the histological nature of the tumour and to alleviate any diagnostic uncertainty (362).

4.6.7 Characteristic imaging findings of Ampullary cancer

Patients with ampullary cancer usually present early with symptoms of obstructive jaundice with small tumours that are often not apparent on CT scan (363). However, secondary radiological findings such as marked bile duct dilatation, in association with mild to moderate dilatation of the pancreatic duct, could be seen (364). These small tumours are difficult to distinguish from other causes of bulging papilla such as papillitis, papillary stenosis, choledochocele, Brunner gland adenoma, lipoma, fibroma, lymphangioma, and paraganglioma (365).

Larger ampullary tumors however, usually appears as polypoidal or an infiltrative mass with approximately 62% of lesions manifest at imaging as a discrete nodular mass that causes an irregular filling defect at the distal margin of the pancreaticobiliary junction (366, 367).

At non–contrast CT, ampullary cancer typically appears as intraductal soft-tissue mass that is hypoattenuating relative to the hepatic parenchyma with an attenuation of approximately 40 HU (363). During arterial and portal venous phase, ampullary cancer usually enhances with lobulated or infiltrating borders (368).

For infiltrative mass, it manifests as an irregularly thickened ductal wall that obliterates the lumen and demonstrates delayed prolonged enhancement (363).

4.6.8 Characteristic imaging findings of Bile duct cancer

With the advances in scanning technology, MDCT has become the non-invasive diagnostic modality of choice for assessing and staging bile duct cancers. With the promising results of the CT cholangiography, this could be considered as an alternative diagnostic tool when MR cholangiography is contraindicated.

Cholangiocarcinoma is classified as either intrahepatic (15%) or extra hepatic which is classified as nodular, sclerosing, or papillary types (369) (370).

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The radiological features of cholangiocarcinomas vary depending on the anatomical location of the tumours in relation to the biliary tree when examined by CT scan. Features include tumour mass lesion associated with bile duct dilatation in the exophytic type, bile duct wall thickening could be demonstrated in the infiltrative type, while the polypoidal variety could present as intraductal tissue (371).

On non-contrast MDCT, cholangiocarcinoma usually appear as a hypo- or isoattenuating lesion in relation to the normal hepatic parenchyma. The tumours usually stay hypoattenuating during the arterial and the portal venous phases. This radiological feature reflects the hypovascular nature of these tumours (372-374). However, a study has concluded that hyperenhancement of a stenosed bile duct during the portal venous phase could be considered a sign of malignancy (375); this however has a low specificity of 19%.

The development of the non-invasive CT cholangiography using IV contrasts has helped in delineating the anatomical details of the biliary tree and found to be superior to the use of the oral contrast as they provide high quality opacification of the biliary tree. However, the use of this modality could be limited in patients with high-grade biliary obstruction as it is dependent on the secretory function of the biliary system (376).

The MDCT and the CT cholangiography have limitations detecting early or small tumours especially the infiltrating stricture-forming variety, also benign strictures or benign lesions at the porta-hepatis which can imitate cholangiocarcinoma (377). Also, the use of CT cholangiography could be limited in patients with high-grade biliary obstruction or significantly high serum bilirubin as it is dependent on the secretory function of the biliary system (376). This has been resolved by the use of PET/CT in the diagnosis and staging of cholangiocarcinoma.

4.6.9 Assessment of vascular status

Vascular involvement, determined by the extent the tumour involves the vessel's cross sectional circumference (355), is the most important factor in the preoperative radiological assessment of resectability of periampullary cancers in absence of lymph node or distant metastasis. The use of 3D reconstruction images makes the assessment of

the vascular involvement more apparent than using the axial images alone. MDCT has a reported sensitivity of 77-90% and specificity of 81-100% in diagnosing peri-pancreatic vascular infiltration (330, 378). The following major vessels were reported in relation to PHM: Superior Mesenteric Artery (SMA), Hepatic Artery (HA), Coeliac Trunk (CA), Superior Mesenteric vein (SMV) and Portal vein (PV) (352, 379).

These following terms have been used to describe the degree of vascular involvement (259).

Abutment: Less than 180-degree vascular involvement or contiguity <50% i.e. Peri-vascular fat planes partially obliterated with the vessel encompassing less than 180 degree of its circumference.

Encasement: More than 180-degree vascular involvement or contiguity ≥ 50% i.e. Peri-vascular fat planes completely obliterated with the vessel encompassing more than 180 degree of its circumference.

The degree of arterial invasion is recognized by the following criteria (325, 378, 380, 381)

1. Obliteration of the normal fat between pancreatic margin and the adjacent arteries (HA, CA, SMA).
2. > 180-degree contact between tumor and arteries.
3. Morphologic changes in the artery including narrowing and contour abnormalities.

The criteria of venous involvement that preclude surgery are different from those of the arterial involvement and subjected to a great debate in the literature. The degree of venous invasion is recognized by any of the following (325, 378, 380, 381):

I. Tumour-to-vessel circumferential contiguity of ≥ 50%.
II. >180-degree contact between the tumor and the vein.

III. Loss of a patent Porto-splenic confluence.

IV. 360° encasement of the PV or SMV.

V. A change in the vessel contour or calibre regardless the degree of contact between tumour and vessel.

VI. The "teardrop" configuration of the SMV (382).

Confirmation of venous invasion is best demonstrated in images obtained during the hepatic phase with a reported specificity as high as 100% (324, 378).

The recent advances in venous graft technology allowing reconstructible resection of limited venous invasion, has contributed to this debate. Ishkawa and his colleagues defined five types of tumour abutment along SMV-PV confluence in order to standardize criteria for venous involvement (383). Type (I): normal, (II) smooth shift without narrowing, (III): unilateral narrowing, (IV) bilateral narrowing, (V) bilateral narrowing with collateral veins.

4.6.10 Grading systems of vascular invasion

Loyer and his working group adopted the first attempt to categories tumour vessel relationship in 1996 (384). Using thin section CT images, A-F grading system was designed to classify the vascular involvement in patients with pancreatic adenocarcinoma. In 1997, Lu and his colleagues adopted a five-point scale system based on the circumferential contiguity of tumour to the vessels with reported a sensitivity of 84%, specificity of 98%, positive predictive value of 95% and negative predictive value of 93% for vessel unresectability (385).

In Germany, Klauss and his working group developed a new invasion score (0-6) depending on the length of the tumour contact and the circumferential tumour involvement separately (386). Invasion score of 11 or more is considered evidence of vascular infiltration. They reported a sensitivity of 90.9%, specificity of 98.7% positive

predictive value of 99.4%, negative predictive value of 99.4% and overall accuracy of 98.2% when evaluating the degree of vascular invasion.

Fang and his colleagues (387) have implemented another classification system based on the gap between the tumour and the blood vessels using 3D reconstructed CT images. Five types have been described in determining the resectability. The vessels described include the portal vein, superior mesenteric artery, inferior vena cava, superior mesenteric vein, left renal vein, right renal vein, hepatic artery, celiac trunk, and abdominal aorta. They reported a sensitivity, specificity, positive and negative predictive values of 100% in assessing resectability of pancreatic and peri-ampullary tumours.

4.6.11 Assessment of Lymph node status

The accuracy of assessing nodal disease by different radiological modalities is limited with reported sensitivity of the CT to diagnose nodal deposits is 14%, with a specificity of 85% (388). The presence of positive lymph node metastases is a poor prognostic indicator whether it is metastatic deposits or via direct invasion. A size greater than 10 mm in short axis (antero-posterior diameter) on cross section imaging modalities has been used as diagnostic criteria for metastatic lymphadenopathy (259, 332, 337, 355). The size is not however a discriminative feature for lymph node metastasis (329). Other criteria have been reported including morphological nodal changes such as poorly defined boundaries, rounded shape alteration, and hypodense conversion appearance are more specific but less sensitive findings (355).

Involvement of pancreatic and peripancreatic lymph nodes should not prevent an attempt at curative surgical resection, as they could be resected en-block with the primary tumour. Nevertheless, involvement of remote lymph nodes beyond the extent of the Whipple operation (e.g. para aortic, mesenteric or porta hepatis) is however considered a contraindication for curative resections (332, 389, 390). The use of PET/CT as adjunct tool

in staging has aided the identification of suspicious nodes for biopsy with a reported sensitivity of 46%-71% and specificity of 63%-100% for detecting suspicious nodal disease outside the conventional surgical field (391-393). However it is limited in small-volume disease, as it cannot differentiate between inflammatory vs. metastatic lymphadenopathy.

4.6.12 Assessment of distant metastasis

Pancreatic cancer commonly metastases to liver, peritoneum, lungs and less commonly bones. Pre-operative evaluation of metastatic deposits is a crucial part of the pre-operative work-up, as evidence of remote metastasis is a contraindication for an attempt at surgical resection. CT has a reported sensitivity of 75%-80% in detecting liver metastasis (313, 327, 394). The hepatic metastases are best evaluated on MDCT portal venous phase as solid hypovascular masses (331). If these lesions are small (≤ 10mm), they often reported as "indeterminate" as it is difficult to identify their nature due to difficulty in measuring their attenuation, which could be caused by pseudo enhancement and/or partial volume averaging. These lesions are best assessed by MRI (390).

Pancreatic spread to the peritoneum is usually a small volume disease and it is difficult to be detected using CT and better assessed by laparoscopy. In advanced disease, peritoneal carcinomatosis is detected on MDCT images as peritoneal thickening with contrast enhancement associated with ascites (390). Ascites is a common manifestation of cancer end-stage and it is present in about 20% of pancreatic cancer patients (395).

4.6.13 Radiological staging systems

The widely used cancer staging system known as TNM (Tumour, Node, Metastasis) staging system describes the cancer in relation to its anatomical local, regional and distant extension.

Pierre Denoix (396) (France) between 1943 and 1952 was the first to devise this most widely used staging system (397).

In 1987, the TNM staging system was combined with the American Joint Committee on Cancer (AJCC) into the most widely accepted and commonly used staging system for pancreatic cancer (398, 399). This staging system incorporates three main categories. The (T) stage describes the primary tumour stage, size and extent. The (N) - lymph node stage describes the lymph node involvement. The (M) - metastases describes the presence or absence of regional or remote metastatic deposits. The staging system has undergone several revisions and development till the seventh edition (Table 4.1), which became effective in January 2007 (397, 400). The eighth edition has been recently published (401). The Peninsula HPB cancer centre is currently using this staging system.

TNM	Pancreatic adenocarcinoma	Bile Duct cancer	Ampullary cancer
T stage			
Tx	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma in situ		
T1	Limited to pancreas, ≤ 2 cm in its greatest dimension	Confined to bile duct	Limited to ampulla or sphincter of Oddi
T2	Limited to pancreas, > 2 cm in its greatest dimension	Invades beyond bile duct wall	Invades duodenal wall
T3	Extends beyond pancreas without involvement of coeliac axis or superior mesenteric artery	Invades gallbladder, liver, pancreas, duodenum, or other adjacent organs	Invades pancreas
T4	Involves coeliac axis or superior mesenteric artery	Involves the coeliac axis or the superior mesenteric artery	Invades peripancreatic soft tissues, or other adjacent organs or structures
N stage			
Nx	Regional lymph node cannot be assessed		
N0	No regional nodal metastasis		
N1	Regional nodal metastasis		
M stage			
M0	No Distant metastasis		
M1	Distant metastasis		

Table 4.1 TNM staging system

Notes

1. Anatomical sub-sites of the pancreas include head, body, tail, pancreatic duct and Islets of Langerhans (endocrine pancreas).
2. Tis also includes the 'PanIN–III' classification.
3. Tumours of the head of the pancreas are those arising to the right of the left border of the superior mesenteric vein.
4. Tumours of the body are those arising between the left border of the superior mesenteric vein and left border of the aorta.
5. The uncinate process is considered as part of the head.
6. Tumours of the tail are those arising between the left border of the aorta and the hilum of the spleen.
7. The regional (peripancreatic) lymph nodes are demonstrated in (Table 4.2).

Superior	Superior to head and body
Inferior	Inferior to head and body
Anterior	Anterior pancreatico-duodenal, pyloric (for tumours of head only), and proximal mesenteric
Posterior	Posterior pancreatico-duodenal, common bile duct, and proximal mesenteric
Splenic	Hilum of spleen and tail of pancreas (for tumours of body and tail only)
Coeliac	For tumours of head only

Table 4.2 Regional peripancreatic lymph nodes distribution (402)

4.7 Definition of Resectability

It is generally agreed that tumour resectability is classified into two major categories:

(A) Potentially resectable group that includes the resectable and the borderline resectable tumours.

(B) Non resectable group which includes the locally advanced tumours and metastatic tumours (399).

Several classification systems have been designed such as the National Comprehensive Cancer Network (NCCN) group system based on the tumour location (pancreatic head vs. body& tail), extent and the tumour-vessel relationship (403). Another classification system by the multidisciplinary pancreatic cancer group at the Medical College of Wisconsin (MCW) based on the tumour-vessel relationship (399).

The American Joint Committee on Cancer (AJCC) has defined criteria for resection (Table 4.3) based on the TNM classification system (398). This system is currently used at the Peninsula HPB cancer centre.

Classification	**Stage**	**Median Survival in Months**
Resectable	IA (T1 N0 M0)	17-23
	IB (T2 N0 M0)	
	IIA (T3 N0 M0)	
	IIB (T1-3 N1 M0)	
Borderline resectable	III (T4 any N M0)	Up to 20
Locally advanced/ unresectable	III (T4 any N M0)	8-14
	III/ IV (any T any N M1)	4-6

Table 4.3 AJCC classification, Staging and Prognosis, adopted from Al-Hawary et al. 2013(398).

4.8 Borderline resectable pancreatic cancer (BLR)

The term "borderline resectability" which was first introduced in an article by Maurer and his colleagues in 1999 (404). There is a great debate in the literature about the definition of BLR in order to reach an agreement that might shape treatment strategies.

The American Joint Committee on Cancer (AJCC) has defined BLR based on the TNM stage with median survival rate of 20 months (398).

The NCCN defined BLR based on the tumour anatomical location (pancreatic head vs. body& tail), extent and the tumour-vessel relationship (403).

The MD Anderson Cancer Centre group introduced a definition of borderline resectable tumour, which was classified into three groups (Table 4.4) (405, 406).

Group	Definition
A	Abutment of SMA, coeliac axis Abutment or short segment encasement of HA Short segment occlusion of SMV, PV or SMV-PV confluence (amenable to reconstructive resection)
B	Known lymph node involvement Findings suggestive of metastatic disease
C	Comorbid conditions requiring preoperative workup Improving marginal performance status

Table 4.4 M.D. Anderson classification system for borderline resectable pancreatic cancer

In 2009, Callery and his colleagues (29) defined borderline resectability as abutment or encasement or reconstructible venous occlusion of SMV and or PV.

4.9 Reporting CT

With increasing centralization of the pancreatic cancer specialized centres, the demand for creating a standard descriptive universal reporting system for pancreatic malignant tumours that could be understood by different specialties, became crucially important. Several attempts have been made to design and to create a unique reporting system but with no general agreement between authors. The Radiologic Society of North America (RSNA) published a guidance template for reporting the primary pancreatic mass available from *http://www.radreport.org/template/0000018* (407). Another radiology reporting template is adopted by the radiology department at the MD Anderson cancer centre (MDACC) (408).

The ideal reporting template should include full description of the primary tumour mass including tumour size, site, enhancement, local extent, assessment and grading of the vascular status clarifying any grade of vascular involvement and stating the grading system that has been used, and assessment of the nodal status and distant metastasis.

4.10 MDCT interpretation pitfalls

Focal and autoimmune pancreatitis may present as discrete hypoattenuating or isoattenuating mass with or without secondary tumour features that mimic pancreatic ductal adenocarcinoma (409). Even pre-operative biopsies showing only inflammatory cells could be misleading because elements of pancreatitis are often associated with pancreatic carcinoma (409, 410). Unless recurrent or chronic, the focal pancreatitis rarely causes upstream duct dilatation of the pancreatic duct. The radiological "duct penetrating" sign (non-dilated pancreatic duct passes through hypoattenuating pancreatic mass) supports the benign diagnosis such as acute or mild chronic pancreatitis (411). Chronic pancreatitis often causes smooth narrowing of both pancreatic and common pancreatic ducts, which could be depicted on MDCT result in a challenging radiological diagnosis.

5 Methods

5.1 Plan of investigations

The Southwest Peninsula HPB Cancer Unit provides pancreatic cancer surgical services to the counties of Devon and Cornwall. Referrals come from five hospitals in a cancer network with a population of 1.7 million. Data relating to population density were obtained from the Office for National Statistics (ONS) (412). The size of the catchment area served by each of the five hospitals in the Peninsula was obtained from South West Public Health Observatory (413), based on the referral practice of general practitioners.

The study cohort included consecutive series of patients referred from the five hospitals across the cancer network and treated at Southwest Peninsula HPB Cancer Unit between January 2006 and May 2014 (Appendix-A).

All patients were discussed at the regional HPB MDT before being offered surgery. The surgical workload is shared non-selectively by four surgeons and is undertaken using standardised surgical techniques. In-patient care follows a standard Enhanced Recovery After Surgery (ERAS) protocol. (Appendix-D) Precise characterisation of the tumour is undertaken and the information relayed to the clinical team. Patients with evidence of metastatic spread are referred for non-operative treatment. Clinically significant features of the morphology of the pancreatic head tumour are recorded in the patients' notes.

Initially a dataset was compiled including patients' demographics, referral details, imaging characteristics, laboratory investigations results, operative details, pathological findings and follow up details. These information were obtained from patients' case notes, G.P records, electronic information systems including i SOFT, I Lab and PACS (Appendix-C)

The date of diagnosis of PHM was taken as the date of the first cross-sectional abdominal imaging which suggested this diagnosis. As the time of receipt of the initial referral is variable and subject to administrative delays, the interval to surgery (IS) was measured from the date of the first imaging modality undertaken which raised the possible diagnosis of PHM to the time of the surgical intervention. The travel distance by road for each patient was obtained from the AA mileage calculator (414)(with permission) using the post-code data. The presence of pre-operative biliary obstruction was defined as any abnormality in liver function tests sufficient to prompt investigation by cross sectional imaging or the requirement for pre-operative biliary drainage or clinically evident jaundice at time of surgery. Pre-operative diabetes was defined as the requirement for hypoglycaemic medications. The American Society of Anaesthesiologists (ASA) grade was determined at the time of surgery by the responsible anaesthetist.

To assess the ability of the pre-operative CT scan to determine the tumour origin, stage and resectability, all pre-operative CT scans of interest were retrieved through the Insignia radiology imaging system from across the five hospitals. All identifiable data were removed and images were then anonymised and uploaded to the Picture Archiving and Communication System (PACS) system. Two radiologists blinded to the final histology result reviewed all scans independently in the same manner as in routine clinical practice using a specially designed focused proforma with review by a third radiologist in cases of discrepancy. Final radiological re-reporting results were correlated with the operative and histopathological outcome. Imaging other than of the primary tumour and the peripancreatic area was not reviewed.

Resectability was defined as the ability to resect the pancreatic head without the use of neoadjuvant chemotherapy. Surgical resection was performed by a classic Whipple resection with pancreatico-gastrostomy reconstruction.

Tumours were classified according to the histological origin (pancreatic, bile duct, ampullary or duodenal). Pathological reporting was undertaken according to Royal College of Pathologists guidelines(23) with axial slicing of the resection specimen. The TNM classification system for malignant tumours (415, 416) was used to determine the final pathology stage.

Survival data were obtained from hospital and general practice records and included all deaths occurring after surgery, including in-hospital mortality. Survival was calculated from the date of the first diagnosis. Follow-up was completed 1st May 2015.

5.2 Study participants

5.2.1 Inclusion criteria

All patients who have undergone attempted surgical resection for presumed pancreatic head malignancy at Southwest Peninsula HPB Cancer Unit between January 2006 and May 2014 were included.

5.2.2 Exclusion criteria

The following patients have been excluded:

- All patients received preoperative neoadjuvant chemo/chemo-radiotherapy.
- All patients undergoing surgical resection not involving the pancreatic head.
- Patients with the final histology other than pancreatic, ampullary, bile duct or duodenal cancer were excluded from the final analysis.
- For assessment of the ability of the staging CT scan to predict the resectability of periampullary cancers, patients were excluded if the pre-operative CT scan of interest could not retrieved.

5.3 Study procedures and interventions

No study-specific procedures or interventions were required. The study was a retrospective review of the Peninsula HPB cancer centre database with review of the preoperative staging CT scan for patients with suspected periampullary cancers.

5.4 Outcome measures

The outcome measures of interest were the resectability of the periampullary tumours and pathological origin of the resected tumour.

5.5 Study questionnaires and forms

A proforma was designed to record the radiological findings of interest (Appendix-B).

5.6 Definition of end of the study

The study ended by completing the dataset, retrieving all relevant information and analyzing the data.

5.7 Source data

The Southwest Peninsula HPB Cancer Unit retains a prospectively maintained database of routinely collected clinical information including demographics, radiology and pathology reports. Imagings of interest were retrieved from the Insignia radiology system.

5.8 Data storage

All data were stored on NHS password protected hard drive. Anonymised data was stored on a project-specific, encrypted portable hard drive. Data will be kept for five years after the study ends.

5.9 Statistical Analysis

5.9.1 Statistical tests

The following statistical tests were used in order to interpret the study findings. I undertook the descriptive statistical analysis, which were rechecked and confirmed by Dr. Shahtahmassebi whom undertook inferential analyses.

Pearson Chi square test (X^2) was used to assess the significance in difference between discrete variables e.g. patients' travel distance, interval to surgery and pathological outcomes. This was to test whether the frequency in the outcome of interest was significantly different between the different groups or it was due to chance. This significance was expressed by *P* value.

Kruskal-Wallis test, non-parametric test, was used to assess the significance of difference between continuous variables e.g. radiological tumour size between two groups e.g. resection vs. non- resections. When comparing the difference across more than two groups e.g. the five referring hospitals, Mann–Whitney U test was used.

To examine the strength of the relationship between variables (how closely related), correlation coefficient (*r)* was used. This was to examine the strength of the relationship rather than the cause-effect relationship between variables, which ranges from -1 to +1. A positive correlation coefficient means that the value of one variable is increased if the value of the other variable is increasing. A negative correlation coefficient means that if one variable increased, the other variable decreased. A perfect correlation could be +1 or -1 while the zero value indicates no correlation. Pearson's correlation coefficient was used when both variables were continuous e.g. patients' travel distance and interval to surgery. Spearman correlation coefficient (non-parametric test) was used

to test the strength of the relationship when one or both variables were non-normally distributed e.g. radiological features and final histological findings. Its significance was expressed by *P* value.

Kaplan–Meier survival curves (non-parametric test) were used to assess patients' survival. Survival times were calculated from time of the diagnosis (date of fist imaging modality that raised the suspicious of periampullary cancer was taken as a reference point) till May 2015. Dates of death (event) were determined by access to General Practice records.

The number at risk (r) at given time period was calculated by subtracting the number of patients died and the number of those who lost follow up (censored) together from the total number of risk at the beginning of that certain time period. Probability of deaths at specific time period was calculated by dividing the number of patients died (d) at this specific period by the number at risk (r) at the same time period.
The probability of survival at a given period was then calculated as (1- d/r).

Kaplan-Meier survival probability of any current time period was calculated by successive multiplication of all survival probabilities that preceding that specific period and the current time period. To examine the overall survival between any sets of two different groups e.g. resections vs. non-resections; log rank test was used. The significance was expressed using the *P* value.

Cox regression analysis (proportional hazards) was used to explore the potential influence of more than one variable e.g. age, gender, ASA grade, travel distance and biliary obstruction on patient's survival. It provides estimate of the survival time and confidence intervals as well as adjusts the effect of the confounders.

Multivariate logistic regression models were used to predict a categorical outcome variable e.g. histological tumour stage from a set of explanatory variables e.g. preoperative variables (e.g. Interval to surgery as a binary variable < or ≥ median), or radiological parameters.

Cohen's Kappa test was used to assess the concordance of responses (inter observer agreement) between the two radiologists re-reporting the scans (recording categorical data) in excess of the agreement that would occur by chance. The K value ranges from zero to one. A value of zero means no significant agreement more than would have been expected by chance, a value of 0.5 means a good agreement, 0.7 means a very good agreement and a value of 1 means a perfect agreement.

5.9.2 Statistical software

The following statistical programs have been used:

- IBM® SPSS® 21
- The R statistical program
- Analyse-it program

5.9.3 Number of participants

As no previous studies have been undertaken to address the outcomes of the two studies, formal power calculations were not possible to undertake at the time of conducting this study. Thus, an interim analysis was undertaken after 50 reports to identify likely positive radiology features to power the remainder of the study (421 patients).

5.9.4 First and second studies

To address the primary objective of the study, continuous variables were compared with Mann-Whitney U test and categorical variables by Chi square test.

In the demonstration of potential association between the travel distance to the regional HPB centre and interval to surgery a logarithmic scale was used to accommodate the wide spread of intervals to surgery. Correlation was assessed by Spearman correlation coefficient

Kaplan-Mayer survival curves were constructed for patients according to the resectability and the pathology subsets. This allowed comparison of outcomes according to tumour origin, resection margin status and pathological stage for the entire cohort.

Kaplan-Meier survival analysis and Cox Proportional Hazard models were used to assess the effect of potential influence of preoperative variables including age, gender, ASA grade, biliary interventions, referring hospital, travel distance and interval to surgery on the post-operative survival.

Multivariate logistic models were then used to examine potential associations between pre-operative variables with the histological tumour stage.

5.9.5 Third and fourth studies

Contingency tables were drawn up for each radiologist comparing continuous and categorical radiology outcomes with pathology reports and surgical outcomes. Concordance between radiologists was assessed using inter-rate reliability measures such as Cohen's kappa test.

Discrepancy: In the case of discrepancy in reporting between two consultant radiologists, a third consultant's opinion was sought to review the scan and to discuss until final agreement is reached

The accuracy of the preoperative CT scan in determining the origin of PHM and the resectability was assessed using Positive predictive value (PPV), Negative predictive value (NPV). The PPV is identified as a group of patients with CT scan suggesting the tumour organ of origin and they have confirmed diagnosis histologically. The NPP is identified as patients with CT diagnosis of certain tumour type, in whom this diagnosis has been ruled out by the histological examination.

5.9.6 Level of statistical significance

An outcome probability of 5% ($P<0.05$) was taken as being statistically significant.

5.10 Criteria for termination of the study

None

5.11 Procedure for accounting for missing, unused, and spurious data

Staging images were not available for ten patients. These patients were excluded from the final analysis.

5.12 Ethics

Southwest Peninsula HPB Cancer Unit records many aspects of each patient's journey from referral to follow-up including imaging and relevant findings from MDT discussion. Patient details were taken from the HPB database, which is currently maintained on NHS Trust password secured hard-drive. The director of studies was responsible for data anonymisation using an investigator-identifiable sequential number. These data were then recorded on an encrypted hard-drive. Relevant anonymised images

were stored on NHS Trust radiology PACS. These images were reviewed by reporting radiologists and the outcomes were recorded on password-secured encrypted hard-drive. Confirmation was obtained from the South West Health Research Authority that under the harmonised Guidance Approval for Research Ethics Committees (REC), neither formal REC review nor patient consent was required for this study. Ethical approval was granted from NRES Committee South Central - Hampshire B for the re-reporting of imaging component of the study, with the following details:

- REC reference: 14/SC/1391
- Protocol number: 14/P/090
- IRAS project ID: 167874
- Ethical approval date: 17.11.2014
- ClinicalTrials.gov Identifier: NCT02296736
- ClinicalTrials.gov registration: 18.11.2014

6 Results

In order to address the study objectives, this MD study was sub-divided into four research questions.

The results provided in this chapter are presented in a journal paper format corresponding to each individual study.

Published papers could be found at the end of the thesis.

6.1 Variation in survival after surgery for peri-ampullary cancer in a regional cancer network

6.1.1 Abstract

Background: Centralisation of specialist surgical services requires that patients are referred to a regional centre for surgery. This process may disadvantage patients who live far from the regional centre or are referred from other hospitals by making referral less likely and by delaying treatment, thereby allowing tumour progression. The aim of this study is to explore the outcome of surgery for peri-ampullary cancer (PC) with respect to referring hospital and travel distance for treatment within a network served by five hospitals.

Materials and Methods: Review of a unit database was undertaken of patients undergoing surgery for PC between January 2006 and May 2014.

Results: 394 patients were studied. Although both the median travel distance for patients from the five hospitals (10.8, 86, 78.8, 54.7 and 89.2 kilometres) ($p<0.05$), and the annual operation rate for PC (2.99, 3.29, 2.13, 3.32 and 3.07 per 100,000) ($p=0.044$) were significantly different, no correlation was noted between patient travel distance and population operation rate at each hospital. No difference was noted between patients from each hospital in terms of resection completion rate or pathological stage of the resected tumours. The median survival after diagnosis for patients referred from different hospitals ranged from 1.2 to 1.7 years and regression analysis revealed that increased travel distance to the regional centre was associated with a small survival advantage.

Conclusion: Although variation in the provision and outcome of surgery for PC between regional hospitals is noted, this is not adversely affected by geographical isolation from the regional centre.

6.1.2 Introduction

Since publication of the Improving Outcomes Document in September 2000 (417) surgery for periampullary cancer (PC) in the UK has been centralised into designated regional Hepato-Pancreatico-Biliary (HPB) centres, each serving a population of approximately two million. This process requires that most hospitals do not undertake pancreatic resection, but perform the initial treatment and assessment of patients with potential PC, before referral to the regional tertiary centre. This separation of secondary from tertiary care in different hospitals has the potential to disadvantage patients referred from hospitals other than the regional centre, as the referral process is likely to be more complex than when secondary and tertiary care are provided on the same site. Inevitably provision of pancreatic surgical services in a single HPB centre within a large area will impose greater difficulty and inconvenience for some patients in travelling to the regional centre, which may adversely affect referral for treatment for patients with PC. Furthermore delays in treatment for patients residing further from the regional centre may allow tumour progression and have an adverse effect on outcomes.

The potential influence of referral between hospitals and geographical isolation on the outcome of surgery for PC has not been assessed and the aim of this study is to assess associations between referring hospital of origin and traveling distance to the regional HPB surgical centre with the population rate of surgery for PC, the interval to surgery, pathological outcome and long-term survival after diagnosis of PC within a cancer network.

6.1.3 Materials and Methods

The Peninsula HPB cancer unit provides pancreatic surgical services to the Peninsula Cancer Network, which serves the largely rural UK counties of Devon and Cornwall, ranking the 7th and 12th least densely populated of the 90 English local

government areas (418). The population of the two counties (1.67 million) is served by four hospitals providing secondary care only, and one hospital, which provides secondary care and also hosts the regional tertiary HPB surgery centre. Surgery and immediate post-operative care are provided by the regional centre. All other treatment including stent insertion, adjuvant chemotherapy and long-term follow-up are provided by local hospitals. All hospitals are linked by a weekly audio-visual MDT with the regional centre. Referral and transfer of patients follows agreed protocols and is coordinated by nurse specialists.

Details of a consecutive series of patients having surgery at the Peninsula HPB unit between January 2006 and May 2014 were studied. Demographic, operative and pathology data were retrieved from the unit database. Included patients were those who underwent surgery for PC where final histology revealed a diagnosis of pancreatic, ampullary, distal bile duct or duodenal adenocarcinoma, or those where resection could not be completed and intra-operative biopsy confirmed the presence of adenocarcinoma. Patients receiving neo-adjuvant chemotherapy were excluded. The size of the catchment area served by each of the hospitals in the Peninsula was obtained from South West Public Health Observatory (413). The travel distance by road for each patient was obtained from the AA mileage calculator (with permission) using post-code data (419). The interval to surgery was calculated from the date of diagnosis of PC, which was taken as the date of the first cross-sectional abdominal imaging which suggested this diagnosis. The presence of biliary obstruction was defined as either clinically evident jaundice at the time of surgery or the requirement for pre-operative biliary drainage. Pre-operative diabetes was defined as the requirement for hypoglycaemic medication. The workload in the HPB surgical centre is shared non-selectively by four surgeons and is undertaken using standardised techniques, and in-patient care follows a standard protocol. The American Society of Anaesthesiologists (ASA) grade was determined at the time of surgery by the responsible anaesthetist. Resected specimens were analysed according to Royal College of Pathologists

guidelines (23) and the TNM classification systems (402) was used to describe pathological stage. Survival data were obtained from hospital and general practice records and included all deaths occurring after surgery, including in-hospital mortality. Survival times were calculated to include the interval prior to surgery and therefore were taken from the date of the first cross-sectional image, which raised the suspicion of PC. Survival data for the whole group of patients referred from each hospital is given as single outcome of interest and is reported as median and range. Follow-up was completed 1st May 2015.

Differences in demographics, operation rates, travel distance, interval to surgery and pathology outcome were compared between hospitals (pathology results for patients with duodenal cancer were not included due to low numbers). Difference in discrete variables was assessed by Pearson Chi square test and continuous variables by Kruskal-Wallis test. Correlation was assessed by Spearman correlation coefficient. To explore potential associations with patient survival a Cox regression analysis of pre-operative factors including age, gender, ASA grade, travel distance and the presence of biliary obstruction at presentation was undertaken. In addition, patient survival across five hospitals was compared using Kaplan–Meier survival curves and between hospital pairs by Cox regression analysis.

6.1.4 Results

During the study period 394 patients fulfilling the study criteria underwent surgery to attempt resection of PC at the regional HPB surgery centre (hospital A) (Figure 6-1). The median age (66.7 years, range 39.4- 86.4) and gender mix (56.3% male) of the whole group did not vary between patients referred from hospital A, or from hospitals providing secondary care only (hospital B to E) (Table 6.1).

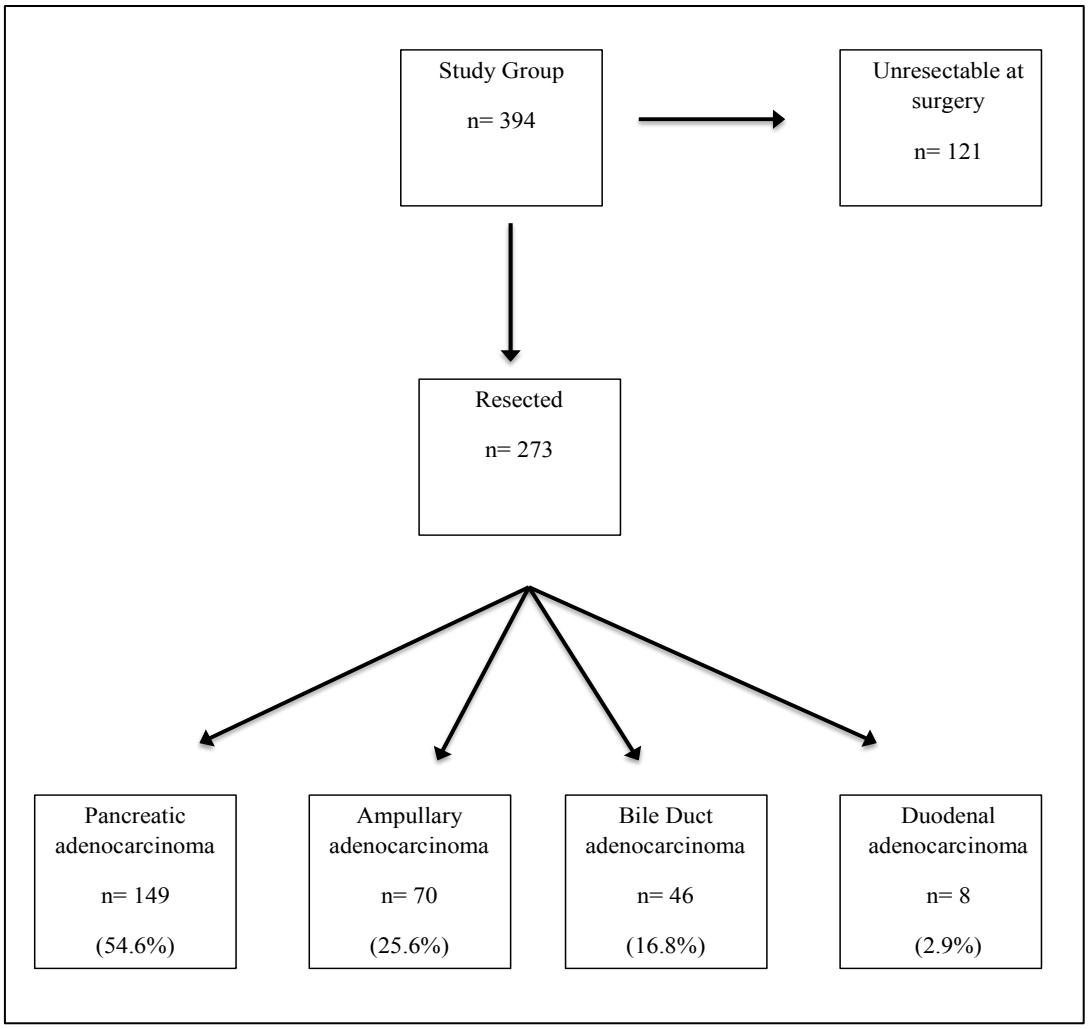


Figure 6-1 Patients undergoing surgery for periampullary cancer at Peninsula HPB Centre between January 2006 and May 2014

The number of operations for PC undertaken as a proportion of the local population however varied significantly between referring hospitals (Table 6.1). The median distance patients were required to travel for care was 61.4 kilometers and was significantly less for patients referred from within the catchment area of the regional HPB surgery centre to that for patients referred from all other hospitals in the Peninsula. No correlation was noted between the median travel distance to the regional centre of patients from the referring hospitals and the operation rate at that hospital ($p = .855$). The second lowest population operation rate was noted from the population receiving secondary care from the hospital hosting the regional HPB centre.

Referring hospital		(A)	(B)	(C)	(D)	(E)	P
n=394 (%)		111(28.2)	97(24.6)	70(17.8)	74 (18.8)	42 (10.6)	
Population served		464,437	368,313	410,213	278,555	171,227	
Annual operation rate for PC per 100000		2.99	3.29	2.13	3.32	3.07	0.04
Median Travel Distance (kilometres) (range)		10.8 (2.4-112)	85.9 (45.2-155.8)	78.8 (10.1-130.3)	54.7 (2.4-96.2)	98.3(63-138.6)	.000
Median age (range)		65.7 (41.2-82.0)	68.4 (41.7-84.0)	65.5 (39.4-78.6)	65.6 (45.9-86.4)	70.2 (50.7-84.4)	.105
Gender (% Male)		53.2	58.8	58.6	58.1	52.4	.880
ASA Grade (%)	1	8 (7.2)	8 (8.2)	8 (11.4)	7 (9.5)	0	.416
	2	56(50.5)	53(54.6)	39(55.7)	41(55.4)	22(52.4)	
	3	28 (25.2)	26 (26.8)	18 (25.7)	18 (24.3)	14(33.3)	
	4	2 (1.8)	1 (1)	0	0	0	
	Missing	17 (15.3)	9 (9.3)	5 (7.1)	8 (10.8)	6 (14.3)	
Diabetes	Yes (%)	13 (11.7)	10 (10.3)	7 (10.0)	6 (8.1)	5 (11.9)	.987
	Missing	12 (10.8)	17 (17.5)	14 (20.0)	15 (20.3)	4 (9.5)	
Jaundice at Presentation (%)		91 (82.0)	82 (84.5)	56 (80)	65 (87.8)	36 (85.7)	.641
Median interval to surgery (days) (range)		47 (5-551)	52 (1-459)	56.5 (16-379)	47 (16-246)	51.5 (6-477)	.108
Resection completed (%)		73 (65.7)	68 (70)	51 (72.8)	51 (68.9)	30 (71.4)	.880
30-day mortality (%)		4 (3.6)	1 (1)	2 (2.8)	1 (1.3)	2 (4.7)	.610

Table 6.1 Details of 394 patients undergoing surgery for peri-ampullary cancer between January 2006 and May 2014, displayed by referring hospital of origin. Hospital A hosts the regional HPB cancer centre.

The distribution of ASA grades, the proportion of patients with diabetes, biliary obstruction at the time of surgery and pre-operative biliary intervention did not differ between hospitals (Table 6.1). The median interval from first investigation suggesting a diagnosis of PC to surgery was 49 days (interquartile range 34-69 days) and was similar

between referring hospitals. Correlation analysis revealed no association between the travel distance to the regional HPB surgery centre and the interval to surgery ($p = 0.15$). In-patient 30-day mortality occurred in 10 (2.5%) patients and did not differ between hospitals.

Tumour resection was completed in 273 patients (69.3%) and the completion rate did not differ between hospitals (Table 6.2). In 121 patients the tumour was inoperable at the time of surgery either due to the presence of vascular invasion (70) or distant metastases (47). In four patients the reason for irresectability was not recorded. Histological diagnoses of the resected specimens are shown in (Figure 6-1).

Analysis of pathological outcomes revealed no difference between patients from the referral zone of the regional centre and those from other hospitals in the region, in terms of resection completion rate, tumour size, nodal status and resection margin status (Table 6.2). Similarly the distribution of the main diagnoses of PC did not differ between patients from the regional centre and those from other hospitals.

N= 265	A 111	B 97	C 70	D 74	E 42	P
Pancreatic cancer *(n =149)*	40	38	22	28	21	
T size (mm) (range)	30 (15-48)	31.5 (16-60)	30.5 (15-70)	32.5 (12-50)	30 (18-65)	.620
N1disease (%)	35 (87.5)	33 (86.8)	19 (86.4)	23 (82.1)	17 (81)	.940
R1 resection (%)	34 (85)	24 (63.1)	18 (81.8)	24 (85.7)	19 (90.5)	.052
Ampullary cancer *(n= 70)*	21	18	12	13	6	
T size (mm) (range)	25 (12-80)	22.5 (5-65)	23.5 (15-60)	22 (11-65)	28 (8-50)	.933
N1disease (%)	14 (66.6)	10 (55.5)	6 (50)	5 (38.5)	4 (66.6)	.551
R1 resection (%)	7 (33.3)	1 (5.5)	2 (16.6)	2 (15.4)	2 (33.3)	.230
Bile duct cancer *(n=46)*	10	10	13	10	3	
T size (mm) (range)	25.5 (10-70)	27 (10-45)	25 (10-40)	20 (12-50)	15 (12-20)	.216
N1disease (%)	7 (70)	7 (70)	4 (30.7)	7 (70)	1 (33.3)	.172
R1 resection (%)	5 (50)	6 (60)	5 (38.5)	5 (50)	2 (66.6)	.839

Table 6.2 Histopathological stage for 265 patients undergoing resection of pancreatic, ampullary and distal bile duct cancer at the regional HPB centre (A) displayed by referring hospital of origin

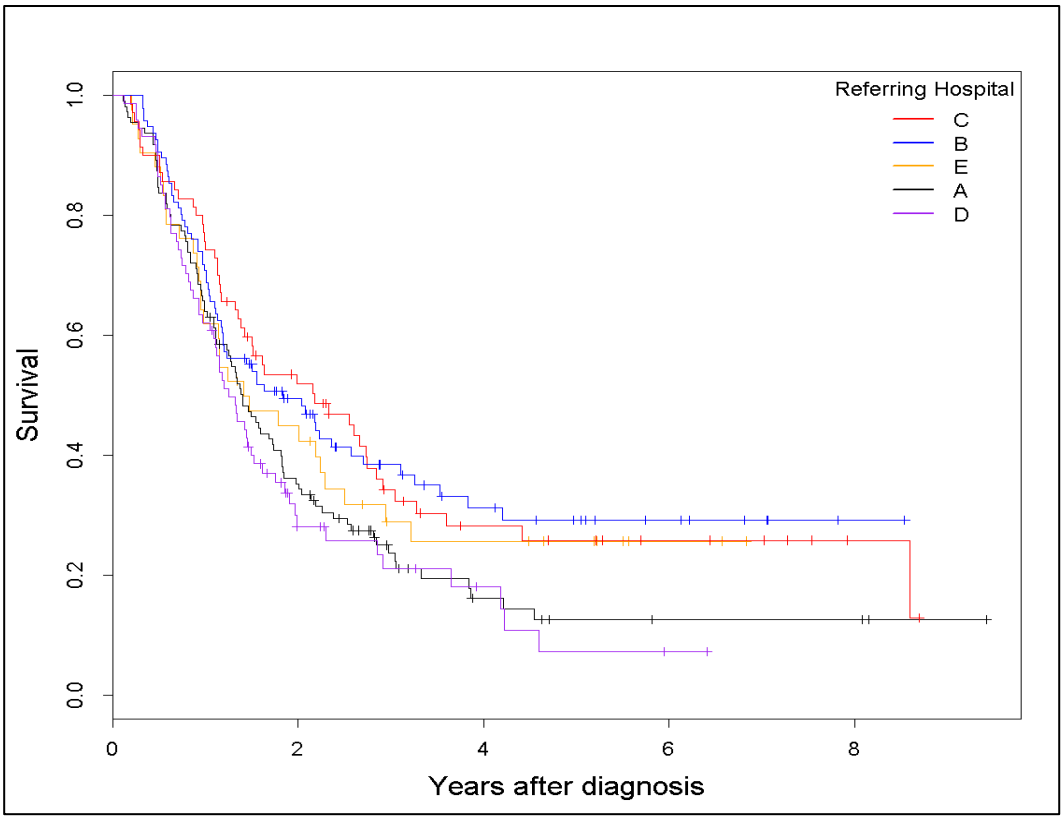
After a median follow-up of 4.5 years (1.3-9.5 years) the median survival (range) of the study group was 1.45 (0.11 – 9.4) years and was similar in males (1.44, 0.13-9.3 years) and females (1.45, 0.11-8.7 years). Two patients were lost to follow-up. Survival was greater in patients where resection was completed (1.85, 0.14-9.4 years) than in those where the tumour could not be removed (0.9, 0.11-2.8 years). The median survival of patients travelling more than the median distance for treatment was 1.5 (0.14-8.7) years compared to 1.4 (0.11-9.4) years for those travelling less than the median travel distance (p=0.234). Cox regression analysis of the association of pre-operative variables including

individual patient travel distance however revealed a significant survival advantage associated with increased travel distance to the regional HPB centre (Table 6.3).

		Hazard Ratio	Lower .95	Upper .95	P-value
Gender		0.956	0.744	1.229	0.728
Age		1.009	0.995	1.022	0.217
Distance (km)		0.996	0.993	0.999	0.029
Jaundice		0.967	0.686	1.364	0.852
ASA	1 vs. 2	0.945	0.678	1.317	0.739
	2 vs. 3&4	1.117	0.888	1.407	0.344

Table 6.3 Cox regression analysis of potential association of pre-operative factors including travel distance to regional HPB centre with survival after diagnosis for 394 patients undergoing surgery for periampullary cancer

Further survival analysis revealed that the referring hospital of origin was associated with outcome (Figure 6-2), with median survival ranging from 1.2 (0.14-6.4) years (patients from hospital D) to 1.5 (0.3-8.8) years (patients from hospital B).



Number at risk

Hospital/years	0	2	4	6	8
A	111	37	9	7	4
B	97	38	18	7	2
C	70	30	13	7	2
D	74	17	4	1	0
E	42	18	6	1	0

Figure 6-2 Survival from diagnosis of 394 patients undergoing surgery for periampullary cancer at Peninsula HPB surgery centre between January 2006 and May 2014, according to hospital of referral (P = 0.032)

Pair by pair regression analysis comparing patients from the catchment area of the regional HPB centre revealed no difference in survival from diagnosis for patients from three hospitals C, D and E, but confirmed the significantly decreased hazard ratio of death of patients referred from hospital B (Table 6.4).

A vs.	Hazard Ratio	lower .95	upper .95	P-value
B	0.6934	0.5011	0.9594	0.0271*
C	0.7042	0.4952	1.0013	0.0508
D	1.1121	0.7983	1.5493	0.5299
E	0.8228	0.5435	1.2456	0.3565

Table 6.4 Paired regression analysis of association of hospital of referral (B to E) with survival compared to referral from Hospital A among 394 patients undergoing surgery for peri-ampullary cancer

6.1.5 Discussion

The main findings of this study are:

1) Within the Peninsula Cancer Network the population operation rate for PC varies significantly between hospital catchment areas but this variation is not related to travel distance to the regional HPB surgical centre and

2) Individual patient travel distance to the regional centre does not adversely affect the time to surgery, pathological outcome or survival in patients with PC.

3) The provision of secondary and tertiary care in different hospitals does not adversely affect patient outcomes.

Centralisation of pancreatic surgical services has led to improved outcomes including higher resection rates (34, 35), lower operative mortality (36, 37) and improved long-term survival (38). Similar improvements with centralisation have been noted for liver (420), oesophageal (421), complex urological (422) and vascular surgery (423). Despite these findings the population benefits of regionalisation are more difficult to demonstrate. Although studies using hospital data have demonstrated improved outcomes associated with centralisation of surgical services for patients who receive treatment (35, 45, 424), these studies may be biased by selection of patients at the regional centres and do not take

into account patients who are not referred for treatment. Studies demonstrating improved population outcomes as a result of regionalisation of complex surgery are more difficult to undertake. The potential disadvantages of centralisation of services include a more complex referral pathway when secondary and tertiary care are provided in different hospitals, and an increased burden of travel for patients living further from the centre, which may discourage referral and attendance for treatment. These consequences of centralisation have been noted (425, 426) and the potential risk is greatest in areas of dispersed population. This has led to controversy over the implementation of centralisation of surgical services in rural communities (427), where the risk of limitation of access due to distance may outweigh the benefit of improved technical outcomes. The observation that operation rates are not adversely affected by distance to the HPB surgical centre, or by referral from a different hospital, and that travel distance itself does not influence the outcome of surgery for PC are important, as they show that regionalisation of surgical services does not necessarily lead to limitations in access or increased patient selection at the HPB surgical centre.

The small variation in operation rate noted between hospitals may reflect differences in levels of comorbidity and suitability for surgery, but may be due to different referral practices within each hospital. The observation that the referring hospital of origin is also associated with long-term survival after surgery for PC is therefore an interesting new finding. Many factors contribute to variation in local survival rates and levels of comorbidity are likely to play a major role. It is interesting to note however that long-term survival is lowest in patients from the hospital with the highest population rate of surgery for PC. This may result from referral of more marginal cases, which is not revealed by the measures of comorbidity and tumour burden used in this study. Variation in population operation rate for PC may also explain some of the variation noted in outcome between high-volume hospitals undertaking pancreatic surgery (428).

The strength of this analysis lies in the accurate collection of individual travel distance to the regional HPB surgery centre in a large consecutive series of patients, and its correlation with prospectively audited outcomes. In this study a single measure of survival of all patients has been used, without division by diagnosis, to allow simple comparison between hospitals. This figure includes deaths due to surgical complications, which accounts for the short survival in some patients. A weakness of the study lies in the characterisation of comorbidity. A more discriminating scoring system is required to investigate the potential association of comorbidity with variations in population operation rate for PC. The relatively long median interval to surgery noted in this study, even for patients with biliary obstruction (47 days), is accounted for by the increasing complexity in the patient pre-operative pathway. This pathway however imposes a similar interval to surgery on patients regardless of geographical isolation from the regional centre. In a small number of patients a long interval to surgery was due to investigations being undertaken in patients with self-resolving jaundice, which was not pursued due to patient improvement. The studied group is limited to those who have been referred to the centre for being potential resectable, however it does not capture those who have not been referred and deemed unfit or unresectable at the referral hospital. The resection rate is lower in this series partly due to a low resection rate at the beginning of the decade which is now been resolved with improved radiological techniques and improved surgical techniques, the current non resection rate is less than 10%.

6.1.6 Conclusion

This study confirms that centralisation of HPB surgical services can be implemented without imposing disadvantage in surgical outcomes on patients due to travel distance to the HPB surgical centre or referral between hospitals for treatment.

6.2 Assessment of the effect of interval from presentation to surgery on outcome in patients with peri-ampullary malignancy

6.2.1 Abstract

Background: Delay between diagnosis of peri-ampullary cancer (PC) and surgery may allow tumour progression and affect outcome. The aim of this study was to explore associations of interval to surgery (IS) with pathological outcomes and survival in patients with PC.

Method: A database review of all patients undergoing surgery between 2006 and 2014 was undertaken. IS was measured from diagnosis by imaging. Potential association between IS and survival was measured using Cox regression analysis, and between IS and pathological outcome with multivariate logistic analysis.

Results: 388 patients underwent surgery. The median IS was 49 days (1-551 days), and was not associated with any of the evaluated outcomes in patients with pancreatic (149) or distal bile duct (46) cancer. For patients with ampullary cancer (71) longer IS was associated with improved survival, with median survival of 27.5 months for patients waiting ≤ median IS (35) and 38.3 months for patients waiting > median IS (36) for surgery (p=0.041). A higher rate of margin positivity (31.4%) was also noted among patients who waited less than the median IS compared to those waiting longer than this interval (11.4%) (p=0.032).

Conclusion: For patients with ampullary cancer there is a paradoxical improvement in outcome among those with a longer IS, which may be explained by progression to inoperability of more aggressive lesions.

6.2.2 Introduction

Peri-ampullary cancer (PC) most commonly originates within the pancreas, the distal common bile duct, or the duodenal ampulla. The organ of origin of PC is usually determined by pathological examination after resection and has important implications for prognosis. Five-year survival after surgical resection varies from 6.5%-20% for pancreatic cancer (3-9), 19.2%-30% for bile duct cancer (3, 5, 7, 8, 17, 18) and 33%-45% for ampullary cancer (3, 5, 7, 8). For many patients their disease is inoperable at the time of presentation due to local invasion or the presence of distant metastases. For those with operable tumours there will usually be an interval between radiological diagnosis and surgery, to allow referral, assessment and operative planning. In England, the National Cancer Plan stipulates a maximum interval of 62 days from primary referral to treatment for most solid cancers (429), although this figure is not based on evidence of safety for each tumour type. Tumour progression may take place during this interval, rendering tumours inoperable and long-term survival may potentially be affected.

Within any patient cohort there is likely to be a range of intervals between diagnosis and surgery, with some patients undergoing surgery very quickly, and some waiting many months. As PC is an aggressive malignancy, this period may constitute a significant part of the natural history of the disease. Analysis of the potential association of interval to surgery with pathological and surgical outcomes may reveal aspects of the behaviour of these tumours, and determine if the 62 day target to surgery disadvantages patients by allowing tumour progression.

This study aimed to investigate the interval to surgery in a consecutive series of patients undergoing surgery with the intention to resect PC and to explore the association of IS to resectability, tumour stage and overall survival.

6.2.3 Material and methods

Review of a prospectively maintained database of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and May 2014 was undertaken. Referrals came from five hospitals in a cancer network with a population of 1.7 million. The study cohort included patients with a histological diagnosis of pancreatic, bile duct or ampullary cancer, or those where the tumour was unresectable and biopsy confirmed the presence of adenocarcinoma. Patients receiving neoadjuvant chemotherapy were excluded. No patients were excluded from surgery due to disease progression in the interval between referral and surgery. Demographic and clinical data were retrieved. Pre-operative biliary obstruction was defined as any abnormality in liver function tests sufficient to prompt investigation by cross sectional imaging. As the time of receipt of the initial referral is variable and subject to administrative delays, the interval to surgery (IS) was measured from the date of the first imaging modality undertaken which raised the possible diagnosis of pancreatic head malignancy to the time of the surgical intervention, by review of individual radiology records. Surgical resection was performed by a classic Whipple resection with reconstruction by pancreatico-gastrostomy. Pathological reporting was undertaken according to Royal College of Pathologists guidelines(23) with axial slicing of the resection specimen. Tumours were classified according to histological origin (pancreatic, bile duct or ampullary) and nodal status and margin involvement status were retrieved from histology reports.

Continuous variables were compared with Kruskal-Wallis test and categorical variables by Chi square test. The mean and variance of tumour size across different tumour types were compared using Bayesian double generalised linear models.

Dates of death were determined by access to General Practice records and survival times calculated from the time of diagnosis. Kaplan-Meier survival analysis and Cox Proportional Hazard models were used to assess the effect of interval to surgery on post-

operative survival. Multivariate logistic regression models were then used to explore potential associations between pre-operative variables including IS as a binary variable (< or ≥ median) with histological tumour stage.

6.2.4 Results

388 patients (223 (57%) males) with a median (range) age 67 (41-86) years fulfilling the study criteria underwent surgical exploration during the study period and resection was completed in 266 patients (69%) (Table 6.5).

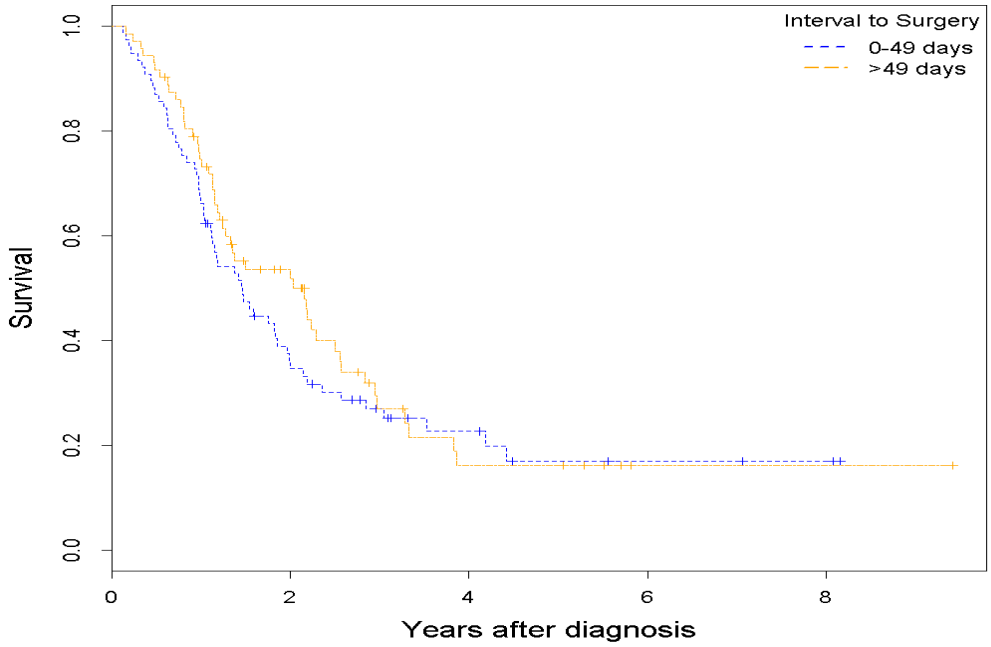
n=266 (%)		Cancer Origin			p
		Pancreas n=149 (56%)	Bile duct n=46 (17%)	Ampulla n=71 (27%)	
Median age (range)		67.9 (41.3- 82.1)	65.7 (43.7-84.1)	66.2 (411.2-86.4)	.312
Gender (% male)		55	69.6	53.5	.171
ASA (%)	1	6 (4)	4 (8.7)	9 (12.7)	.056
	2	84 (56.4)	22 (47.8)	42 (59.2)	
	3	44 (29.5)	15 (32.6)	14 (19.7)	
	4	1 (0.7)	0	0	
	Missing	14 (9.4)	5 (10.8)	6 (8.4)	
Median IS (range) (days)		48 (1-551)	50 (5-294)	51 (14-477)	.881
Median tumour size (range) (mm)		30 (12-70)	22 (10-70)	25 (5-80)	.002
Involved lymph nodes (%)		127 (85.2)	26 (56.5)	40 (56.3)	.0001
Involved resection margin (%)		119 (79.9)	23 (50)	15 (21.1)	.0001
30 day post-operative mortality		3 (2)	0	3 (4.2)	0.275

Table 6.5 Interval to surgery and pathological outcome among 266 patients undergoing resection of peri-ampullary cancer.

In 122 (31%) patients the tumour was found to be inoperable due to local invasion of vascular structures (n=70 (57%)) or the development of distant metastases (n=47 (63%)). Operative details could not be retrieved in three (1%) patients, tumour mass could not be identified in one patient and one patient did not tolerate surgery. Lateral resections of a small venous patch were undertaken in 32 (12%) patients. The median IS for 388 patients was 49 (1-551) days, and was similar in groups undergoing resection (49 days, range 1-551) or surgical exploration only (50 days, range 11-512) (P=0.940). The IS in 331 patients (85.3%) with biliary obstruction at the time of initial presentation was 47 days (1-512) compared to 69 (14-551) in those without this complication (p=0.001). Pancreatic tumours were noted to be larger than both ampullary and bile duct tumours (Table 6.5).

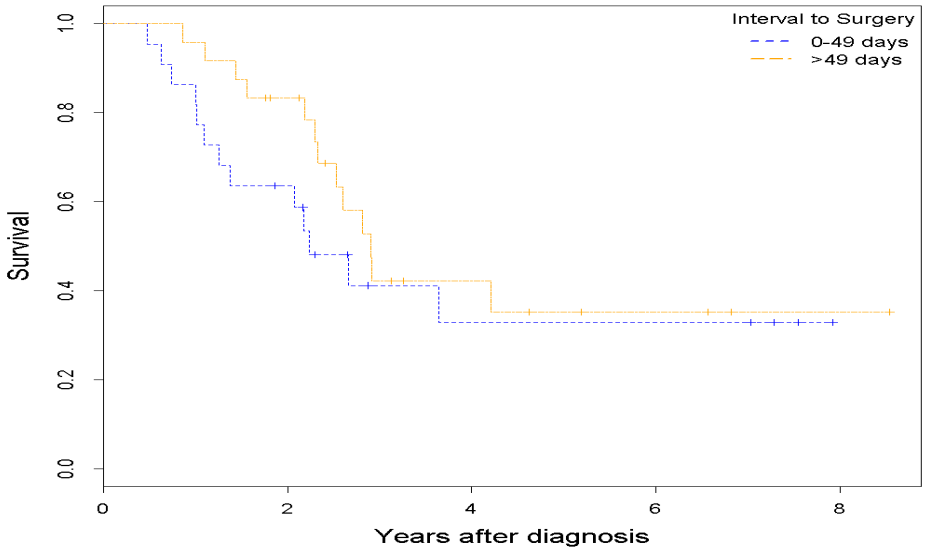
In regression analysis the variance in size of ampullary tumours was noted to be greater than both pancreatic tumours (coefficient = -1.075; credible interval -1.441 to -0.704) and bile duct tumours (coefficient = -0.63; credible interval -1.096 to -0.165).

After minimum follow-up of 12 months the median survival (range) from diagnosis of the whole cohort was 17.2 months (1.4-114.6) and was significantly longer in patients undergoing surgical resection (23.7 months, range 1.5-114.6) compared to those having surgical exploration only (11.2 months, range 1.4-75.7) The median survival (range) of patients undergoing resection of pancreatic, bile duct and ampullary cancer was 17.3 (1.5-114.6), 28.1 (5.8-104) and 33.3 (2.1-107.1) months respectively. No patients were lost to follow-up. Pre-operative IS was not associated with survival for patients undergoing resection of pancreatic or bile duct cancer, but a positive association was noted for patients with ampullary cancer (Figure 6-3).



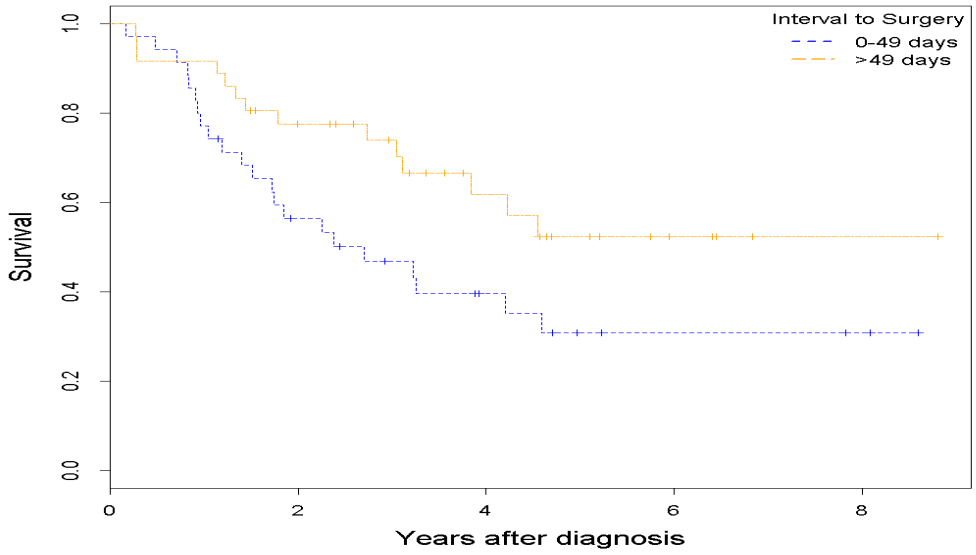
Number at risk (Pancreatic cancer)

IS/Years	0	2	4	6	8
0-49 days	77	25	9	4	2
> 49 days	72	30	6	1	1



Number at risk (Bile duct cancer)

IS/Years	0	2	4	6	8
0-49 days	22	13	4	4	0
> 49 days	24	18	6	3	1



Number at risk (Ampullary cancer)

IS/Years	0	2	4	6	8
0-49 days	35	18	9	3	2
> 49 days	36	25	13	4	1

Figure 6-3 Survival curves of patients undergoing pancreatic head resection for a) pancreatic (149), b) bile duct (46) and c) ampullary cancer (71), divided into subsets determined by the median interval to surgery from initial investigation. P = .419, .321 and .043* respectively.

Cox regression analysis of survival data confirmed the reduced hazard of death associated with a longer IS in patients with ampullary cancer only (Table 6.6).

Tumour type	Hazard Ratio	95% CI	P
Pancreas (149)	0.679	0.314-1.467	0.324
Bile duct (46)	0.855	0.584-1.251	0.419
Ampulla (71)	0.506	0.259-0.991	0.047*

Table 6.6 Cox regression analysis of association of interval to surgery with survival of patient cohorts, determined by tumour origin.

Multivariate analysis of potential associations between pre-operative factors and histological outcomes and survival confirms the reduced risk of positive resection margin in patients with a longer interval to surgery (Table 6.7).

	Tumour Size			Nodal status			Resection margin status		
	Coeffi cient	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
IS (</> 49)	-0.14	-0.403 0.123	0.232	0.604	0.221 1.654	0.326	0.226	0.058 0.877	.032
Gender	-0.51	-0.743 -0.277	0.000	0.512	0.183 1.432	0.202	0.795	0.224 2.818	.722
Age	-0.017	-0.029 -0.005	0.005	0.996	0.947 1.048	0.878	0.996	0.934 1.063	.912
Bilary obstruc tion at present ation	-0.161	-0.484 0.162	0.312	2.330	0.589 9.225	0.228	0.413	0.081 2.118	.289

Table 6.7 Multivariate analysis of potential associations with tumour size, nodal status and resection margin status among 71 patients undergoing resection of ampullary cancer

The proportion of ampullary cancer specimens removed within less than the median IS (49 days) with involved margins was 31%, compared to 11.4% among those removed after this interval from diagnosis (p=0.032). An association between tumour size with age and female gender is also noted (Table 6.7).

6.2.5 Discussion

Patients with PC may suffer significant delays between presentation and surgery. This may be contributed to by the vague nature of symptoms at the time of presentation (430, 431), the need for biliary drainage (268), delays incurred during referral to regional centres and capacity issues restricting access to operating time. Because of perceived delays in the treatment of cancer cases NHS guidelines introduced a target of 62 days from referral to treatment for most solid tumours in 2000 (429). Concerns may be raised that this delay will reduce the operability of the pancreatic head lesion, allow tumour progression and impair long-term survival. The main finding of this study is that no association is noted between delay to surgery and any outcome in patients with pancreatic or distal bile duct cancer, but that a longer interval to surgery is paradoxically associated with improved outcome in patients with ampullary cancer. A proportional increase in survival is noted with each extra months delay prior to surgery associated with a hazard ratio of death of 0.55 after surgical resection. In corroboration of this finding the chance of an involved resection margin is also reduced for patients with ampullary cancer who wait longer for surgery.

In this series a high percentage of resected patients were shown to have ampullary cancer (26%). This is consistent with the adoption of a standardised pathological reporting protocol, which has led to higher rates of diagnoses other than pancreatic cancer in peri-ampullary malignancy (24, 432). PC usually presents with biliary obstruction caused by mass effect and operability is determined by the sequence of invasion, as vascular invasion is a major cause of irresectability (352, 433, 434). Lesions of the ampulla

lie furthest from the vascular structures and may be less likely to be inoperable than lesions of the pancreatic parenchyma, which encases the junction between superior mesenteric and portal vein. Surgery is offered to patients who do not have invasion of vascular structures or distant metastases detected on pre-operative imaging, though these findings are often encountered at the time of surgery. This may be caused by understaging by CT scan (435) or by tumour progression in the interval to surgery, which is more likely in aggressive tumours. These results suggest that for pancreatic and bile duct tumours the timing of surgery in relation to pre-operative imaging within the range measured in the study has no effect on resectability, tumour stage or survival after diagnosis. This implies that the operative findings and surgical outcome are determined before imaging takes place and these tumours change little in the interval to surgery. For ampullary tumours however it appears that a longer wait for surgery results in selection of a subset of patients whose tumours remain resectable, with better prognostic characteristics, as shown by the reduced risk of an involved resection margin and improved long-term survival. This may be explained by the progression of a more aggressive subset of ampullary tumours in the interval to surgery leading to inoperability. This more aggressive subset probably includes older patients; in whom resected ampullary tumours are shown to be larger. In support of this concept we have noted a greater variance in size of ampullary tumours than pancreatic and bile duct tumours. Less aggressive ampullary tumours remain confined to the region of the ampulla while others progress to invade vascular structures. As ampullary tumours are located a greater distance from the vascular structures than pancreatic and bile duct tumours they are likely to cause vascular obstruction as a relatively delayed event compared to biliary obstruction. Results for the whole cohort however do not show an association between interval to surgery and resectability. It is probable that the small proportion of patients with ampullary cancer who progress to inoperability is masked in the larger group of patients with pancreatic and bile duct cancer, where IS is shown to have no effect on resectability and outcome.

In the event of inoperability usually a biopsy is taken and the presence of malignancy confirmed. Determining the organ of origin in this situation is difficult however, as this requires examination of the spatial relationship of periampullary lesions (23). Histological tissue stains have low specificity in determining precise tumour phenotype (25). Usually in this situation a diagnosis of adenocarcinoma is made and patients often referred for palliative treatment with chemotherapy targeted at pancreatic cancer. Our results provide indirect evidence that among this patient group there will also be patients with ampullary cancer, which has progressed to involve vascular structures.

A potential weakness of this study is the variable timing of the initial imaging. Often this was performed after the development of progressive jaundice, so there was an uninterrupted time line from presentation to surgery. In some patients however an initial presentation with spontaneously resolving biliary obstruction was investigated which revealed potential PC, but the issue was not taken forward due to clinical improvement. This presentation accounts for the very long IS in some patients. Although spontaneously resolving biliary obstruction has been reported previously in ampullary cancer (436), we have noted a similar phenomenon in pancreatic and bile duct cancer in this study. Another potential weakness is the lack of discrimination of ampullary tumours into intestinal or pancreatico-biliary phenotype. These two tumours have different anatomical and morphological characteristics, in addition to different prognosis. It is possible that the phenomenon we have observed occurs differentially in these two subsets. Distinguishing between these two phenotypes however does not form part of the Royal College of Pathologists' dataset (23).

Previous evidence has shown that delayed diagnosis and a prolonged interval to surgery have an adverse outcome in other tumour types including breast cancer (437), non-small cell lung cancer (438), and urological cancer (439). There is little data available however on what constitutes a safe interval to surgery after diagnosis. The 62 day interval

adopted as a target for treatment of most solid tumours in England was selected as a pragmatic figure without evidence of beneficial effect for each tumour type. Although there is evidence that late diagnosis has a negative effect on outcome in pancreatic cancer, as shown by the low resection rate (440), the study shows that following symptomatic presentation delay of up to two months prior to resection has no further effect on outcome in pancreatic and bile duct cancer. For ampullary cancer however a delay to surgery within the 62-day target period has a measurable effect, with some lesions progressing to inoperability, and improved outcome of the selected patients whose tumours remain resectable. This finding has significant implications for planning surgery in patients with PC, as the final histological tumour type is not known until surgery is completed, and early surgery for these patients is therefore preferable. Also these findings suggest that in some patients with inoperable PC the tumour may originate within the ampulla, rather than the pancreas. This may have implications for the selection of palliative chemotherapy in this patient group.

6.3 Systematic evaluation of radiological findings in the assessment of resectability of peri-ampullary cancer by CT using different contrast phase protocols

6.3.1 Abstract

Aims: To determine the relative significance of radiological signs in determining the resectability of peri-ampullary cancer (PC) and to assess the value of multi-phase imaging in detecting these findings.

Materials and Methods: Blinded, double re-reporting of pre-operative imaging from five hospitals was undertaken of 411 patients undergoing surgery for PC over an eight year period, of whom 119 patients were found to be inoperable at the time of surgery.

Results: The median tumour size was 26.7 mm and the proportion of patients reported to have regional lymphadenopathy (RL), venous (VI) and arterial involvement (AI) was 24.7%, 11.5% and 3.9% respectively and was similar regardless of the number of contrast phases undertaken. Significant associations were however noted between individual risk factors: VI was closely associated with tumour size ($p=0.002$) and AI ($p< 0.0001$). In multi-variable analysis AI, VI and RL were independently associated with resectability (relative risk of resection =0.05, 0.31 and 0.51 respectively). Tumour size however was not associated with resectability when VI was included in the multivariate model.

Conclusions: The use of multiple vascular contrast phases has no measureable impact on the rate of determination of tumour resectability of PC. In pre-operative staging AI is the most significant adverse finding for resectability. Large tumour diameter is not an adverse finding in isolation from other risk factors.

6.3.2 Introduction

Determination of tumour resectability is a major aspect of the interpretation of pre-operative imaging of peri-ampullary cancer (PC). The findings of distant metastases and local invasion resulting in occlusion of major arteries or veins are contraindications to attempted surgical resection, whereas lesser degrees of arterial involvement (AI) and venous involvement (VI), including abutment and tapering, are relative contraindications, as imaging can sometimes be inaccurate in determining these findings (441-444), and vein resection can be undertaken where incomplete venous occlusion is noted (445-447). Tumour size (448) and regional lymphadenopathy (RL) (332, 449) have also been shown to be associated with unresectability, although RL is a relative contraindication as these nodes are removed as part of a Whipple procedure (240). This finding may however be a surrogate marker of an aggressive malignancy, which will progress rapidly to become inoperable.

Despite pre-operative imaging to exclude patients with contraindications to surgery a proportion of patients with PC proceeding to operation are found to be inoperable, either due to unresectable invasion of vascular structures or the presence of metastatic disease. This may result from either understaging by CT or rapid tumour progression in the interval between imaging and surgery.

Pre-operative staging of PC is commonly undertaken by contrast-enhanced CT scan. Some authorities recommend tri-phasic imaging (324), including pre-contrast phase, arterial phase and portal phase; although the benefits of this over monophasic scans (portal venous phase only) and biphasic scans (arterial and portal phases) have not been demonstrated. This has implications in terms of radiation exposure and resource utilisation. There have also been major improvements in CT scan technology in recent years with the development of multi-detector imaging (450), which would be expected to

lead to a reduction in the proportion of false negative findings, and may have reduced the need for multi-phase imaging.

The principal study aim is to determine a hierarchy of radiological findings in predicting the resectability of PC in patients undergoing surgery at a regional centre within a Cancer Network serving five hospitals (A-E) and to investigate the cause of unresectability (local invasion or metastatic disease) associated with these findings. Secondary aims were to explore the effect of varied imaging protocols in the detection of these findings to determine potential advantages of multi-phase imaging in clinical practice.

6.3.3 Material and Methods

Details of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and January 2014 were collected in a prospective database. Patients were offered surgery following review of imaging at a specialist HPB MDT and all scans were performed on 64-slice multi-detector CT (MDCT). Relevant abdominal CT scans were retrieved from referring hospitals, anonymised and uploaded to a dedicated research hard-drive. Images were then re-reported independently by two radiologists with higher training in pancreatico-biliary imaging using standard criteria (451). The number of vascular contrast phases was recorded for each patient and the proportion of patients having mono, bi and tri-phasic imaging in each of the referring hospitals was determined, along with the association of the number of scan phases with the main radiological findings. Specific data fields were created to collect information relating to hospital of origin, the presence of a biliary stent inserted at ERCP, tumour size, regional nodal status (presence of lymph nodes >1cm in transverse diameter) and vascular involvement status. Radiological evidence of arterial and venous involvement (Figure 6-4 and 6-5) was defined according to published criteria (451).

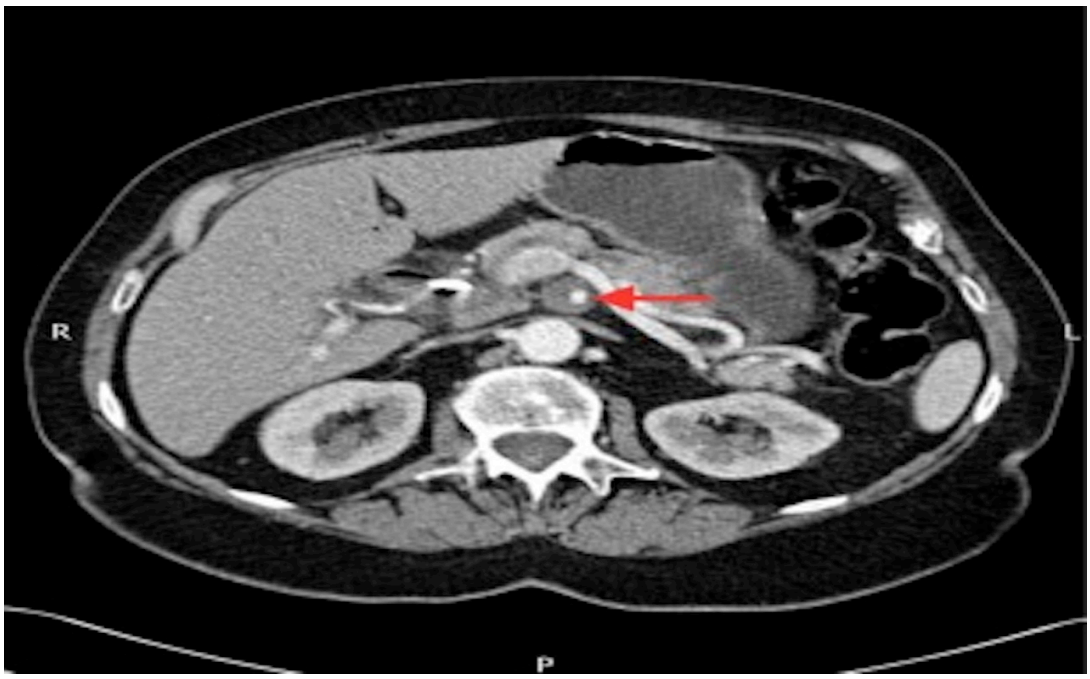


Figure 6-4 MDCT imaging demonstrating SMA involvement by PC (Arrow)

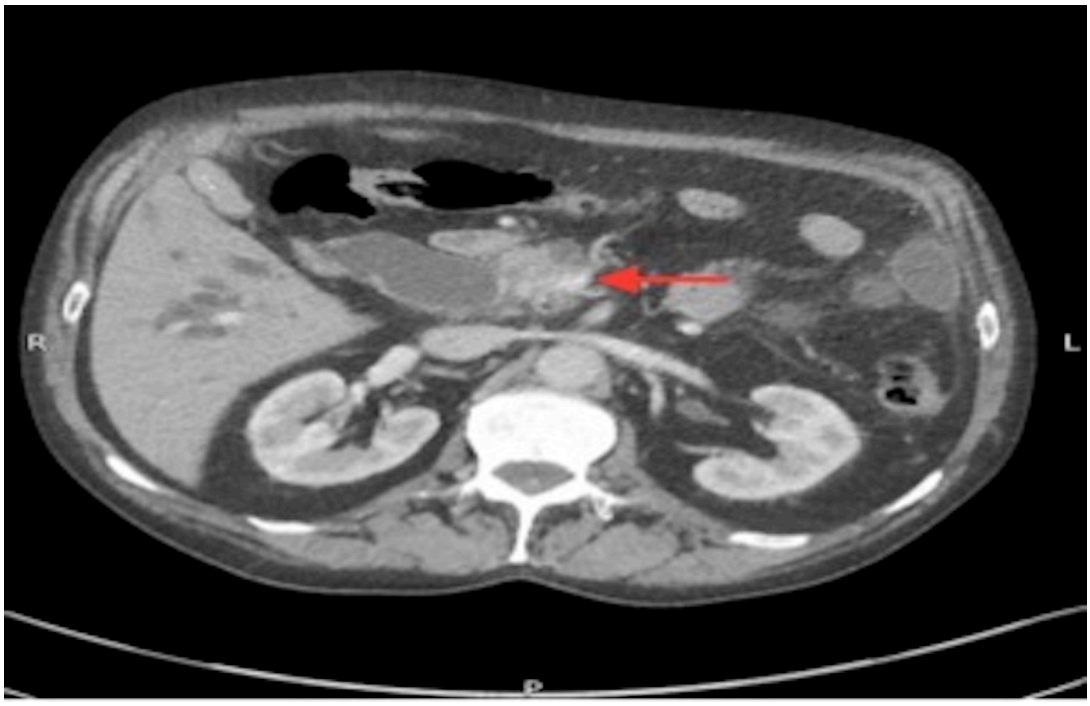


Figure 6-5 MDCT imaging demonstrating SMV involvement by PC (Arrow)

In the assessment of binary variables (e.g. nodal status) a positive outcome was recorded only when both radiologists agreed on the finding. For tumour size the mean of the two findings was taken.

At surgery initially a search for metastatic disease was undertaken before an attempt at dissection of the primary tumour. The tumour was considered to be unresectable due to local invasion when the operating surgeon was unable to resect the tumour after trial dissection without undertaking arterial resection or where there was occlusion or extensive invasion of the portal or superior mesenteric vein. Data retrieved from the database included the operative finding of either unexpected distant metastases or local invasion by tumour into vascular structures. The proportion of resectable tumours was recorded for consecutive quartiles (two year intervals) of the study period. To explore further the predictive value of radiological findings the operative outcome among patients where the tumours were found to be unresectable were categorised into the finding of metastatic disease or local invasion.

Discrete variables and interdependence of radiological findings were analysed by Chi-square test and continuous variables by Mann-Whitney. Estimates of the relative value of radiological parameters in the prediction of resectability of PC were determined by logistic regression analysis.

6.3.4 Results

Operative details and relevant pre-operative imaging were available in 409 patients (Figure 6-6), of median age 66.9 (28-86) years, of whom 55.8% were male. The median age (66.7 v 67.5 years), percentage of male patients (54.5% v 59.8%) and median interval between imaging and surgery (42 v 39 days, p=0.419) did not differ between patients proceeding to resection and those where the lesion was found to be unresectable.

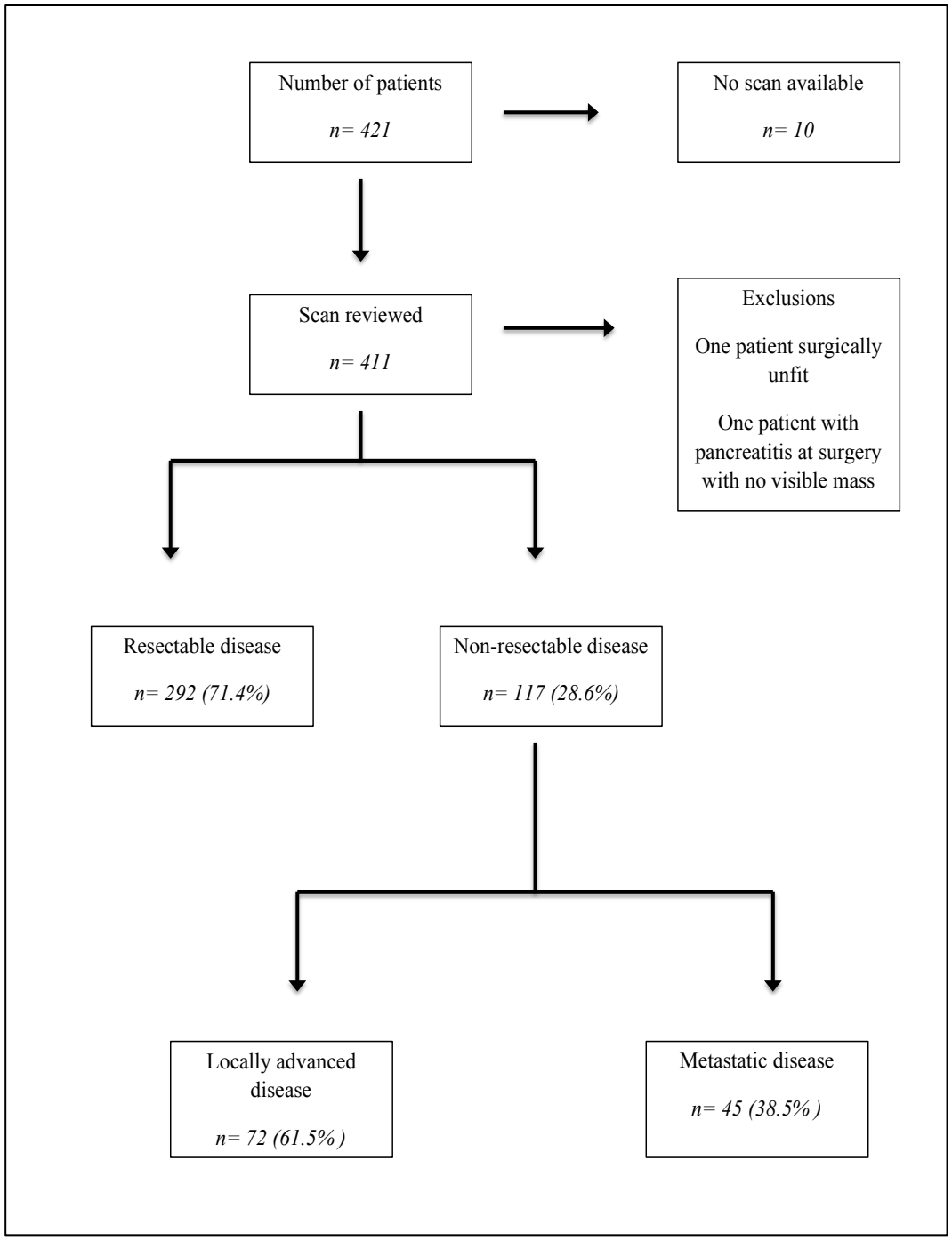


Figure 6-6 Flow chart of patients undergoing surgery for PC between January 2006 and January 2014

Analysis of images revealed a similar proportion of mono-, bi- and tri-phasic scans. There was variation in the number of vascular contrast phases undertaken in scans from different hospitals; however the rate of detection of the main radiological end-points did not differ according to the number of contrast phases undertaken (Table 6.8).

n = 409		Monophasic (134, 32.7%)	Biphasic (149, 36.4%)	Triphasic (126, 31%)	P
Hospital	A (119)	20 (16.8)	52 (43.7)	46 (38.6)	0.0001
	B (97)	45 (46.4)	50 (51.5)	2 (2.1)	
	C (78)	24 (30.7)	9 (11.5)	45 (57.7)	
	D (71)	24 (33.8)	21(29.5)	26 (36.6)	
	E (44)	21 (47.7)	17 (38.6)	6 (13.6)	
AI (16)		3 (2.4)	8 (5.4)	5 (4)	0.398
VI (47)		20 (15)	11 (7.4)	16 (12.7)	0.122
RL (101)		28 (21)	42 (28.2)	31 (24.6)	0.83
Tumour visible (250)		72 (53.7)	99 (66.4)	79 (62.7)	0.83
Median tumour size (range)		25.25 (11.5-70)	26.25 (10.5-58)	27.75 (8-64.5)	0.39
Resection completed (292)		102 (76.1)	107 (71.8)	83 (65.8)	0.187

Table 6.8 Radiological findings and surgical resection rate according to the number of CT scan phases for 409 patients undergoing attempted surgical resection for PC

In particular the proportion of patients noted to have AI did not differ between patients where only portal venous imaging was performed (3 of 134) and those where additional arterial phase imaging (bi- and tri-phasic scans) was also performed (13 of 275) (p=0.223). The primary tumour was visible in 250 patients (61.1%), with no difference in the rate of detection in patients having different contrast phase protocols

(Table 6.8). Similarly the median tumour size was 26.7 (8-70) mm and did not differ between patients having different scan phases (p= 0.39). Where a tumour was visible RL, VI and AI were noted in 101 (40.4%), 47 (18.8%) and 16 (6.4%) of patients respectively. Among the 159 patients where no primary tumour was visible, RL was noted in 40 (25%) patients. Tumour size was noted to be greater in patients with RL (28.5mm v 26mm), AI (30.7mm v 26.5mm) and VI (33mm v 25.5mm) than in those without these findings (p= 0.02, 0.03 and 0.0001 respectively). In evaluation of interdependence of pre-operative risk factors VI was noted to be strongly associated with AI (p=0.000). Of the 16 patients with AI, 8 (50%) also were noted to have VI. The finding of RL was not significantly associated with either AI (p=0.472) or VI (p=0.108).

Biliary stents had been inserted prior to CT scan in 73 (17.8%) patients. The proportion of patients with radiologically detectable RL did not differ between those who had (17/72, 23.6%) and those who had not (84/337, 25%) had a stent inserted prior to CT scan (p=0.814).

Surgical resection of the PC was completed in 292 patients (71.4%). Resection was completed more commonly among the 159 patients where no lesion was visible (126, 79%) than among the 250 patients where the tumour was visible (166, 66.4%) (p=0.005). Among the 155 patients with a visible tumour and no adverse risk factors (RL, AI or VI) on pre-operative imaging, the median tumour size did not differ between the 121 patients where the tumour was resectable (24.5 mm, IQR 20.5-30.42) and the 34 patients where the tumour was not resectable (26.7mm, IQR 20-28.5mm) (p=0.55).

Of the 17 patients with VI on pre-operative imaging where resection was completed, partial venous resection was necessary in three (17.6%) patients. Vein resection was also required in five of the 348 patients (1.4%) where VI was not noted pre-operatively.

The final pathological diagnosis of resected specimens is shown in (Table 6.9).

Tumour origin	N (%)	Median tumour size (range) mm	Histological lymph node involvement (%)
Pancreatic adenocarcinoma	132 (45.2)	30 (12-65)	122 (92.4)
Ampullary adenocarcinoma	66 (22.6)	25 (5-80)	37 (56)
Bile duct adenocarcinoma	47 (16.1)	25 (10-70)	25 (53.2)
Duodenal adenocarcinoma	7 (2.4)	40 (30-55)	4 (47)
Tubulo-villous adenoma	15 (5.1)	30 (24-55)	
Inflammatory disease	12 (4.1)		
Neuroendocrine tumour	6 (2)	18 (10-25)	3 (50)
Metastasis	4 (1.4)	35 (25-45)	
Gastro Intestinal Stromal cell tumour (GIST)	1 (0.03)		0 (0)
Others (Benign)	2 (0.6)		

Table 6.9 Histological outcome of 292 patients undergoing surgical resection for presumed periampullary cancer.

In univariate analysis the presence of a visible tumour, tumour size, RL, AI and VI on pre-operative imaging were all associated with unresectability of the tumour (Table 6.10). However in multivariate analysis the strongest association with tumour resectability was with the presence of AI (Table 6.10). Tumour size and VI were found to be mutually exclusive for significance in the multi-variate model.

Imaging characteristic	Tumour resectability		UVA	MVA		
	Yes (292)	No (117)	p	Exponent	95% CI of Exponent	P
Median tumour size (mm)(range)	25.5 (8-70)	28 (11.5-64.5)	0.01	0.46	(0.193-1.084)	0.076
RL (101) (%)	63 (21.6)	39 (32.8)	0.017	0.51	(0.272-0.949)	0.047
AI (16) (%)	2 (0.68)	14 (11.7)	0.000	0.05	(0.007-0.445)	0.007
VI (47) (%)	17 (5.82)	30 (25.2)	0.000	0.31	(0.152-0.638)	0.001

Table 6.10 Univariate and multivariate analysis of the association of the preoperative radiological risk factors and surgical resectability of PC in 409 patients

In the 117 patients where the tumour was not resected this was due to the finding of hepatic metastatic disease in 45 patients (37.8%) or local invasion of vascular structures in 72 patients (60.5%). The proportion of patients with unresectable disease was 16/67 (23.8%), 35/93 (37.6%), 32/119 (26.2%) and 34/130 (26.1%) (p=0.17) in consecutive time quartiles of the study. No difference was noted in the reasons for unresectability (local invasion or metastatic disease) among patients with different pre-operative radiological findings (Table 6.11).

n=117 Radiological finding	Local invasion (n= 72, 61.5%)	Metastatic disease (n=45, 38.5%)	Chi Sq	P
Tumour visible (84, 71.8%)	49 (58.3)	35 (41.6)	1.3	0.256
Median tumour size (mm) (range)	28.25 (11.5-64.5)	27.75 (16.5-55.5)	0.838	0.36
RL (38, 32.5%)	23 (60.5)	15 (39.5)	0.024	0.876
AI (16, 13.7%)	9 (56.2)	5 (31.25)	0.051	0.822
VI (30, 25.6%)	22 (73.3)	8 (26.6)	2.37	0.123
No adverse radiological findings (54, 46.1%)	32 (59.2)	22 (40.7)	0.22	0.639

Table 6.11 Reasons for non-resection (local invasion or metastatic disease) among 117 patients undergoing attempted surgical resection for periampullary cancer with different pre-operative radiological findings

6.3.5 Discussion

This study allows the determination of a hierarchy of relative contraindications to resection of peri-ampullary cancer, based on a systematic assessment of radiological findings. In multivariable analysis the likelihood of completing surgical resection was reduced by a factor of 0.05, 0.31 and 0.51 by a finding of AI, VI and RL respectively, compared to a patient with none of these findings. In the absence of these findings tumour size was not associated with resectability. The study also revealed significant interdependence of radiological signs, with VI closely associated with tumour size ($p<0.0001$) and with AI ($p=0.000$). The study demonstrated that the proportion of patients with unresectable disease at the time of surgery has not declined over the eight-year period of the study, and that the radiological findings are similar regardless of the number of scan phases undertaken. In addition pre-operative radiological findings were not able to

predict the reason the pancreatic tumour was not resectable at the time of surgery (metastatic disease or local progression).

Many studies have shown that AI and VI are risk factors for non-resection of pancreatic tumours (352, 403, 452). Most have focused on assessing the accuracy of MDCT in identifying these risk factors in comparison with operative findings or histology (329, 453, 454). This study has used a structured reporting protocol to assess the relative risk that pre-operative identification of these findings entails for individual patients in terms of tumour resectability. AI is shown to be the most significant adverse finding, with a relative risk of resection of 0.05 compared to a patient without this finding. This may be due to the hepatic and superior mesenteric arteries lying further from the duodenal ampulla than venous structures, denoting a greater degree of invasion. The observation that the radiological findings of AI and VI are associated with each other may also reflect the spatial relationship of these structures, with VI occurring first followed by AI.

The significance of radiological evidence of RL has been less well investigated previously. It is interesting to note that the presence of RL was not influenced by the insertion of biliary stents, so this finding should be attributed to a malignant, rather than inflammatory process. RL was also not associated with other signs of local tumour progression, and is only weakly associated with primary tumour size. The development of lymph node metastases in PC may therefore depend on different biological processes to primary tumour enlargement and local invasion. RL was however independently associated with tumour irresectability. This is probably due to this finding being a marker of a more aggressive malignancy. In a large proportion (69%) of patients with RL however the tumour remains resectable at surgery.

Our study confirms that although tumour size is associated with invasion of vascular structures, size alone does not lead to an increased risk of non-resection in the

absence of other adverse findings. This is significant as some centres have used tumour size alone as a factor in the decision to offer surgery for PC (448).

The observation that 20% of patients with no detectable tumour radiologically are found to be inoperable at the time of surgery is an interesting finding. This suggests that although the interval from imaging to surgery has only a small impact on resectability in large series(455) there may be a more aggressive subset where progression proceeds rapidly. Similarly among the 271 patients where no adverse radiological signs were identified 54 (19.9%) were still found to be inoperable at the time of surgery. Caution must be exercised therefore in the interpretation of radiological findings when counseling patients. In addition although vein resection was required in 17.6% of patients undergoing resection where VI was noted on pre-operative imaging it was also necessary in 1.4% of cases without VI on pre-operative imaging. These observations emphasize the limitations of pre-operative imaging in planning surgery for PC.

The weaknesses of this study mainly relate to the non-standardised imaging protocols undertaken in different centres, and its retrospective nature. This study however represents an analysis of the value of pre-operative imaging in routine clinical practice, rather than under trial conditions, and the results are therefore likely to be relevant to other centres undertaking this type of surgery. Of particular interest is the finding that the radiological findings and resection rate are similar regardless of the number of contrast phases. Although multi-phase pancreatic–protocol CT is considered the 'gold-standard' in assessing resectability of PC (324), our results indicate that the resectability rate is unaltered by the CT technique used. It is possible that with a larger study the use of arterial phase contrast may lead to greater sensitivity in the detection of AI. This however does not seem necessary in patients with small tumours and no evidence of VI, where the risk of AI is very low. Another limiting point is lack of best imaging technique, in terms of CT phases, to identify resectability.

The study is also limited by the number of radiologists undertaking re-reporting (two). The agreement between radiologists is being addressed separately and it is possible that the results have been biased by individual radiologists performance.

The analysis of surgical outcomes has revealed the most common cause for non-resection was invasion of vascular structures (60.5%), with metastatic disease a less common finding (37.8%). Patients noted to have AI or VI on pre-operative imaging had a similar likelihood of being inoperable due to metastatic disease or local invasion at the time of surgery, suggesting that these findings are markers of aggressive malignancy. CT has a high resolution for hepatic metastases, which has increased in recent years (456). Despite this the proportion of patients with unresectable disease has remained largely unchanged over the period of study. This finding suggests that disease progression between imaging and the time of surgery may be a more significant cause of inoperability than under-staging by CT. There may therefore be an irreducible number of patients with rapidly progressive disease who will be unresectable at the time of surgery, regardless of the quality of the imaging and reporting undertaken.

The strength of this study lies in its large size and in the assessment of imaging of heterogeneous techniques from different hospitals. Other studies have shown similar risk factors for non-resection (250, 457), and a similar rate of non-resection (250, 457) at the time of surgery, and there is little available evidence that this rate has declined with improved imaging. This may be due to alterations in the threshold for undertaking surgery in borderline cases and improvements in surgical technique. The study however reveals significant limitations in the ability of MDCT to predict the presence of surgically significant operative findings.

6.4 Estimation of the organ of origin of peri-ampullary malignancy by pre-operative CT scan

6.4.1 Abstract

Background: Tumours occurring within the pancreatic head commonly arise from the pancreas, duodenal ampulla, distal bile duct or duodenum. Because these lesions may cause biliary obstruction they often present with painless jaundice. They are difficult to distinguish on standard pre-operative imaging. Treatment of these lesions was previously surgical, therefore determination of organ of origin not important. Increasingly neo-adjuvant therapy is offered, which may need to be tailored to the organ of origin.

Aim: We wished to assess the ability of specialist reporting of pre-operative CT scans to determine the organ of origin of PC.

Methods: Blinded re-reporting of pre-operative imaging from five hospitals was undertaken of consecutive cohort of 411 patients undergoing surgery for PC between January 2006 and May 2014 were undertaken. A modified reporting template was designed featuring the radiological findings of interest for PC. Radiological identification of tumour site was determined by the presence of the main tumour bulk within the pancreatic head parenchyma. Radiologists made an estimate of the pathological organ of origin of the PC based on all the reported features. Cohen's Kappa statistic test was used to determine the inter-observer agreement between radiologists.

Results: Each pathological tumour type was noted to have distinct radiological features. Localisation of a visible tumour within the pancreatic parenchyma was seen most commonly in pancreatic cancer (92%) than other tumour types ($p<0.0001$). Local invasion into the duodenum was a characteristic feature seen in 79% of patients with ampullary tumours and isolated dilation of the bile duct without dilation of the pancreatic duct was

seen most commonly in patients with ampullary or bile duct cancer. In the assessment of tumour origin good agreement (kappa=0.6, 0.51-0.68) was noted between the consensus radiology opinion and the final histology result. Overall accuracy was greatest for ampullary cancer (88.1%) and lowest for pancreatic cancer (83.2%).

Conclusion: Radiological assessment of pre-operative imaging provides a high degree of accuracy in predicting the organ of origin of peri-ampullary cancer.

6.4.2 Introduction

With the introduction of standardised reporting of pancreaticoduodenectomy specimens (23) a larger number of patients have been diagnosed with tumours other than pancreatic cancer, than was the case previously (24). This is significant as trials of adjuvant chemotherapy are stratified and targeted at the specific tumour origin (245, 458). The development and popularisation of neoadjuvant chemotherapy for pancreatic cancer requires accurate pre-operative prediction of the organ of origin of PC, to allow directed therapy. We wished to assess the ability of focused re-reporting of pre-operative CT scans of patients undergoing Whipple's pancreaticoduodenectomy to predict the organ of origin of the resected tumour, by comparison with final pathology.

6.4.3 Methods

A consecutive series of patients undergoing Whipple's pancreaticoduodenectomy (PD) procedure for PC between January 2006 and May 2014 were examined. Preoperative CT images were retrieved from Insignia PACS (Picture Archiving and Communication System). All images were anonymised and kept on a secure encrypted hard drive. Relevant scans were re-reported by three radiologists with specialist training in pancreatico-biliary imaging.

A template of relevant radiological features was constructed based largely on the Radiology Reporting Template of the Society of Abdominal Radiology and the American Pancreatic Association (451) (Appendix B). Features which are either very rare or unlikely to be related to tumour aetiology (e.g. the presence of venous collaterals and thrombus within portal or mesenteric veins) were not included. The features were also simplified. Each feature was reported as a binary outcome, regardless of the degree to which it was noted (for example the degree of vascular invasion). Local invasion by tumour into duodenum, colon, stomach or adrenal gland was also noted. Features of biliary

morphology were recorded only in patients who had not undergone insertion of a biliary stent prior to undertaking CT. The shape of bile duct stricture (abrupt or tapering) was determined by 3D image reconstruction.

Surgery was undertaken by standard techniques, with excision of the pylorus in all patients. Histological examination of the resected specimen was undertaken according to Royal College of Pathologists guidelines (23) with axial slicing of the resection specimen. Determination of the organ of origin was undertaken by the reporting pathologist using a combination of tumour localisation and histological features, including cellular atypia in adjacent structures.

CT scans were performed in the initial referring hospital and imported for re-reporting. Scan protocols differed between each hospital, in particular in relation to the number of contrast phases undertaken. Scans were reported by radiologists blinded to the clinical details and the final histopathology results. Two radiologists recorded outcomes for the features noted in Appendix B. Each feature was recorded as present only if both radiologists agreed on the finding. Where there was agreement on the features these were then categorised according to the final pathological tumour origin. For continuous data (size) the mean of the two outcomes was recorded. The tumour site was determined by estimating the site of the main tumour bulk within the pancreatic head. Local invasion was noted where tumour was seen in the stomach, duodenum, or adrenal gland. The radiologists then made a prediction of the organ of origin of the peri-ampullary tumour. Where there was a discrepancy in this prediction a third PB radiologist gave a further independent opinion blinded to the previous reports, and the majority opinion (when achieved) was recorded. Where three differing opinions were made of the tumour origin the outcome ‘other’ was recorded.

Statistical analysis

Inter-observer agreement in recording categorical data was assessed by Cohen's Kappa statistic. This method is commonly used to evaluate concordance in radiology reporting. A value of 0 indicates agreement purely due to chance and 1 indicates perfect agreement. The spectrum of values is arbitrarily divided into five categories for descriptive purposes: 0-20 poor, 20-40 fair, 40-60 moderate, 60-80 good, and 80-100 very good agreements. Categorical outcome data were then compared by the chi-square method. Inter-observer agreement in assessing continuous data (tumour size) was assessed by Spearman's Correlation test and Mann-Whitney test. Analyses were performed using Analyse-It software.

6.4.4 Results

During the study period 411 patients underwent surgery for PC. The median age was 66 (27-86) years and there were 230 (56%) males. 334 patients (81.2%) presented initially with features of biliary obstruction, five with duodenal obstruction, six with upper GI bleeding and six tumours were detected as an incidental finding. Seventy-two (17.5%) patients underwent ERCP and stent insertion prior to CT scan. Re-reported pre-operative radiological features of the pancreatic head of the patients undergoing surgery along with Kappa estimates of radiologists' agreement are shown in (Table 6.12)

N=411		Y/Y	%	Y/N	%	N/N	%	Kappa (95% CI)
Tumour mass visible		254	62	105	25.5	52	12.6	0.35 (0.25-0.46)
Regional LN		102	24.8	133	32.4	176	42.8	0.35 (0.25-0.44)
Pancreatic calcification		13	3.2	35	8.5	363	88.3	0.3 (0.2-0.6)
CBD enhancement (in non-stented patients, n=339)		39	11.5	140	41.3	159	47	0.18 (0.08-0.2)
CBD wall thickening (n=339)		0	0	4	1.2	335	98.8	0
CBD stricture morphology (n=339)	Tapering	49	14.4	131	38.6	159	46.9	0.22 (0.05-0.23)
	Abrupt	120	35.4	141	41.6	78	23	0.17 (0.06-0.27

Duct Diameters					
	Median (Radiologist A)	Range	Median (Radiologist B)	Range	Correlation
Median PD diameter mm	6	1-75	5	1-20	0.538
Median CBD diameter mm	17	4-38	16	2-31	0.822

Table 6.12 Radiological pancreatic findings among 411 patients undergoing surgery for PC.

Agreement was reached on the presence of a visible tumour mass in 254 (62%) patients, in whom arterial phase imaging had been undertaken in 170 patients. In 10 cases there was no radiological agreement regarding the number of contrast phases undertaken. In the 79 patients where local invasion was noted by both radiologists this involved the

duodenum in 76 patients (96.2%). In two patients invasion of the stomach was noted (Table 6.13).

N=254		Concordant outcome	%	Kappa
Gross local-isation of tumour mass	Pancreas	184	44.7	0.66 (0.55-0.77)
	Bile duct	2	0.5	
	Ampulla	31	7.5	
	Duodenum	5	1.2	
	No agreement	32	12.6	
Arterial enhancement (assessable in 170 cases)		4	2.35	0.38 (0.036-0.73)
Venous enhancement (assessable in 244 cases)		4	1.63	0.33 (0-0.67)
Local invasion by tumour		79	31.1	0.165 (0.05-0.28)
Arterial invasion		13	5.1	0.60 (0.41-0.8)
Venous invasion		47	18.5	0.34 (0.22-0.47)

Table 6.13 Radiological features reported by two radiologists among 254 patients undergoing surgery for PC where tumour mass visible

In initial reporting of the images by two radiologists in determining the organ of origin of PC agreement was reached on 296 occasions (72%) (Kappa= 0.51, CI =0.44-57). Resection of the tumour mass was completed in 292 patients (71%) and a diagnosis of pancreatic, ampullary, bile duct or duodenal cancer noted in 252 patients (Figure 6.7). The radiological findings associated with these diagnoses are shown in Table 6.14

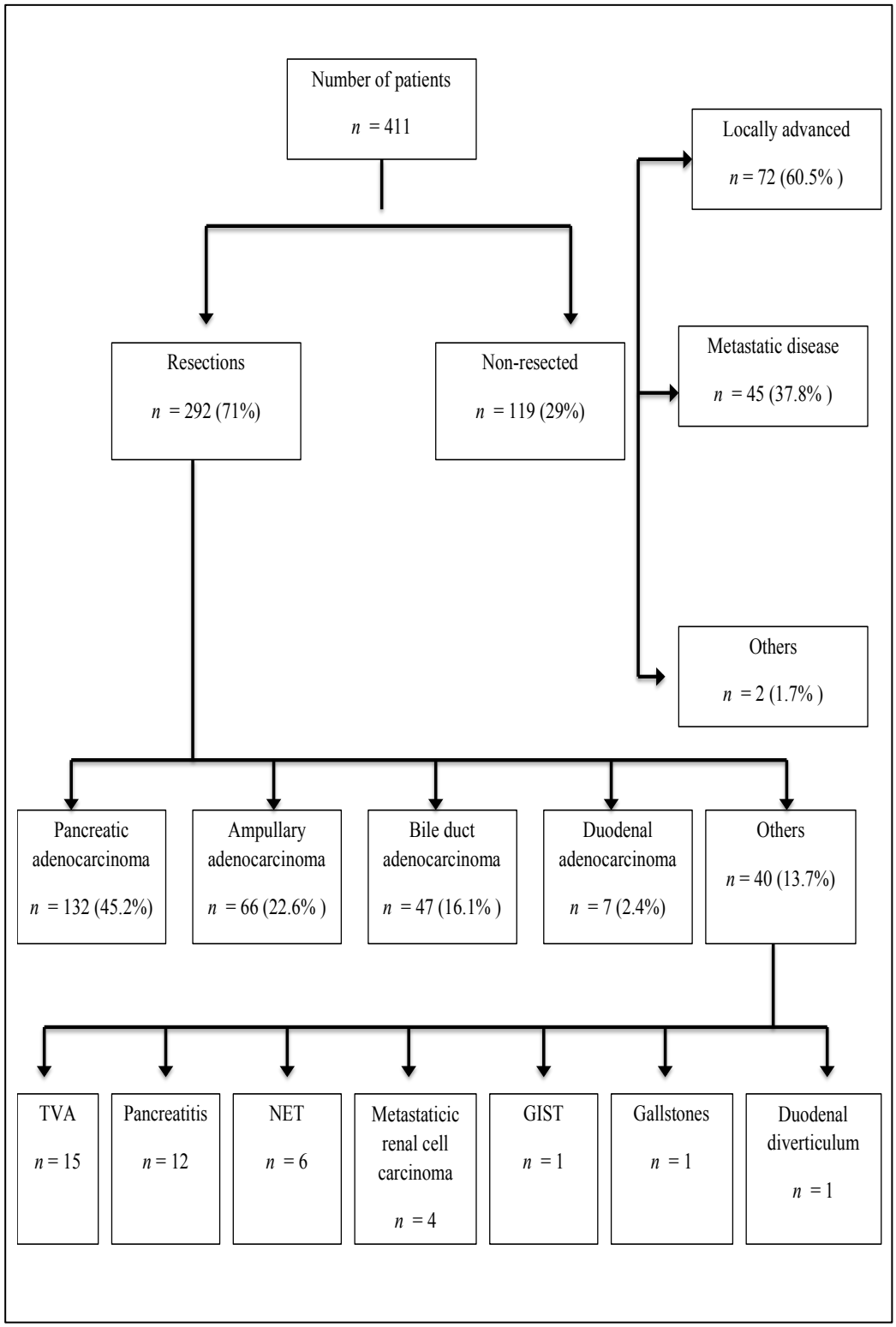


Figure 6-7 Flow chart of patients undergoing surgery for PC between January 2006 and May 2014 with pathological outcome

		Pathological tumour origin (For resected malignant tumours)					
		Pancreas (%)	Ampulla (%)	Bile duct (%)	Duodenum (%)	X^2	p
N= 252		132 (52.3)	66 (26.2)	47 (18.6)	7 (2.7)		
Tumour visible (143)		95 (71.9)	29 (43.9)	14 (29.8)	5 (71.4)	31.4	0.0001
Median tumour size (mm)		27(12-70)	22(12-58)	22(11-43)	40(14-54)		0.724
Gross localisation of visible tumour mass (143)	Pancreatic parenchyma (101)	87 (91.6)	2 (6.9)	10 (71.4)	2 (40)	113.5	<.0001
	Ampulla (18)	1 (1.0)	15 (51.7)	1 (2.12)	1 (20)		
	Bile duct (2)	0	0	2 (14.2)	0		
	Duodenum (3)	0	2 (6.9)	0	1 (20)		
	No agreement (19)	7 (7.4)	10 (34.5)	1 (7.1)	1 (20)		
Local invasion (48) (Stomach or Duodenum)		19 (20)	23 (79.3)	3 (21.4)	3 (60)	37.5	<.0001
Arterial invasion (2)		0	0	1 (7.1)	1 (20)		
Venous invasion (15)		12 (12.6)	1 (3.4)	1 (7.1)	1 (20)	2.6	0.45
Pancreatic calcification (5)		4 (4.2)	1 (3.4)	1 (7.1)	0	0.636	0.888
Regional lymphadenopathy (57)		32 (24.2)	15 (22.7)	9 (19.1)	1 (20)	0.800	0.849
Patients where bile duct characteristics assessable (no stent) (n=204)		113	51	33	7		
CBD enhancement (24)		11(9.7%)	5(9.8%)	8(24.2 %)	0/7 (0%)	6.52	0.089
CBD wall thickening		0	0	0	0	N/A	N/A

Tapering stricture (%)	20 (17.7)	7 (13.7)	2 (6)	1 (14.2)	4.638	.098
Abrupt stricture (%)	36 (31.8)	21 (41.1)	17 (51.5)	1 (14.2)		
CBD diameter (mm)	17 (4-27)	18 (7-25)	18 (10-30)	9 (6-18)	0.040	0.573
PD diameter mm (all)	6.8 (1.5-24)	5(2-15)	3.5 (1.5-11)	2(2-2.5)	0.347	0.000
PD diameter mm (non-stented)	7(1.5-24)	5.5 (2-15)	4.5 (2-11)	2(2-5.5)	0.312	0.000

Table 6.14 Radiological features among 252 patients undergoing pancreatic head resection for peri-ampullary malignancy categorised according to pathological tumour origin

Radiological prediction by two radiologists of the tumour origin among all patients is shown in table 6.15

N=411		Radiology 1				
	Tumour origin	Pancreas	Ampulla	Bile duct	Duodenum	Others
Radiology 2	Pancreas	205	13	12	4	2
	Ampulla	25	54	6	3	1
	Bile duct	18	15	29	0	4
	Duodenum	3	3	2	8	2
	Others	0	0	0	1	1

Table 6.15 Radiological prediction of the pathological tumour origin among 411 patients undergoing surgery for PC, Observed agreement 0.72, Kappa 0.51 (0.44-57)

Third reporting of the 115 disputed cases allowed a majority opinion to be reached in a further 104 cases. In the remaining eleven cases no agreement was reached.

A radiological prediction of the organ of origin of PC was therefore possible in 400 (97.3%) patients, and of these surgical resection was completed in 281, allowing correlation with histology. Among these patients 244 diagnoses of pancreatic (127), ampullary (65), bile duct (45) or duodenal cancer (7) were made by histological examination. In addition in 37 patients alternative diagnoses were made including tubulo-villous adenoma (15), pancreatitis (10), renal metastases (4), neuro-endocrine tumour (6), gastro-intestinal stromal tumour (1) and gallstones (1). Correlation of the radiological prediction of tumour origin with the findings on pathological examination after resection is shown in Table 6.16.

N=244	Consensus Radiological prediction (244)			
Final pathological diagnosis	Pancreas (140)	Ampulla (60)	Bile duct (37)	Duodenum (7)
Pancreas (127)	113	6	7	1
Ampulla (65)	6	48	8	3
Bile duct (45)	17	5	22	1
Duodenum (7)	4	1	0	2
PPV	0.81	0.8	0.59	0.28
NPV	0.86	0.91	0.89	0.98
Accuracy (%)	83.2	88.1	84.4	

Table 6.16 Correlation of radiological prediction of tumour origin based on independent reporting by three radiologists with pathological outcome in 244 patients undergoing resection for malignant tumours, Observed agreement =0.758, kappa=0.6 (0.51-0.68)

6.4.5 Discussion

The main findings of this study are that the radiological features within the pancreatic head in cases of suspected peri-ampullary malignancy used in the radiology reporting template vary widely in frequency depending on the organ of origin of the peri-ampullary tumour, and collective evaluation of these features allows an estimation of the organ of origin of the tumour in the majority of cases (97%). Radiologists' performance in reporting these individual features varied (kappa 0.2 -0.63), with a median kappa value of 0.35 (fair agreement). Better agreement in making an overall assessment of the tumour organ of origin (kappa =0.51) was noted, suggesting that information from many sources was used in determining this opinion. Where agreement or majority opinion was reached by radiologists a high degree of accuracy was noted in the prediction of all tumour types except duodenal cancer, with a good level of concordance noted between radiological and pathological opinions (agreement= 0.758, Kappa=0.6, CI=0.51-0.68). The PPV of radiological estimation was highest for pancreatic cancer (0.84) and lowest for duodenal cancer (0.4).

This surgical series has reported a similar distribution of cases of pancreatic (45%), ampullary (22%), bile duct (16%) and duodenal (7%) cancer as other studies (459, 460). The proportion of patients with benign disease is also similar to other work (461, 462). Distinguishing between these malignant tumour origins has not previously been a clinical or radiological priority, as the mainstay of treatment has been surgical resection, which is undertaken in a similar fashion regardless of the final diagnosis. Increasingly however neoadjuvant treatment is being used to downsize tumours (463, 464) and to improve post-operative survival (465-467), and this treatment may be better targeted at the specific tumour of origin. Gemcitabine and platinum-based neo-adjuvant chemotherapy has been used in cases of PC (468) as these treatments have been evaluated as adjuvant chemotherapy in the three main tumour types (466, 467) However differences

in agent effectiveness when used in the adjuvant and neo-adjuvant settings has been noted (469) and evaluation of novel neoadjuvant therapies stratified according to tumour origin may reveal differences in effectiveness..

In blinded re-reporting of CT images many radiological features were detectable in a significantly different proportion according to tumour type (Table 6.14). Three main themes were noted:

1) Tumour visibility ($p=0.0001$) and location within the parenchyma of the pancreatic head ($p<0.0001$) were strongly associated with pancreatic cancer. When visible however the tumour size did not differ between the three tumour types.
2) Radiological evidence of local invasion was most commonly seen into the duodenum, and was strongly associated with ampullary cancer ($p<0.0001$).
3) Dilation of the common bile duct without dilation of the pancreatic duct was a more common feature of bile duct and duodenal cancer (=<0.0001).

Other imaging characteristics of the individual tumour types were also noted. Despite commonly being reported as sclerosing tumours one-third of distal bile duct tumours were present as a visible mass, which was most commonly seen within the pancreatic parenchyma, rather than localised to the intra-pancreatic distal common bile duct. Although common bile duct enhancement and abrupt, rather than tapering bile duct strictures, have previously been associated with bile duct tumours (375, 470, 471), these observations did not reach significance in this study ($p=0.089$ and 0.102 respectively), and were also commonly noted in pancreatic and ampullary tumours. Venous invasion was noted rarely but was seen in ampullary (3.4%) and bile duct cancer (7.1%) as well as pancreatic cancer (13%). The highest degree of concordance noted was in the reporting of arterial invasion (0.63). Very few of these cases were however resectable at the time of surgery to allow correlation with histology so no comment can be made regarding

association with different tumour types. On six occasions (1.4%) tumour enhancement during a vascular contrast phase was noted (2 venous, 2 arterial and 2 in both phases). Two of these were shown to be bile duct tumours; one ampullary tumour, one renal metastasis and two were not resected. This feature has low value therefore in determining tumour origin, although it may have value in excluding a diagnosis of pancreatic cancer. Despite the fact that histological evidence of lymph node involvement is more common in pancreatic than either ampullary or bile duct cancer (472), radiological evidence of regional lymphadenopathy was seen broadly equally in all tumour types and concordance in reporting this finding was fair (kappa =0.35). CT scan is known to have low sensitivity in detecting metastases in normal sized lymph nodes (473, 474).

The association of the three main significant radiological features with pancreatic (475), ampullary (476) and bile duct cancer (470) have been reported previously. These associations however have been described largely within radiology teaching resources and large-scale correlation with pathological findings has not been undertaken. The strength of this study lies in a systematic evaluation of their frequency in a large series of cases of PC and a demonstration of their value in permitting a determination of the organ of origin of PC. No previous attempt has been made to quantify the accuracy of radiological estimation of the organ of origin of PC and our results demonstrate a high level of accuracy. Importantly there is a discriminating feature for each of the most common tumour types. Other investigations may be useful in differentiating rarer tumours. For example duodenal tumours often a have a characteristic clinical presentation and can be diagnosed by endoscopy, and neuroendocrine tumours can be diagnosed by serological tests. Similarly pancreatitis can present a diagnostic challenge when a pancreatic mass is noted, and in this series twelve patients were noted to have this diagnosis on final histology. The radiological features of these lesions have not been assessed in detail as other clinical and serological information contribute to the assessment of these patients.

A potential weakness of the study is the lack of quality control of radiological reporting. Although the concordance rate between radiologists in determining radiological features was not high, similar variation has been noted in describing findings in other tumour sites (477, 478). Comparison with reporting of PC from other centres would be very interesting. Only two radiologists were undertaking re-reporting of the CT scans, one of them used to be a member of the MDT meetings, which is another limitation of this study.

In summary although this study reveals a high degree of accuracy in determining tumour origin radiology cannot currently by itself provide the degree of accuracy required by oncologists in administering neo-adjuvant treatment, and chemotherapy is rarely administered based on radiological evidence alone without a tissue diagnosis (479). This area of study may become more important as the use of neo-adjuvant chemotherapy expands and refinements in imaging technology could focus on these areas to improve differentiation of tumour origin.

With improvements in imaging and reporting, along with information from other sources, in the future it should be possible to determine the organ of origin of PC pre-operatively with sufficient accuracy to guide pre-operative treatments. In clinical practice other findings can be taken into account. For example endoscopic assessment of the duodenum and ampulla are useful in defining the origin of tumours from these sites, and elevated serum tumour markers are more typically seen in pancreatic cancer (77, 480). A useful future study would be a prospective evaluation of the ability of multi-disciplinary teams to assess the organ of origin of PC by combining radiological with clinical and biochemical data. This may allow the elaboration of a scoring system that could be validated in different centres.

7 Conclusion

The provision of regionalised pancreatic cancer services into major centres does not adversely affect patient outcomes. In this research study, we noted although there is a significant variation in the patients' travel distance across the referring hospitals within the cancer network; however the individual patient's travelling distance to the regional centre did not adversely affect the outcomes.

There was no association between delay to surgery up to two months following the initial diagnosis and the outcome in patients with pancreatic or bile duct cancer, however we noted slight survival improvement in small cohort of patients with ampullary cancer.

While evaluating the role of CT scan in the preoperative assessment of tumour resectability in patients with PHM, we have noted that there is no additional benefit for the use of the arterial phase. Also, it was noted that the radiological tumour size has no effect on resectability in the absence of vascular involvement.

Using a focused proforma is a good adjunct in reporting CT scan with a good reliability predicting the site of tumour mass in patients with suspected PHM.

This project highlights important aspects in the preoperative pathway in patients with PHM as it supports the regionalisation of pancreatic cancer services as part of the British Government policy and we recommend using a standardised reporting template when reporting CT scan for suspecting PHM.

We recommend using a standard pancreatic protocol CT scan for all patients referred to the Peninsula HPB cancer centre. We also recommend using the proposed reporting template while interpreting the staging CT scans. For histological assessment of ampullary carcinoma, we recommend incorporation of the histological differentiation

(pancreaticobiliary vs. intestinal) into the final histological report, as this is an important factor to consider while assessing survival in this group of patients.

8 Appendix

8.1 Appendix A: The study flow chart

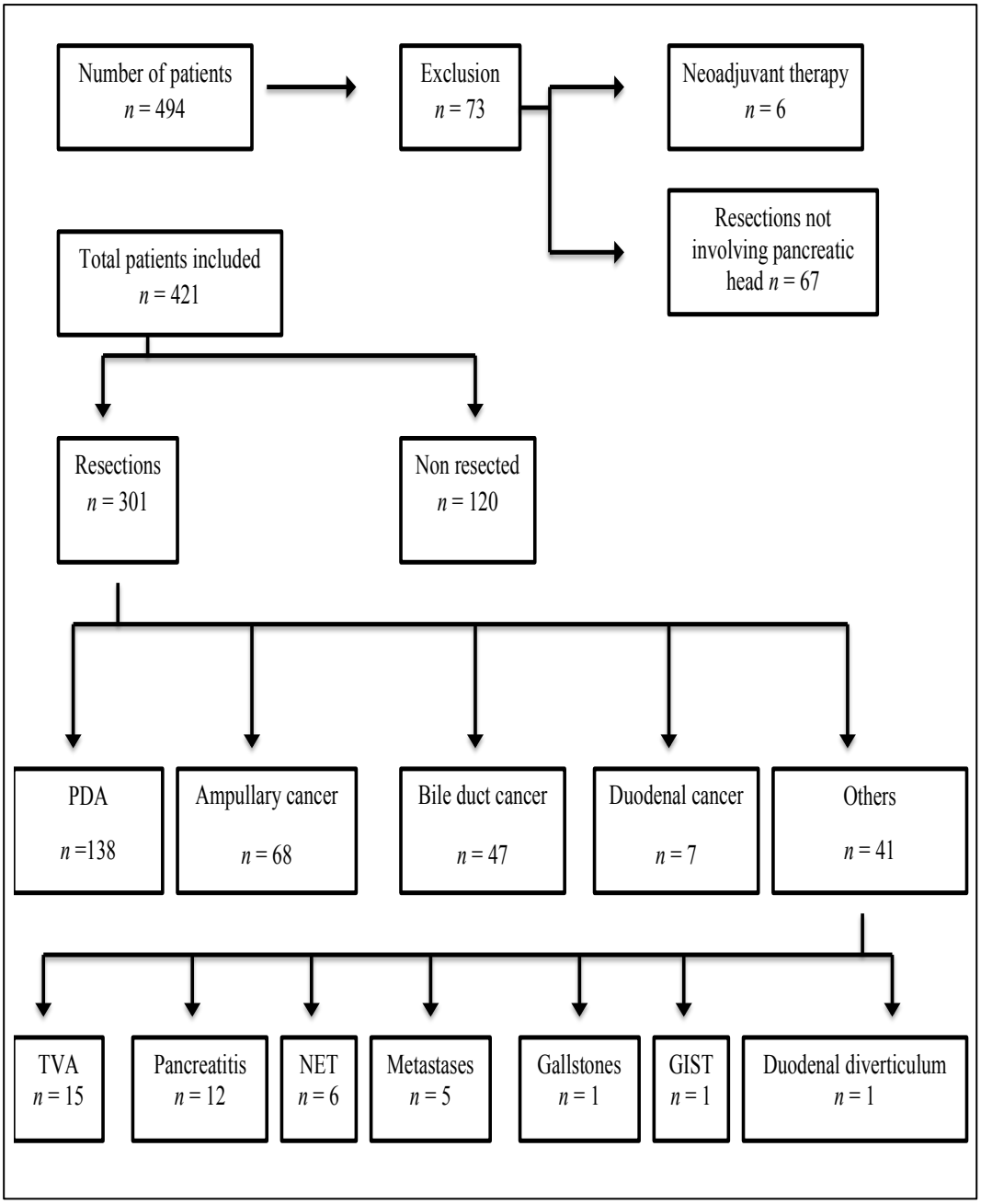


Figure 8-1 Flow chart showing details of patient population included in HPB database for use in this study. Different subsets of this population were used for each specific research question

8.2 Appendix B: Radiology reporting template

Type of scan	Monophasic	
	Biphasic	
	Triphasic	
Visible mass	Yes	
	No	
Site	Pancreas	Head
		Neck
		Uncinate
	Ampulla	
	Bile duct	
	Duodenum	
Tumour Size	(mm)	
Enhancement phase	Arterial	
	Venous	
	Arterial & Venous	
	None	
Enhancement type	Homogenous	
	Heterogeneous/ patchy	
	Rim/ peripheral	
Local invasion	Stomach	
	Duodenum	
	Transverse colon	
	Adrenal	
Pancreatic and Common bile duct diameter	(mm)	

Bile duct wall enhancement	Yes	
	No	
Bile duct wall changes	Tapering	
	Abrupt	
	Thickening	
	None	
Calcifications	Yes	Ductal
		Parenchymal
	No	
Lymph nodes Enlargement (I.e. > 10 mm in transverse axis)	Yes	Anterior
		Posterior
		Superior
		Inferior
	No	
Arterial vascular invasion (HA, SMA, Coeliac Trunk)	Grade 0	
	Grade 1	
	Grade 2	
Venous vascular invasion (PV, SMV)		

Table 8.1 Radiology reporting proforma

8.3 Appendix C: Recorded data included in the study

<table>
<tr><td colspan="4">Preoperative</td></tr>
<tr><td colspan="2">• Age</td><td>• Gender</td><td>Male
Female</td></tr>
<tr><td colspan="2">• Referring Hospital (A-E)</td><td>• ASA grade</td><td>1
2
3
4</td></tr>
<tr><td>• Jaundice at presentation</td><td>Yes
No</td><td>• DM</td><td>Yes
No</td></tr>
<tr><td>• Biliary stent</td><td>Yes
No</td><td colspan="2">• CT scan findings (see reporting template)</td></tr>
<tr><td colspan="2">• Travel distance to regional centre</td><td colspan="2">• Interval to surgery (Median and range)</td></tr>
<tr><td colspan="4">Operative</td></tr>
<tr><td>• Resectability</td><td>Yes
No</td><td>• Reason for non-resection</td><td>Local/vascular invasion
Metastatic disease</td></tr>
<tr><td colspan="4">Postoperative</td></tr>
<tr><td>• Histological tumour type</td><td>Pancreatic adenocarcinoma
Ampullary carcinoma
Bile Duct cancer
Duodenal cancer
Others</td><td>• Lymph node involvement</td><td>Yes
No</td></tr>
<tr><td>• Resection margin involvement</td><td>Yes
No</td><td colspan="2">• Survival time</td></tr>
</table>

Plymouth Hospitals NHS
NHS Trust

Post Op ERAS pathway
Whipple's (Pancreatico-Duodenectomy) Resection

Surname:
First Name:
Hospital Number:
NHS Number:
DOB:
Affix patient label here

Operation Date: **Surgeon:**

Type of Surgery:

Patient can be discharged once criteria met

DATE:										
	Day of Operation (Day 0)	**1st Day after Op (Day 1)**	**2nd Day after Op (Day 2)**	**3rd Day after OP (Day 3)**	**4th Day after OP (Day 4)**	**5th Day after OP (Day 5)**	**6th Day after OP (Day 6)**	**7th Day after OP (Day 7)**	**8th Day after OP (Day 8)**	**Discharge Criteria**
Monitoring	Hourly obs (minimum) Cardiac monitoring Oxygen via mask ☐	2-4 hourly obs (min) **STOP** oxygen and cardiac monitoring ☐	4-6 hourly obs (min) ☐	4-6 hourly obs (min) ☐	6 hourly obs (min) ☐	6 hourly obs (min) ☐	6 hourly obs (min) ☐	6 hourly obs (min) ☐	6 hourly obs (min) ☐	Obs stable ☐
DVT prophylaxis	TEDs Clexane at **6 hrs post-op** ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	TED Stockings Clexane ☐	**Home** with Clexane for **28 days.** ☐
Pain Control	Epidural IV paracetamol ☐	As per Day 0 ☐	As per Day 0 plus ☐	**REMOVE epidural** Oral analgesia ☐	Oral analgesia ☐	Oral analgesia ☐	Oral analgesia ☐	Oral analgesia ☐	Oral analgesia ☐	Pain controlled ☐
Ranitidine	IV - 50mg TDS ☐	IV - 50mg TDS ☐	IV - 50mg TDS ☐	Oral - 150mg BD ☐	Oral - 150mg BD ☐	Oral - 150mg BD ☐	Oral - 150mg BD - **FINAL DOSE DAY 6** ☐			
NG Tube	In place ☐		Spigot it if <500ml in 24 hrs ☐	**REMOVE if** <500 ml in 24 hrs & patient not vomiting ☐						
Abdominal Drain	In place x2 ☐	In place x2 ☐	In place x2 ☐	Check drain fluid for Amylase (DFA). * For pancreatic leak, DFA should be >3 x serum amylase **REMOVE** if **NO** bile/ enteric/pancreatic leak ☐						Patient ***can be*** discharged with drain if they have a pancreatic leak but are otherwise well ☐
Urinary Catheter	In place ☐	In place ☐	**REMOVE** unless contra-indicated ☐							
IV Fluids	In place ☐	In place ☐	If drinking well, **stop** ☐	**STOP** ☐						
Investigations	CXR in recovery/HDU FBC, LFTs, U&Es, clotting screen - APPT & PT ☐	FBC, LFTs, U&E, clotting screen - APPT & PT ☐		FBC, LFTs, U&E, clotting screen - APPT & PT, **Amylase (DFA)** ☐		FBC, LFTs, U&E ☐		FBC, LFTs, U&E ☐		All results acceptable levels ☐
Drinking & Eating	Sips of water ☐	Sips of water ☐	Free fluids ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Normal diet and free fluids CREON 40,000 with meals CREON 25,000 with snacks ☐	Eating and drinking Understands how to use CREON, TTA includes CREON ☐
Wound Care	None ☐	Check wounds, **only** change dressings **if** leaking ☐	If wound is dry, **REMOVE** dressing ☐							Wound satisfactory Wound care advice given ☐
Exercise	Keep head of bed raised to at least 30° Show & encourage deep breathing & leg exercises ☐	Keep bed head raised > 30° Assist pt to sit out and mobilise 2-4 times Encourage leg and breathing exercises ☐	Keep bed head raised > 30° Assist pt to sit out and mobilise 4 times Encourage leg and breathing exercises ☐	Keep bed raised to >30° Pt to sit out and mobilise 4 times Encourage leg and breathing exercises ☐	Keep bed head raised to >30° Mobilise fully ☐	Keep bed head raised to >30° Mobilise fully ☐	Keep bed head raised to >30° Mobilise fully ☐	Keep bed head raised to >30° Mobilise fully ☐	Keep bed head raised to >30° Mobilise fully ☐	Independently mobilising - to patient's norm ☐
Personal Care	Assist pt with personal care ☐	Assist pt with personal care ☐	Encourage pt to self care and dress in day clothes ☐	Encourage pt to self care and dress in day clothes ☐	Pt dressed in day clothes ☐	Pt dressed in day clothes ☐	Pt dressed in day clothes ☐	Pt dressed in day clothes ☐	Pt self caring - to patient's norm ☐	Independent - to patient's norm ☐
Additional Instructions										

Tick box to confirm tasks completed and record any variance from plan overleaf
To be filed in the Nursing Notes

Post- Operative HPB Pathway - record reason for variance from pathway

Goal	Reason for Variance	Action Taken	Date	Signature / Role

Anaesthetist to complete both pre and intra op sections

GOAL	Goal Achieved – Yes / No/ free text	If goal NOT achieved record reason for variance	Date & Signature
Pre-Operative HPB ERAS Pathway			
Attended Pre Op Assessment			
Patient given ERAS booklet			
Given CHO drink (NOT Diabetics)			
Patient likely to be complex discharge (Alice 3 / 3 +)			
Discharge plan in place			
Day of surgery admission			
Drank pre op CHO drinks (no, some, all) NOT Diabetics			
Pre Op HB > 11.0			
Pre Op HbA1C (only Pancreas)			
Appropriate bed booked (as per guidelines)			
Intra Operative HPB ERAS Pathway			
Warming mattress			
Fluid warmer			
Bair hugger			
NP temp probe			
Individualised fluid therapy			
Cardiac output monitoring			
Time per op antibiotics administered			
Abx within 60 mins KTS?			
Abx (state)			
BM <12 throughout			
DVT risk assmt completed			
In theatre DVT prophylaxis			
NG tube removed (Liver)			
PONV prophylaxis			
• Epidural (Open) • PCA + /- block (Lap) • PCA +/- spinal (Lap) • PCA +/- pleural (Lap Asst)			

Amr et al. BMC Surgery (2017) 17:23
DOI 10.1186/s12893-017-0220-3

BMC Surgery

RESEARCH ARTICLE Open Access

Variation in survival after surgery for peri-ampullary cancer in a regional cancer network

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Abstract

Background: Centralisation of specialist surgical services requires that patients are referred to a regional centre for surgery. This process may disadvantage patients who live far from the regional centre or are referred from other hospitals by making referral less likely and by delaying treatment, thereby allowing tumour progression. The aim of this study is to explore the outcome of surgery for peri-ampullary cancer (PC) with respect to referring hospital and travel distance for treatment within a network served by five hospitals.

Methods: Review of a unit database was undertaken of patients undergoing surgery for PC between January 2006 and May 2014.

Results: 394 patients were studied. Although both the median travel distance for patients from the five hospitals (10.8, 86, 78.8, 54.7 and 89.2 km) ($p < 0.05$), and the annual operation rate for PC (2.99, 3.29, 2.13, 3.32 and 3.07 per 100,000) ($p = 0.044$) were significantly different, no correlation was noted between patient travel distance and population operation rate at each hospital. No difference was noted between patients from each hospital in terms of resection completion rate or pathological stage of the resected tumours. The median survival after diagnosis for patients referred from different hospitals ranged from 1.2 to 1.7 years and regression analysis revealed that increased travel distance to the regional centre was associated with a small survival advantage.

Conclusion: Although variation in the provision and outcome of surgery for PC between regional hospitals is noted, this is not adversely affected by geographical isolation from the regional centre.

Trial registration: This study is part of post-graduate research degree project. The study is registered with ClinicalTrials.gov (unique identifier NCT02296736) November 18, 2014.

Keywords: Ampulla, Bile duct, Pancreatic, Cancer, Centralized hospital services

Background

Since publication of the Improving Outcomes Document in September 2000 [1] surgery for periampullary cancer (PC) in the UK has been centralised into designated regional Hepato-Pancreatico-Biliary (HPB) centres, each serving a population of approximately two million. This process requires that most hospitals do not undertake pancreatic resection, but perform the initial treatment and assessment of patients with potential PC, before referral to the regional tertiary centre. This separation of secondary from tertiary care in different hospitals has the potential to disadvantage patients referred from hospitals other than the regional centre, as the referral process is likely to be more complex than when secondary and tertiary care are provided on the same site. Inevitably provision of pancreatic surgical services in a single HPB centre within a large area will impose greater difficulty and inconvenience for some patients in travelling to the regional centre, which may adversely affect referral for treatment for patients with PC.

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Furthermore delays in treatment for patients residing further from the regional centre may allow tumour progression and have an adverse effect on outcomes.

The potential influence of referral between hospitals and geographical isolation on the outcome of surgery for PC has not been assessed and the aim of this study is to assess associations between referring hospital of origin and traveling distance to the regional HPB surgical centre with the population rate of surgery for PC, the interval to surgery, pathological outcome and long-term survival after diagnosis of PC within a cancer network.

Methods

The Peninsula HPB unit provides pancreatic surgical services to the Peninsula Cancer Network, which serves the largely rural UK counties of Devon and Cornwall, ranking the 7th and 12th least densely populated of 90 English local government areas [2]. The population of the two counties (1.67 million) is served by four hospitals providing secondary care only, and one hospital which provides secondary care and also hosts the regional tertiary HPB surgery centre. Surgery and immediate post-operative care are provided by the regional centre. All other treatment including stent insertion, adjuvant chemotherapy and long-term follow-up are provided by local hospitals. All hospitals are linked by a weekly audio-visual MDT with the regional centre. Referral and transfer of patients follows agreed protocols and is coordinated by nurse specialists.

Details of a consecutive series of patients having surgery at the Peninsula HPB unit between January 2006 and May 2014 were studied. Demographic, operative and pathology data were retrieved from the unit database. Included patients were those who underwent surgery for PC where final histology revealed a diagnosis of pancreatic, ampullary, distal bile duct or duodenal adenocarcinoma, or those where resection could not be completed and intra-operative biopsy confirmed the presence of adenocarcinoma. Patients receiving neo-adjuvant chemotherapy were excluded. The size of the catchment area served by each of the hospitals in the Peninsula was obtained from South West Public Health Observatory [3]. The travel distance by road for each patient was obtained from the AA mileage calculator (with permission) using post-code data [4]. The interval to surgery was calculated from the date of diagnosis of PC, which was taken as the date of the first cross-sectional abdominal imaging which suggested this diagnosis. The presence of biliary obstruction was defined as either clinically evident jaundice at the time of surgery or the requirement for pre-operative biliary drainage. Pre-operative diabetes was defined as the requirement for hypoglycaemic medication. The workload in the HPB surgical centre is shared non-selectively by four surgeons and is undertaken using standardised techniques, and in-patient care follows a standard protocol. The American Society of Anaesthesiologists (ASA) grade was determined at the time of surgery by the responsible anaesthetist. Resected specimens were analysed according to Royal College of Pathologists guidelines [5] and the TNM classification systems [6] was used to describe pathological stage. Survival data were obtained from hospital and general practice records and included all deaths occurring after surgery, including in-hospital mortality. Survival times were calculated to include the interval prior to surgery and therefore were taken from the date of the first cross-sectional image which raised the suspicion of PC. Survival data for the whole group of patients referred from each hospital is given as single outcome of interest and is reported as median and range. Follow-up was completed 1st May 2015.

Differences in demographics, operation rates, travel distance, interval to surgery and pathology outcome were compared between hospitals (pathology results for patients with duodenal cancer were not included due to low numbers). Difference in discrete variables was assessed by Pearson Chi square test and continuous variables by Kruskal-Wallis test. Correlation was assessed by Spearman correlation coefficient. To explore potential associations with patient survival a Cox regression analysis of pre-operative factors including age, gender, ASA grade, travel distance and the presence of biliary obstruction at presentation was undertaken. In addition, patient survival across five hospitals was compared using Kaplan–Meier survival curves and between hospital pairs by Cox regression analysis.

Results

During the study period 394 patients fulfilling the study criteria underwent surgery to attempt resection of PC at the regional HPB surgery centre (hospital A) (Fig. 1). The median age (66.7 years, range 39.4- 86.4) and gender mix (56.3% male) of the whole group did not vary between patients referred from hospital A, or from hospitals providing secondary care only (hospital B to E) (Table 1). The number of operations for PC undertaken as a proportion of the local population however varied significantly between referring hospitals (Table 1). The median distance patients were required to travel for care was 61.4 km and was significantly less for patients referred from within the catchment area of the regional HPB surgery centre to that for patients referred from all other hospitals in the Peninsula. No correlation was noted between the median travel distance to the regional centre of patients from the referring hospitals and the operation rate at that hospital ($p = .855$). The second lowest population operation rate was noted from the

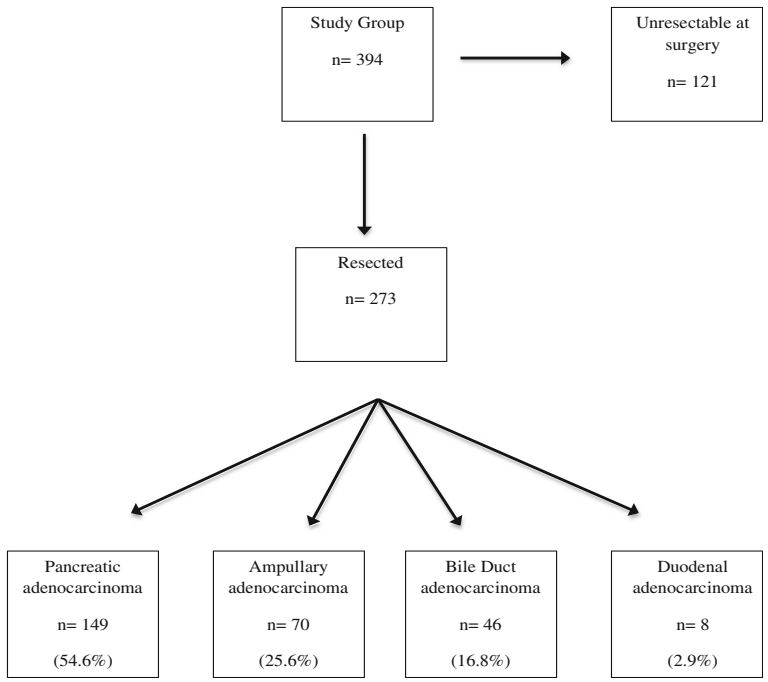


Fig. 1 Patients undergoing surgery for PC at Peninsula HPB Centre between January 2006 and May 2014

population receiving secondary care from the hospital hosting the regional HPB centre.

The distribution of ASA grades, the proportion of patients with diabetes, biliary obstruction at the time of surgery and pre-operative biliary intervention did not differ between hospitals (Table 1). The median interval from first investigation suggesting a diagnosis of PC to surgery was 49 days (interquartile range 34–69 days) and was similar between referring hospitals. Correlation analysis revealed no association between the travel

Table 1 Details of 394 patients undergoing surgery for peri-ampullary cancer between January 2006 and May 2014, displayed by referring hospital of origin. Hospital A hosts the regional HPB cancer centre

Referring hospital		(A)	(B)	(C)	(D)	(E)	*P*
n = 394 (%)		111 (28.2)	97 (24.6)	70 (17.8)	74 (18.8)	42 (10.6)	
Population served		464,437	368,313	410,213	278,555	171,227	
Annual operation rate for PC per 100000		2.99	3.29	2.13	3.32	3.07	0.044
Median Travel Distance (kilometres) (range)		10.8 (2.4–112)	85.9 (45.2–155.8)	78.8 (10.1–130.3)	54.7 (2.4–96.2)	98.3 (63–138.6)	.000
Median age (range)		65.7 (41.2–82.0)	68.4 (41.7–84.0)	65.5 (39.4–78.6)	65.6 (45.9–86.4)	70.2 (50.7–84.4)	.105
Gender (% Male)		53.2	58.8	58.6	58.1	52.4	.880
ASA Grade (%)	1	8 (7.2)	8 (8.2)	8 (11.4)	7 (9.5)	0	.416
	2	56 (50.5)	53 (54.6)	39 (55.7)	41 (55.4)	22 (52.4)	
	3	28 (25.2)	26 (26.8)	18 (25.7)	18 (24.3)	14 (33.3)	
	4	2 (1.8)	1 (1)	0	0	0	
	Missing	17 (15.3)	9 (9.3)	5 (7.1)	8 (10.8)	6 (14.3)	
Diabetes	Yes (%)	13 (11.7)	10 (10.3)	7 (10.0)	6 (8.1)	5 (11.9)	.987
	Missing data	12 (10.8)	17 (17.5)	14 (20.0)	15 (20.3)	4 (9.5)	
Jaundice at Presentation (%)		91 (82.0)	82 (84.5)	56 (80)	65 (87.8)	36 (85.7)	.641
Median interval to surgery (days) (range)		47 (5–551)	52 (1–459)	56.5 (16–379)	47 (16–246)	51.5 (6–477)	.108
Resection completed (%)		73 (65.7)	68 (70)	51 (72.8)	51 (68.9)	30 (71.4)	.880
30-day mortality (%)		4 (3.6)	1 (1)	2 (2.8)	1 (1.3)	2 (4.7)	.610

distance to the regional HPB surgery centre and the interval to surgery ($p = .15$). In-patient 30-day mortality occurred in 10 (2.5%) patients and did not differ between hospitals.

Tumour resection was completed in 273 patients (69.3%) and the completion rate did not differ between hospitals (Table 2). In 121 patients the tumour was inoperable at the time of surgery either due to the presence of vascular invasion (70) or distant metastases (47). In four patients the reason for irresectability was not recorded. Histological diagnoses of the resected specimens are shown in Fig. 1. Analysis of pathological outcomes revealed no difference between patients from the referral zone of the regional centre and those from other hospitals in the region, in terms of resection completion rate, tumour size, nodal status and resection margin status (Table 2). Similarly the distribution of the main diagnoses of PC did not differ between patients from the regional centre and those from other hospitals.

After a median follow-up of 4.5 years (1.3–9.5 years) the median survival (range) of the study group was 1.45 (0.11 – 9.4) years and was similar in males (1.44, 0.13–9.3 years) and females (1.45, 0.11–8.7 years). Two patients were lost to follow-up. Survival was greater in patients where resection was completed (1.85, 0.14–9.4 years) than in those where the tumour could not be removed (0.9, 0.11–2.8 years). The median survival of patients travelling more than the median distance for treatment was 1.5 (0.14–8.7) years compared to 1.4 (0.11–9.4) years for those travelling less than the median travel distance ($p = 0.234$). Cox regression analysis of the association of pre-operative variables including individual patient travel distance however revealed a significant survival advantage associated with increased travel distance to the regional HPB centre (Table 3).

Table 3 Cox regression analysis of potential association of pre-operative factors including travel distance to regional HPB centre with survival after diagnosis for 394 patients undergoing surgery for periampullary cancer

		Hazard Ratio	Lower .95	Upper .95	*P*-value
Gender		0.956	0.744	1.229	0.728
Age		1.009	0.995	1.022	0.217
Distance (km)		0.996	0.993	0.999	0.029
Jaundice		0.967	0.686	1.364	0.852
ASA	1 vs 2	0.945	0.678	1.317	0.739
	2 vs 3 & 4	1.117	0.888	1.407	0.344

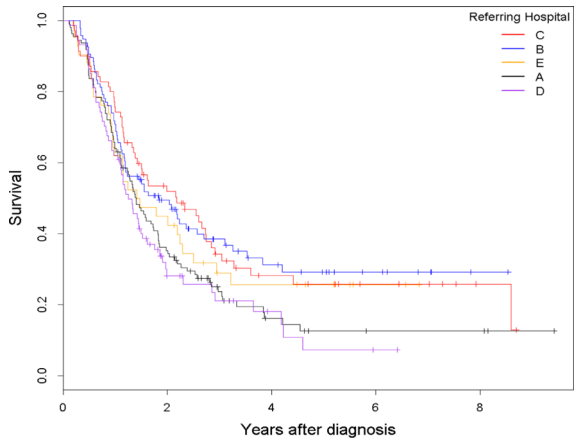
Further survival analysis revealed that the referring hospital of origin was associated with outcome (Fig. 2), with median survival ranging from 1.2 (0.14–6.4) years (patients from hospital D) to 1.5 (0.3–8.8) years (patients from hospital B). Pair by pair regression analysis comparing patients from the catchment area of the regional HPB centre revealed no difference in survival from diagnosis for patients from three hospitals C, D and E, but confirmed the significantly decreased hazard ratio of death of patients referred from hospital B (Table 4).

Discussion

The main findings of this study are: 1) within the Peninsula Cancer Network the population operation rate for PC varies significantly between hospital catchment areas but this variation is not related to travel distance to the regional HPB surgical centre and 2) individual patient travel distance to the regional centre does not adversely affect the time to surgery, pathological outcome or survival in patients with PC and 3) the provision of secondary and tertiary care in different hospitals does not adversely affect patient outcomes.

Table 2 Histopathological stage for 265 patients undergoing resection of pancreatic, ampullary and distal bile duct cancer at the regional HPB centre (A) displayed by referring hospital of origin

N = 265	A 111	B 97	C 70	D 74	E 42	*P*
Pancreatic cancer (*n* = 149)	40	38	22	28	21	
T size (mm) (range)	30 (15–48)	31.50 (16–60)	30.5 (15–70)	32.5 (12–50)	30 (18–65)	.620
N1disease (%)	35 (87.5)	33 (86.8)	19 (86.4)	23 (82.1)	17 (81)	.940
R1 resection (%)	34 (85)	24 (63.1)	18 (81.8)	24 (85.7)	19 (90.5)	.052
Ampullary cancer (*n* = 70)	21	18	12	13	6	
T size (mm) (range)	25 (12–80)	22.5 (5–65)	23.5 (15–60)	22 (11–65)	28 (8–50)	.933
N1disease (%)	14 (66.6)	10 (55.5)	6 (50)	5 (38.5)	4 (66.6)	.551
R1 resection (%)	7 (33.3)	1 (5.5)	2 (16.6)	2 (15.4)	2 (33.3)	.230
Bile duct cancer (*n* = 46)	10	10	13	10	3	
T size (mm) (range)	25.5 (10–70)	27 (10–45)	25 (10–40)	20 (12–50)	15 (12–20)	.216
N1disease (%)	7 (70)	7 (70)	4 (30.7)	7 (70)	1 (33.3)	.172
R1 resection (%)	5 (50)	6 (60)	5 (38.5)	5 (50)	2 (66.6)	.839



Number at risk hospital/years	0	2	4	6	8
A	111	37	9	7	4
B	97	38	18	7	2
C	70	30	13	7	2
D	74	17	4	1	0
E	42	18	6	1	0

Fig. 2 Survival from diagnosis of 394 patients undergoing surgery for periampullary cancer at Peninsula HPB surgery centre between January 2006 and May 2014, according to hospital of referral ($p = 0.032$)

Centralisation of pancreatic surgical services has led to improved outcomes including higher resection rates [7, 8], lower operative mortality [9, 10] and improved long-term survival [11]. Similar improvements with centralisation have been noted for liver [12], oesophageal [13], complex urological [14] and vascular surgery [15]. Despite these findings the population benefits of regionalisation are more difficult to demonstrate. Although studies using hospital data have demonstrated improved outcomes associated with centralisation of surgical services for patients who receive treatment [8, 16, 17], these studies may be biased by selection of patients at the regional centres and do not take into account patients who are not referred for treatment. Studies demonstrating improved population outcomes as a result of regionalisation of complex surgery are more difficult to undertake. The potential disadvantages of centralisation of services include a more complex referral pathway when secondary and tertiary care are provided in different hospitals, and an increased burden of travel for patients living further from the centre, which may discourage referral and attendance for treatment. These consequences of centralisation have been noted [18, 19] and the potential risk is greatest in areas of dispersed population. This has led to controversy over the implementation of centralisation of surgical services in rural communities [20], where the risk of limitation of access due to distance may outweigh the benefit of improved technical outcomes. The observation that operation rates are not adversely affected by distance to the HPB surgical centre, or by referral from a different hospital, and that travel distance itself does not influence the outcome of surgery for PC are important, as they show that regionalisation of surgical services does not necessarily lead to limitations in access or increased patient selection at the HPB surgical centre.

Table 4 Paired regression analysis of association of hospital of referral (B to E) with survival compared to referral from Hospital A among 394 patients undergoing surgery for peri-ampullary cancer

A vs	Hazard Ratio	Lower .95	Upper .95	*P*-value
B	0.6934	0.5011	0.9594	**0.0271**
C	0.7042	0.4952	1.0013	0.0508
D	1.1121	0.7983	1.5493	0.5299
E	0.8228	0.5435	1.2456	0.3565

The data bolded shows a significant findings

The small variation in operation rate noted between hospitals may reflect differences in levels of comorbidity and suitability for surgery, but may be due to different referral practices within each hospital. The observation that the referring hospital of origin is also associated with long-term survival after surgery for PC is therefore an interesting new finding. Many factors contribute to variation in local survival rates and levels of comorbidity are likely to play a major role. It is interesting to note however that long-term survival is lowest in patients from the hospital with the highest population rate of surgery for PC. This may result from referral of more marginal cases, which is not revealed by the measures of comorbidity and tumour burden used in this study. Variation in population operation rate for PC may also explain some of the variation noted in outcome between high-volume hospitals undertaking pancreatic surgery [21].

The strength of this analysis lies in the accurate collection of individual travel distance to the regional HPB surgery centre in a large consecutive series, and its correlation with prospectively audited outcomes. In this study a single measure of survival of all patients has been used, without division by diagnosis, to allow simple comparison between hospitals. This figure includes deaths due to surgical complications, which accounts for the short survival in some patients. A weakness of the study lies in the characterisation of comorbidity. A more discriminating scoring system is required to investigate the potential association of comorbidity with variations in population operation rate for PC. The relatively long median interval to surgery noted in this study, even for patients with biliary obstruction (47 days), is accounted for by the increasing complexity in the patient pre-operative pathway. This pathway however imposes a similar interval to surgery on patients regardless of geographical isolation from the regional centre. In a small number of patients a long interval to surgery was due

to investigations being undertaken in patients with self-resolving jaundice, which was not pursued due to patient improvement.

Conclusion

This study confirms that centralisation of HPB surgical services can be implemented without imposing disadvantage in surgical outcomes on patients due to travel distance to the HPB surgical centre or referral between hospitals for treatment.

Acknowledgements
Not applicable.
The abstract won a Best Poster award at the First World Pancreatic Forum, Bern, Switzerland 18–19 June 2015.

Funding
None.

Availability of data and material
The datasets analysed during the current study is part of MD thesis and available from the corresponding author on reasonable request.

Authors' contributions
Study concepts: BA, DS. Study design: BA, DS. Data acquisition: BA, SA, MB, CB, DS. Quality control of data and algorithms: BA, SA, MB, CB, DS. Data analysis and interpretation: BA, GS, DS. Statistical analysis: BA, GS, DS. Manuscript preparation: BA, GS, DS. Manuscript editing: BA,GS, SA, MB, CB, DS. Manuscript review: BA,GS, SA, MB, CB, DS. All authors have read and approved the final manuscript.

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

Consent for publication
No patient consent was required for this study because patient data were collected in the course of normal hospital care and were anonymised for research purposes.

Ethics approval and consent to participate
Ethical approval for the study was obtained from the South West Health Research Authority Research Ethics Committees.

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Received: 20 September 2016 Accepted: 1 March 2017
Published online: 07 March 2017

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http://dx.doi.org/10.1016/j.hpb.2015.10.013 HPB

ORIGINAL ARTICLE

Assessment of the effect of interval from presentation to surgery on outcome in patients with peri-ampullary malignancy

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Abstract

Background: Delay between diagnosis of peri-ampullary cancer (PC) and surgery may allow tumour progression and affect outcome. The aim of this study was to explore associations of interval to surgery (IS) with pathological outcomes and survival in patients with PC.

Method: A database review of all patients undergoing surgery between 2006 and 2014 was undertaken. IS was measured from diagnosis by imaging. Potential association between IS and survival was measured using Cox regression analysis, and between IS and pathological outcome with multivariate logistic analysis.

Results: 388 patients underwent surgery. The median IS was 49 days (1–551 days), and was not associated with any of the evaluated outcomes in patients with pancreatic (149) or distal bile duct (46) cancer. For patients with ampullary cancer (71) longer IS was associated with improved survival, with median survival of 27.5 months for patients waiting $\leq$ median IS (35) and 38.3 months for patients waiting > median IS (36) for surgery ($p = 0.041$). A higher rate of margin positivity (31.4%) was also noted among patients who waited less than the median IS compared to those waiting longer than this interval (11.4%) ($p = 0.032$).

Conclusion: For patients with ampullary cancer there is a paradoxical improvement in outcome among those with a longer IS, which may be explained by progression to inoperability of more aggressive lesions.

Received 26 October 2015; accepted 28 October 2015

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Introduction

Peri-ampullary cancer (PC) most commonly originates within the pancreas, the distal common bile duct, or the duodenal ampulla. The organ of origin of PC is usually determined by pathological examination after resection and has important implications for prognosis. Five-year survival after surgical resection varies from 6.5%–20% for pancreatic cancer,[1–7] 19.2%–30% for bile duct cancer[1,3,5,6,8,9] and 33%–45% for ampullary cancer.[1,3,5,6] For many patients their disease is inoperable at the time of presentation due to local invasion or the presence of distant metastases. For those with operable tumours there will usually be an interval between radiological diagnosis and surgery, to allow referral, assessment and operative planning. In England, the National Cancer Plan stipulates a maximum interval of 62 days from primary referral to treatment for most solid cancers,[10] although this figure is not based on evidence of safety for each tumour type. Tumour progression may take place during this interval, rendering tumours inoperable and long-term survival may potentially be affected.

Within any patient cohort there is likely to be a range of intervals between diagnosis and surgery, with some patients

The abstract was presented at the World Pancreatic Forum, Bern, Switzerland 18–19 June 2015.

undergoing surgery very quickly, and some waiting many months. As PC is an aggressive malignancy, this period may constitute a significant part of the natural history of the disease. Analysis of the potential association of interval to surgery with pathological and surgical outcomes may reveal aspects of the behaviour of these tumours, and determine if the 62 day target to surgery disadvantages patients by allowing tumour progression.

This study aimed to investigate the interval to surgery in a consecutive series of patients undergoing surgery with the intention to resect PC and to explore the association of IS to resectability, tumour stage and overall survival.

Material and methods

Review of a prospectively maintained database of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and May 2014 was undertaken. Referrals came from five hospitals in a cancer network with a population of 1.7 million. The study cohort included patients with a histological diagnosis of pancreatic, bile duct or ampullary cancer, or those where the tumour was unresectable and biopsy confirmed the presence of adenocarcinoma. Patients receiving neoadjuvant chemotherapy were excluded. No patients were excluded from surgery due to disease progression in the interval between referral and surgery. Demographic and clinical data were retrieved. Pre-operative biliary obstruction was defined as any abnormality in liver function tests sufficient to prompt investigation by cross sectional imaging. As the time of receipt of the initial referral is variable and subject to administrative delays, the interval to surgery (IS) was measured from the date of the first imaging modality undertaken which raised the possible diagnosis of PC to the time of the surgical intervention, by review of individual radiology records. Surgical resection was performed by a classic Whipple resection with reconstruction by pancreaticogastrostomy. Pathological reporting was undertaken according to Royal College of Pathologists guidelines[11] with axial slicing of the resection specimen. Tumours were classified according to histological origin (pancreatic, bile duct or ampullary) and nodal status and margin involvement status were retrieved from histology reports.

Continuous variables were compared with Kruskal–Wallis test and categorical variables by Chi square test. The mean and variance of tumour size across different tumour types were compared using Bayesian double generalised linear models.

Dates of death were determined by access to General Practice records and survival times calculated from the time of diagnosis. Kaplan–Meier survival analysis and Cox Proportional Hazard models were used to assess the effect of interval to surgery on post-operative survival. Multivariate logistic regression models were then used to explore potential associations between pre-operative variables including IS as a binary variable ($<$ or $\geq$ median) with histological tumour stage.

Results

388 patients (223 (57%) males) with a median (range) age 67 (41–86) years fulfilling the study criteria underwent surgical exploration during the study period and resection was completed in 266 patients (69%). In 122 (31%) patients the tumour was found to be inoperable due to local invasion of vascular structures (n = 70 (57%)) or the development of distant metastases (n = 47 (63%)). Operative details could not be retrieved in three (1%) patients, tumour mass could not be identified in one patient and one patient did not tolerate surgery. Lateral resections of a small venous patch were undertaken in 32 (12%) patients. The median IS for 388 patients was 49 (1–551) days, and was similar in groups undergoing resection (49 days, range 1–551) or surgical exploration only (50 days, range 11–512) (p = 0.940).

Table 1 Interval to surgery and pathological outcome among 266 patients undergoing resection of peri-ampullary cancer

n = 266 (%)		Cancer Origin			p
		Pancreas n = 149 (56%)	Bile duct n = 46 (17%)	Ampulla n = 71 (27%)	
Median age (range)		67.9 (41.3–82.1)	65.7 (43.7–84.1)	66.2 (411.2–86.4)	0.312
Gender (% male)		55	69.6	53.5	0.171
ASA (%)	1	6 (4)	4 (8.7)	9 (12.7)	0.056
	2	84 (56.4)	22 (47.8)	42 (59.2)	
	3	44 (29.5)	15 (32.6)	14 (19.7)	
	4	1 (0.7)	0	0	
	Missing	14 (9.4)	5 (10.8)	6 (8.4)	
Median IS (range) (days)		48 (1–551)	50 (5–294)	51 (14–477)	0.881
Median tumour size (range) (mm)		30 (12–70)	22 (10–70)	25 (5–80)	0.002
Involved lymph nodes (%)		127 (85.2)	26 (56.5)	40 (56.3)	0.0001
Involved resection margin (%)		119 (79.9)	23 (50)	15 (21.1)	0.0001
30 day post-operative mortality		3 (2)	0	3 (4.2)	0.275

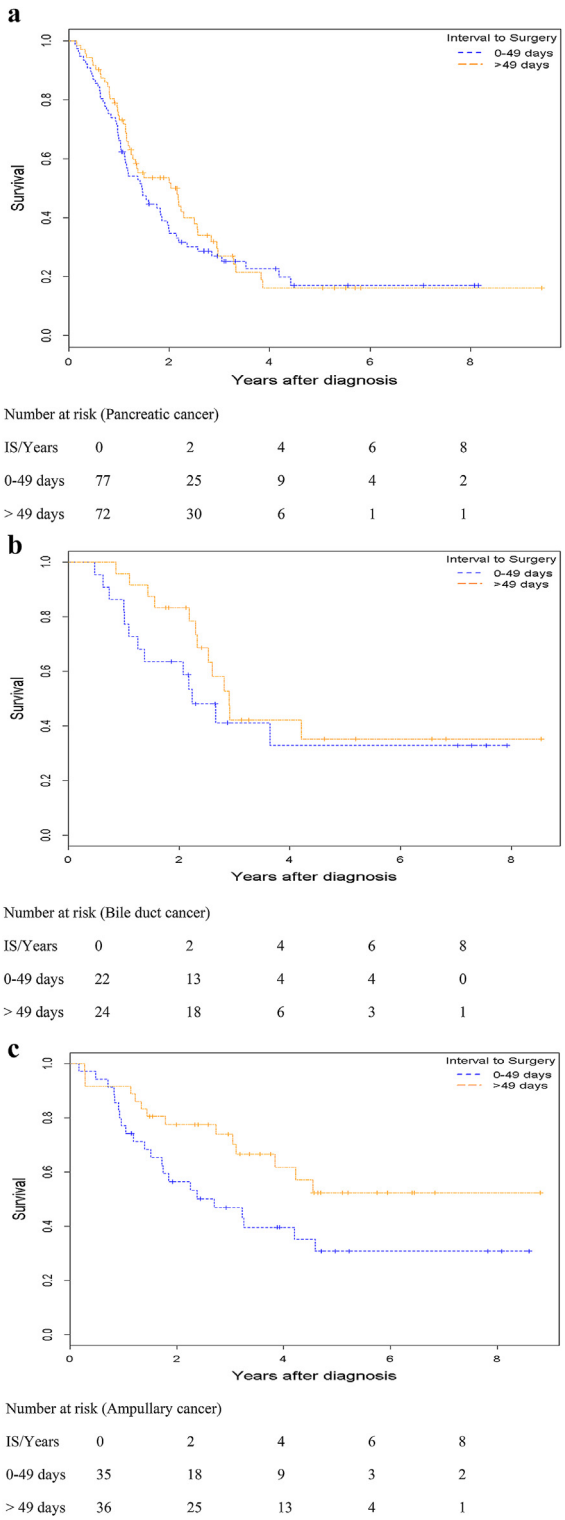

Figure 1 Survival curves of patients undergoing pancreatic head resection for a) pancreatic (149), b) bile duct (46) and c) ampullary cancer (71), divided into subsets determined by the median interval to surgery from initial investigation. p = 0.419, 0.321 and 0.043* respectively

The IS in 331 patients (85.3%) with biliary obstruction at the time of initial presentation was 47 days (1–512) compared to 69 (14–551) in those without this complication (p = 0.001). Pancreatic tumours were noted to be larger than both ampullary and bile duct tumours (Table 1). In regression analysis the variance in size of ampullary tumours was noted to be greater than both pancreatic tumours (coefficient = −1.075; credible interval −1.441 to −0.704) and bile duct tumours (coefficient = −0.63; credible interval −1.096 to −0.165).

After minimum follow-up of 12 months the median survival (range) from diagnosis of the whole cohort was 17.2 months (1.4–114.6) and was significantly longer in patients undergoing surgical resection (23.7 months, range 1.5–114.6) compared to those having surgical exploration only (11.2 months, range 1.4–75.7) The median survival (range) of patients undergoing resection of pancreatic, bile duct and ampullary cancer was 17.3 (1.5–114.6), 28.1 (5.8–104) and 33.3 (2.1–107.1) months respectively. No patients were lost to follow-up. Pre-operative IS was not associated with survival for patients undergoing resection of pancreatic or bile duct cancer, but a positive association was noted for patients with ampullary cancer (Fig. 1). Cox regression analysis of survival data confirmed the reduced hazard of death associated with a longer IS in patients with ampullary cancer only (Table 2). Multivariate analysis of potential associations between pre-operative factors and histological outcomes and survival confirms the reduced risk of positive resection margin in patients with a longer interval to surgery (Table 3). The proportion of ampullary cancer specimens removed within less than the median IS (49 days) with involved margins was 31%, compared to 11.4% among those removed after this interval from diagnosis (p = 0.032). An association between tumour size with age and female gender is also noted (Table 3).

Discussion

Patients with PC may suffer significant delays between presentation and surgery. This may be contributed to by the vague nature of symptoms at the time of presentation,[12,13] the need for biliary drainage,[14] delays incurred during referral to regional centres and capacity issues restricting access to operating time. Because of perceived delays in the treatment of cancer cases NHS guidelines introduced a target of 62 days from referral to treatment for most solid tumours in 2000.[10] Concerns may be raised that this delay will reduce the operability of the pancreatic head

Table 2 Cox regression analysis of association of interval to surgery with survival of patient cohorts, determined by tumour origin

Tumour type	Hazard Ratio	95% confidence	p
Pancreas (149)	0.679	0.314–1.467	0.324
Bile duct (46)	0.855	0.584–1.251	0.419
Ampulla (71)	0.506	0.259–0.991	0.047*

Table 3 Multivariate analysis of potential associations with tumour size, nodal status and resection margin status among 71 patients undergoing resection of ampullary cancer

	Tumour Size				Nodal status				Resection margin status			
	Coefficient	95% Confidence Interval		p	Odds Ratio	95% Confidence Interval		p	Odds Ratio	95% Confidence Interval		p
Interval to surgery (</> 49)	−0.14	−0.403	0.123	0.232	0.604	0.221	1.654	0.326	0.226	0.058	0.877	0.032*
Gender	−0.51	−0.743	−0.277	0.000*	0.512	0.183	1.432	0.202	0.795	0.224	2.818	0.722
Age	−0.017	−0.029	−0.005	0.005*	0.996	0.947	1.048	0.878	0.996	0.934	1.063	0.912
Bilary obstruction at presentation	−0.161	−0.484	0.162	0.312	2.330	0.589	9.225	0.228	0.413	0.081	2.118	0.289

lesion, allow tumour progression and impair long-term survival. The main finding of this study is that no association is noted between delay to surgery and any outcome in patients with pancreatic or distal bile duct cancer, but that a longer interval to surgery is paradoxically associated with improved outcome in patients with ampullary cancer. A proportional increase in survival is noted with each extra months delay prior to surgery associated with a hazard ratio of death of 0.55 after surgical resection. In corroboration of this finding the chance of an involved resection margin is also reduced for patients with ampullary cancer who wait longer for surgery.

In this series a high percentage of resected patients were shown to have ampullary cancer (26%). This is consistent with the adoption of a standardised pathological reporting protocol, which has led to higher rates of diagnoses other than pancreatic cancer in peri-ampullary malignancy.[15,16] PC usually presents with biliary obstruction caused by mass effect and operability is determined by the sequence of invasion, as vascular invasion is a major cause of irresectability.[17–19] Lesions of the ampulla lie furthest from the vascular structures and may be less likely to be inoperable than lesions of the pancreatic parenchyma, which encases the junction between superior mesenteric and portal vein. Surgery is offered to patients who do not have invasion of vascular structures or distant metastases detected on pre-operative imaging, though these findings are often encountered at the time of surgery. This may be caused by understaging by CT scan[20] or by tumour progression in the interval to surgery, which is more likely in aggressive tumours. These results suggest that for pancreatic and bile duct tumours the timing of surgery in relation to pre-operative imaging within the range measured in the study has no effect on resectability, tumour stage or survival after diagnosis. This implies that the operative findings and surgical outcome are determined before imaging takes place and these tumours change little in the interval to surgery. For ampullary tumours however it appears that a longer wait for surgery results in selection of a subset of patients whose tumours remain resectable, with better prognostic characteristics, as shown by the reduced risk of an involved resection margin and improved long-term survival. This may be explained by the progression of a more aggressive subset of ampullary tumours in the interval to surgery leading to inoperability. This more aggressive subset probably includes older patients, in whom resected ampullary tumours are shown to be larger. In support of this concept we have noted a greater variance in size of ampullary tumours than pancreatic and bile duct tumours. Less aggressive ampullary tumours remain confined to the region of the ampulla while others progress to invade vascular structures. As ampullary tumours are located a greater distance from the vascular structures than pancreatic and bile duct tumours they are likely to cause vascular obstruction as a relatively delayed event compared to biliary obstruction. Results for the whole cohort however do not show an association between interval to surgery and resectability. It is probable that the small proportion of patients with ampullary cancer who progress to inoperability is masked in the larger group of patients with pancreatic and bile duct cancer, where IS is shown to have no effect on resectability and outcome.

In the event of inoperability usually a biopsy is taken and the presence of malignancy confirmed. Determining the organ of origin in this situation is difficult however, as this requires examination of the spatial relationship of periampullary lesions.[11] Histological tissue stains have low specificity in determining precise tumour phenotype.[21] Usually in this situation a diagnosis of adenocarcinoma is made and patients often referred for palliative treatment with chemotherapy targeted at pancreatic cancer. Our results provide indirect evidence that among this patient group there will also be patients with ampullary cancer which has progressed to involve vascular structures.

A potential weakness of this study is the variable timing of the initial imaging. Often this was performed after the development of progressive jaundice, so there was an uninterrupted time line from presentation to surgery. In some patients however an initial presentation with spontaneously resolving biliary obstruction was investigated which revealed potential PC, but the issue was not taken forward due to clinical improvement. This presentation accounts for the very long IS in some patients. Although spontaneously resolving biliary obstruction has been reported

previously in ampullary cancer,[22] we have noted a similar phenomenon in pancreatic and bile duct cancer in this study. Another potential weakness is the lack of discrimination of ampullary tumours into intestinal or pancreatico-biliary phenotype. These two tumours have different anatomical and morphological characteristics, in addition to different prognosis. It is possible that the phenomenon we have observed occurs differentially in these two subsets. Distinguishing between these two phenotypes however does not form part of the Royal College of Pathologists' dataset.[11]

Previous evidence has shown that delayed diagnosis and a prolonged interval to surgery has an adverse outcome in other tumour types including breast cancer,[23] non-small cell lung cancer,[24] and urological cancer.[25] There is little data available however on what constitutes a safe interval to surgery after diagnosis. The 62 day interval adopted as a target for treatment of most solid tumours in England was selected as a pragmatic figure without evidence of beneficial effect for each tumour type. Although there is evidence that late diagnosis has a negative effect on outcome in pancreatic cancer, as shown by the low resection rate,[26] the study shows that following symptomatic presentation delay of up to two months prior to resection has no further effect on outcome in pancreatic and bile duct cancer. For ampullary cancer however a delay to surgery within the 62-day target period has a measurable effect, with some lesions progressing to inoperability, and improved outcome of the selected patients whose tumours remain resectable. This finding has significant implications for planning surgery in patients with PC, as the final histological tumour type is not known until surgery is completed, and early surgery for these patients is therefore preferable. Also these findings suggest that in some patients with inoperable PC the tumour may originate within the ampulla, rather than the pancreas. This may have implications for the selection of palliative chemotherapy in this patient group.

Confirmation was obtained from the South West Health Research Authority that under the harmonised Guidance Approval for Research Ethics Committees (REC), REC review was not required because patient data were collected in the course of normal hospital care and were anonymised for research purposes. No patient consent was required for this study.

Conflicts of interest

The authors declare no conflict of interest.

Funding sources

None.

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Clinical Radiology 72 (2017) 691.e11–691.e17

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Systematic evaluation of radiological findings in the assessment of resectability of peri-ampullary cancer by CT using different contrast phase protocols

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ARTICLE INFORMATION

Article history:
Received 30 September 2016
Received in revised form
1 February 2017
Accepted 9 February 2017

AIMS: To determine the relative significance of radiological signs in determining the resectability of peri-ampullary cancer (PC) and to assess the value of multi-phase imaging in detecting these findings.

MATERIALS AND METHODS: Blinded, double re-reporting of preoperative imaging from five hospitals was undertaken of 411 patients undergoing surgery for PC over an 8-year period, of whom 119 patients were found to be inoperable at the time of surgery.

RESULTS: The median tumour size was 26.7 mm and the proportion of patients reported to have regional lymphadenopathy (RL), venous (VI) and arterial involvement (AI) was 24.7%, 11.5%, and 3.9%, respectively and was similar regardless of the number of contrast phases undertaken. Significant associations were, however, noted between individual risk factors: VI was closely associated with tumour size (p=0.002) and AI (p<0.0001). In multivariate analysis AI, VI, and RL were independently associated with resectability (relative risk of resection=0.05, 0.31, and 0.51, respectively). Tumour size, however, was not associated with resectability when VI was included in the multivariate model.

CONCLUSIONS: The use of multiple vascular contrast phases has no measureable impact on the rate of determination of tumour resectability of PC. In preoperative staging, AI is the most significant adverse finding for resectability. Large tumour diameter is not an adverse finding in isolation from other risk factors.

Introduction

Determination of tumour resectability is a major aspect of the interpretation of preoperative imaging of peri-ampullary cancer (PC). The findings of distant metastases and local invasion resulting in occlusion of major arteries or

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http://dx.doi.org/10.1016/j.crad.2017.02.012
0009-9260/

veins are contraindications to attempted surgical resection, whereas lesser degrees of arterial involvement (AI) and venous involvement (VI), including abutment and tapering, are relative contraindications, as imaging can sometimes be inaccurate in determining these findings,[1–4] and vein resection can be undertaken where incomplete venous occlusion is noted.[5–7] Tumour size[8] and regional lymphadenopathy (RL)[9,10] have also been shown to be associated with unresectability, although RL is a relative contraindication as these nodes are removed as part of a Whipple procedure.[11] This finding may, however, be a surrogate marker of an aggressive malignancy, which will progress rapidly to become inoperable.

Despite preoperative imaging to exclude patients with contraindications to surgery a proportion of patients with PC proceeding to operation are found to be inoperable, either due to unresectable invasion of vascular structures or the presence of metastatic disease. This may result from either understaging by computed tomography (CT) or rapid tumour progression in the interval between imaging and surgery.

Preoperative staging of PC is commonly undertaken by contrast-enhanced CT. Some authorities recommend triphasic imaging,[12] including a pre-contrast phase, arterial phase, and portal phase, although the benefits of this over monophasic scans (portal venous phase only) and biphasic scans (arterial and portal phases) have not been demonstrated. This has implications in terms of radiation exposure and resource utilisation. There have also been major improvements in CT technology in recent years with the development of multidetector (MD) imaging,[13] which would be expected to lead to a reduction in the proportion of false-negative findings, and may have reduced the need for multi-phase imaging.

The principal study aim is to determine a hierarchy of radiological findings in predicting the resectability of PC in patients undergoing surgery at a regional centre within a Cancer Network serving five hospitals (A–E) and to investigate the cause of unresectability (local invasion or metastatic disease) associated with these findings. Secondary aims were to explore the effect of varied imaging protocols in the detection of these findings to determine potential advantages of multi-phase imaging in clinical practice.

Material and methods

Details of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and January 2014 were collected in a prospective database. Patients were offered surgery following review of imaging at a specialist hepatobiliary (HPB) multidisciplinary team (MDT) meeting and all scans were performed using 64-section MDCT. Relevant abdominal CT images were retrieved from referring hospitals, anonymised, and uploaded to a dedicated research hard-drive. Images were then re-reported independently by two radiologists with higher training in pancreaticobiliary imaging using standard criteria.[14] The number of vascular contrast phases was recorded for each patient and the proportion of patients having mono-, bi- and tri-phasic imaging in each of the referring hospitals was determined, along with the association of the number of scan phases with the main radiological findings. Specific data fields were created to collect information relating to hospital of origin, the presence of a biliary stent inserted at endoscopic retrograde cholangiopancreatography (ERCP), tumour size, regional nodal status (presence of lymph nodes >1 cm in transverse diameter) and vascular involvement status. Radiological evidence of arterial and venous involvement were defined according to published criteria[14] (Fig 1). In the assessment of a binary variable (e.g., nodal status) a positive outcome was recorded only when both radiologists agreed on the finding. For tumour size, the mean of the two findings was taken.

At surgery, initially a search for metastatic disease was undertaken before an attempt at dissection of the primary tumour. The tumour was considered to be unresectable due to local invasion when the operating surgeon was unable to resect the tumour after trial dissection without undertaking arterial resection or where there was occlusion or extensive invasion of the portal or superior mesenteric vein. Data retrieved from the database included the operative finding of either unexpected distant metastases or local invasion by tumour into vascular structures. The proportion of resectable tumours was recorded for consecutive quartiles (2-year intervals) of the study period. To explore further the predictive value of radiological findings the operative outcome among patients where the tumours were found to be unresectable were categorised into the finding of metastatic disease or local invasion.

Discrete variables and interdependence of radiological findings were analysed using the chi-square test and continuous variables using the Mann–Whitney test. Estimates of the relative value of radiological parameters in the prediction of resectability of PC were determined by logistic regression analysis.

Ethical approval for the study was obtained from the South West Health Research Authority Research Ethics Committees. No patient consent was required for this study because patient data were collected in the course of normal hospital care and were anonymised for research purposes. The study is registered with ClinicalTrials.gov (unique identifier NCT02296736).

Results

Operative details and relevant preoperative imaging were available in 409 patients (Fig 2), of median age 66.9 (28–86) years, of whom 55.8% were men. The median age (66.7 versus 67.5 years), percentage of male patients (54.5% versus 59.8%) and median interval between imaging and surgery (42 versus 39 days, $p=0.419$) did not differ between patients proceeding to resection and those where the lesion was found to be unresectable.

Analysis of images revealed a similar proportion of mono-, bi- and tri-phasic scans. There was variation in the number of vascular contrast phases undertaken in scans

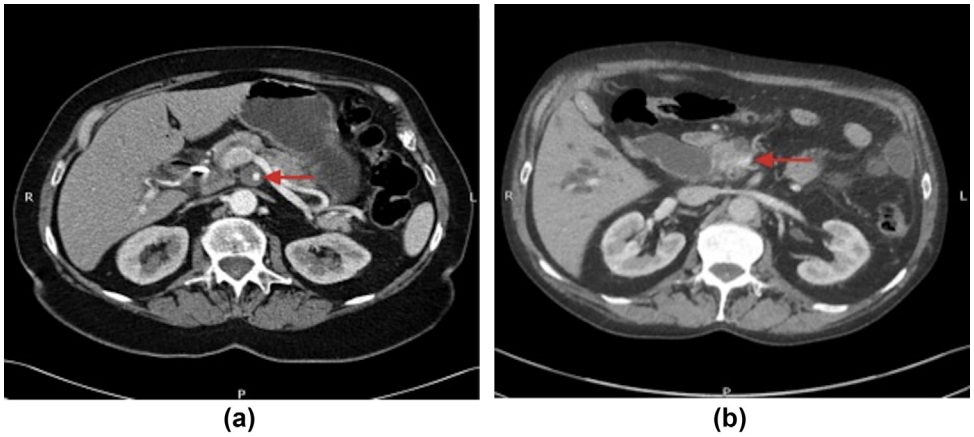

Figure 1 (a) MDCT image demonstrating superior mesenteric artery involvement by PC (arrow). (b) MDCT image demonstrating superior mesenteric vein involvement by PC (arrow).

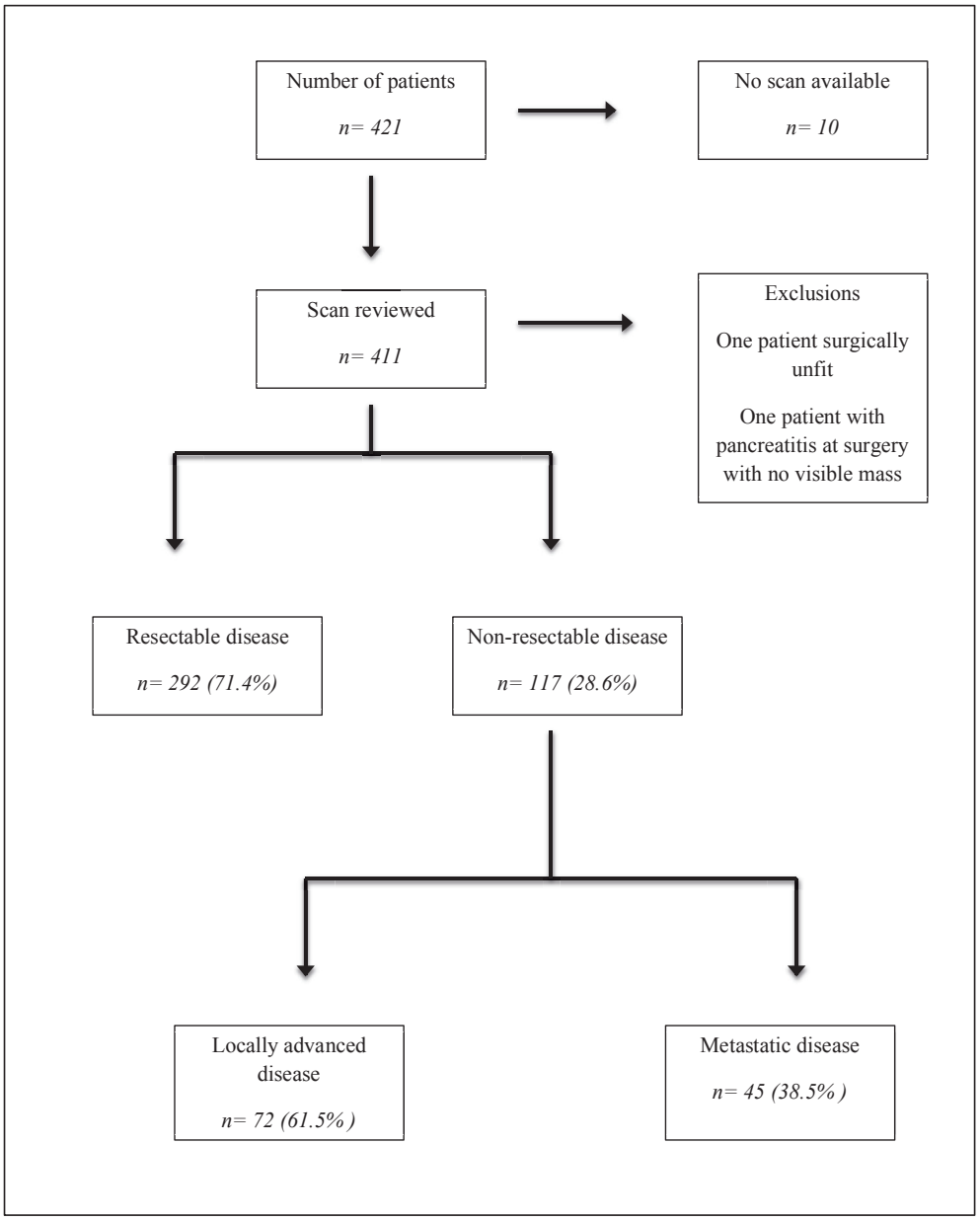

Figure 2 Flow chart of patients undergoing surgery for PC between January 2006 and January 2014.

from different hospitals; however, the rate of detection of the main radiological end-points did not differ according to the number of contrast phases undertaken (Table 1). In particular the proportion of patients noted to have AI did not differ between patients where only portal venous imaging was performed (three of 134) and those where additional arterial phase imaging (bi- and tri-phasic scans) was also performed (13 of 275; p=0.223). The primary tumour was visible in 250 patients (61.1%), with no difference in the rate of detection in patients having different contrast phase protocols (Table 1). Similarly the median tumour size was 26.7 (8–70) mm and did not differ between patients having different scan phases (p=0.39). Where a tumour was visible RL, VI, and AI were noted in 101 (40.4%), 47 (18.8%), and 16 (6.4%) of patients, respectively. Among the 159 patients where no primary tumour was visible, RL was noted in 40 (25%) patients. Tumour size was noted to be greater in patients with RL (28.5 versus 26 mm), AI (30.7 versus 26.5 mm), and VI (33 versus 25.5 mm) than in those without these findings (p=0.02, 0.03, and 0.0001, respectively). On evaluation of the interdependence of preoperative risk factors, VI was noted to be strongly associated with AI (p=0.000). Of the 16 patients with AI, eight (50%) also were noted to have VI. The finding of RL was not significantly associated with either AI (p=0.472) or VI (p=0.108).

Biliary stents had been inserted prior to CT in 73 (17.8%) patients. The proportion of patients with radiologically detectable RL did not differ between those who had (17/72, 23.6%) and those who had not (84/337, 25%) had a stent inserted prior to CT scan (p=0.814).

Surgical resection of the PC was completed in 292 patients (71.4%). Resection was completed more commonly among the 159 patients where no lesion was visible (126, 79%) than among the 250 patients where the tumour was visible (166, 66.4%) (p=0.005). Among the 155 patients with a visible tumour and no adverse risk factors (RL, AI, or VI) on preoperative imaging, the median tumour size did not differ between the 121 patients where the tumour was resectable (24.5 mm, interquartile range (IQR): 20.5–30.42) and the 34 patients where the tumour was not resectable (26.7 mm, IQR: 20–28.5 mm; p=0.55).

Of the 17 patients with VI on preoperative imaging where resection was completed, partial venous resection was necessary in three (17.6%) patients. Vein resection was also required in five of the 348 patients (1.4%) where VI was not noted preoperatively. The final pathological diagnosis of resected specimens is shown in Table 2.

At univariate analysis, the presence of a visible tumour, tumour size, RL, AI, and VI on preoperative imaging were all associated with unresectability of the tumour (Table 3); however, in the multivariate analysis the strongest association with tumour resectability was with the presence of AI (Table 3). Tumour size and VI were found to be mutually exclusive for significance in the multivariate model.

In the 117 patients where the tumour was not resected, this was due to the finding of hepatic metastatic disease in 45 patients (37.8%) or local invasion of vascular structures in 72 patients (60.5%). The proportion of patients with unresectable disease was 16/67 (23.8%), 35/93 (37.6%), 32/119 (26.2%), and 34/130 (26.1%) (p=0.17) in consecutive time quartiles of the study. No difference was noted in the reasons for unresectability (local invasion or metastatic disease) among patients with different preoperative radiological findings (Table 4).

Discussion

The present study enabled the determination of a hierarchy of relative contraindications to resection of PC, based on a systematic assessment of radiological findings. In multivariable analysis, the likelihood of completing surgical resection was reduced by a factor of 0.05, 0.31, and 0.51 by a finding of AI, VI, and RL, respectively, compared to a patient with none of these findings. In the absence of these findings, tumour size was not associated with resectability. The study also revealed significant interdependence of radiological signs, with VI closely associated with tumour size (p<0.0001) and with AI (p=0.000). The present study demonstrated that the proportion of patients with unresectable disease at the time of surgery has not declined over the 8-year period of the study, and that the radiological findings are similar regardless of the number of scan phases undertaken. In addition, preoperative radiological findings

Table 1
Radiological findings and surgical resection rate according to the number of computed tomography phases for 409 patients undergoing attempted surgical resection for peri-ampullary cancer.

		Monophasic (n=134, 32.7%)	Biphasic (n=149, 36.4%)	Triphasic (n=126, 31%)	p-Value
Hospital	A (n=119)	20 (16.8)	52 (43.7)	46 (38.6)	0.0001
	B (n=97)	45 (46.4)	50 (51.5)	2 (2.1)	
	C (n=78)	24 (30.7)	9 (11.5)	45 (57.7)	
	D (n=71)	24 (33.8)	21 (29.5)	26 (36.6)	
	E (n=44)	21 (47.7)	17 (38.6)	6 (13.6)	
AI (n=16)		3 (2.4)	8 (5.4)	5 (4)	0.398
VI (n=47)		20 (15)	11 (7.4)	16 (12.7)	0.122
RL (n=101)		28 (21)	42 (28.2)	31 (24.6)	0.83
Tumour visible (n=250)		72 (53.7)	99 (66.4)	79 (62.7)	0.83
Median tumour size (average)		25.25 (11.5–70)	26.25 (10.5–58)	27.75 (8–64.5)	0.39
Resection completed (n=292)		102 (76.1)	107 (71.8)	83 (65.8)	0.187

Data are n (%).
AI, arterial involvement; VI, venous involvement; RL, regional lymphadenopathy.

Table 2
Histological outcome of 292 patients undergoing surgical resection for presumed peri-ampullary cancer.

Tumour origin	*n* (%)	Median tumour size (range) mm	Histological lymph node involvement, *n* (%)
Pancreatic adenocarcinoma	132 (45.2)	30 (12–65)	122 (92.4)
Ampullary adenocarcinoma	66 (22.6)	25 (5–80)	37 (56)
Bile duct adenocarcinoma	47 (16.1)	25 (10–70)	25 (53.2)
Duodenal adenocarcinoma	7 (2.4)	40 (30–55)	4 (47)
Tubulo-villous adenoma	15 (5.1)	30 (24–55)	
Inflammatory disease	12 (4.1)		
Neuroendocrine tumour	6 (2)	18 (10–25)	3 (50)
Metastasis	4 (1.4)	35 (25–45)	
Gastrointestinal stromal cell tumour (GIST)	1 (0.03)		0 (0)
Others (benign)	2 (0.6)		

Table 3
Univariate and multivariate analysis of the association of the preoperative radiological risk factors and surgical resectability of peri-ampullary cancer in 409 patients.

Imaging characteristic	Tumour resectability		UVA	MVA		
	Yes (*n*=292)	No (*n*=117)	*p*-Value	Exponent	95% CI of exponent	*p*-Value
Median tumour size, mm (range)	25.5 (8–70)	28 (11.5–64.5)	0.01	0.46	(0.193–1.084)	0.076
RL (*n*=101), *n* (%)	63 (21.6)	39 (32.8)	0.017	0.51	(0.272–0.949)	0.047
AI (*n*=16), *n* (%)	2 (0.68)	14 (11.7)	0.000	0.05	(0.007–0.445)	0.007
VI (*n*=47), *n* (%)	17 (5.82)	30 (25.2)	0.000	0.31	(0.152–0.638)	0.001

UVA = univariate analysis; MVA = multivariate analysis; AI, arterial involvement; VI, venous involvement; RL, regional lymphadenopathy.

Table 4
Reasons for non-resection (local invasion or metastatic disease) among 117 patients undergoing attempted surgical resection for peri-ampullary cancer with different preoperative radiological findings.

Radiological finding	Local progression (*n*=72)	Metastatic disease (*n*=45)	Chi^2	*p*-Value
Tumour visible (*n*=*84*, 71.8%)	49 (58.3)	35 (41.6)	1.3	0.256
Median tumour size, mm (range)	28.25 (11.5–64.5)	27.75 (16.5–55.5)	0.838	0.36
RL (*n*=38, 32.5%)	23 (60.5)	15 (39.5)	0.024	0.876
AI (*n*=16, 13.7%)	9 (56.2)	5 (31.25)	0.051	0.822
VI (*n*=30, 25.6%)	22 (73.3)	8 (26.6)	2.37	0.123
No adverse radiological findings (*n*=54, 46.1%)	32 (59.2)	22 (40.7)	0.22	0.639

AI, arterial involvement; VI, venous involvement; RL, regional lymphadenopathy.

were not able to predict the reason the pancreatic tumour was not resectable at the time of surgery (metastatic disease or local progression).

Many studies have shown that AI and VI are risk factors for non-resection of pancreatic tumours.[15–17] Most have focussed on assessing the accuracy of MDCT in identifying these risk factors in comparison with operative findings or histology.[18–20] This study has used a structured reporting protocol to assess the relative risk that preoperative identification of these findings entails for individual patients in terms of tumour resectability. AI is shown to be the most significant adverse finding, with a relative risk of resection of 0.05 compared to a patient without this finding. This may be due to the hepatic and superior mesenteric arteries lying further from the duodenal ampulla than venous structures, denoting a greater degree of invasion. The observation that the radiological findings of AI and VI are associated with each other may also reflect the spatial relationship of these structures, with VI occurring first followed by AI.

The significance of radiological evidence of RL has been less well investigated previously. It is interesting to note that the presence of RL was not influenced by the insertion of biliary stents, so this finding should be attributed to a malignant, rather than inflammatory process. RL was also not associated with other signs of local tumour progression, and is only weakly associated with primary tumour size. The development of lymph node metastases in PC may therefore depend on different biological processes to primary tumour enlargement and local invasion. RL was however independently associated with tumour unresectability. This is probably due to this finding being a marker of a more aggressive malignancy. In a large proportion (69%) of patients with RL however the tumour remains resectable at surgery.

The present study confirms that although tumour size is associated with invasion of vascular structures, size alone does not lead to an increased risk of non-resection in the absence of other adverse findings. This is significant as some centres have used tumour size alone as a factor in the decision to offer surgery for PC.[8]

The observation that 20% of patients with no detectable tumour radiologically are found to be inoperable at the time

of surgery is an interesting finding. This suggests that although the interval from imaging to surgery has only a small impact on resectability in large series,[21] there may be a more aggressive subset where progression proceeds rapidly. Similarly, among the 271 patients where no adverse radiological signs were identified, 54 (19.9%) were still found to be inoperable at the time of surgery. Caution must be exercised, therefore, in the interpretation of radiological findings when counselling patients. In addition, although vein resection was required in 17.6% of patients undergoing resection where VI was noted on preoperative imaging, it was also necessary in 1.4% of cases without VI on preoperative imaging. These observations emphasise the limitations of preoperative imaging in planning surgery for PC.

The weaknesses of this study mainly relate to the non-standardised imaging protocols undertaken in different centres, and its retrospective nature. This study, however, represents an analysis of the value of preoperative imaging in routine clinical practice, rather than under trial conditions, and the results are therefore likely to be relevant to other centres undertaking this type of surgery. Of particular interest is the finding that the radiological findings and resection rate are similar regardless of the number of contrast phases. Although multi-phase pancreatic-protocol CT is considered the reference standard in assessing resectability of PC,[12] the results of the present study indicate that the resectability rate is unaltered by the CT technique used. It is possible that with a larger study the use of arterial phase contrast may lead to greater sensitivity in the detection of AI. This, however, does not seem necessary in patients with small tumours and no evidence of VI, where the risk of AI is very low. The study is also limited by the number of radiologists undertaking rereporting (two). The agreement between radiologists is being addressed separately, and it is possible that the results have been biased by individual radiologists performance.

The analysis of surgical outcomes has revealed the most common cause for non-resection was invasion of vascular structures (60.5%), with metastatic disease a less common finding (37.8%). Patients noted to have AI or VI on preoperative imaging had a similar likelihood of being inoperable due to metastatic disease or local invasion at the time of surgery, suggesting that these findings are markers of aggressive malignancy. CT has a high resolution for hepatic metastases, which has increased in recent years.[22] Despite this the proportion of patients with unresectable disease has remained largely unchanged over the period of study. This finding suggests that disease progression between imaging and the time of surgery may be a more significant cause of inoperability than understaging by CT. There may therefore be an irreducible number of patients with rapidly progressive disease who will be unresectable at the time of surgery, regardless of the quality of the imaging and reporting undertaken.

The strength of this study lies in its large size and in the assessment of imaging of heterogeneous technique from different hospitals. Other studies have shown similar risk factors for non-resection,[23,24] and a similar rate of non-resection[23,24] at the time of surgery, and there is little available evidence that this rate has declined with improved imaging. This may be due to alterations in the threshold for undertaking surgery in borderline cases and improvements in surgical technique. The study however reveals significant limitations in the ability of MDCT to predict the presence of surgically significant operative findings.

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