

PANCREATICODUODENECTOMY FOR
PERIAMPULLARY CANCER IN SARAWAK:
A 3-YEAR SURVIVAL ANALYSIS AND FACTORS
AFFECTING IT

BY

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A dissertation submitted in fulfillment of the requirement for
the degree of Master of Surgery (General Surgery)

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ABSTRACT

Periampullary cancers incidence has been uprising worldwide which resulted in increasing morbidity and mortality. The distinct anatomy of that region often can give rise to different types of cancers. However, they are subjected to a common procedure – pancreaticoduodenectomy. The survivals after curative resection varies geographically and multiple cohort studies has shown to give different factors affecting the survival of periampullary cancers. Therefore, this study is to determine the overall survival and to identify the sociodemographic, peri-operative and histopathological factors affecting periampullary cancers after pancreaticoduodenectomy in Sarawak. Retrospective collected demographic, clinical features, peri-operative parameters histopathological features of all patient with periampullary cancers who underwent pancreaticoduodenectomy from January 2013 till June 2018. Overall survival and 3-year survival probability are determined using Kaplan-Meier curve. The affecting factors are analysed cox regression for univariate and multivariate analysis. A total of 56 patients with median for overall survival is 17.43 months (SD 2.86 months). The 3-year survival rate of this cohort is 14.0%. Iban (P = 0.006) and other minorities ethnic (P = 0.005) in Sarawak shown to have a poor prognosis. Pre-operative biliary drainage is the only factor with significant difference (P<0.001, 95% CI 0.091 – 0.748) in univariate and multivariate analysis. Operating duration (P=0.006) and numbers of packed red blood cells transfused (P=0.018) are also significantly affecting the survivals after adjustment. Marginal involvement (P =0.024) and tumour types (P=0.055) are the histopathological factors with worst prognosis. The periampullary cancer survival rates in Sarawak was seen less comparable to other region. Ethnicity had been known to be a significant predictor in overall survival from the socio-demographic characteristic. Pre-operative biliary drainage, number of packed red cell blood transfusion and operative time were important peri-operative factors with significantly worsened the survival. Tumour types and marginal involvement were also strongly associated with poorer survival probability.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion; it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Surgery (General Surgery)

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DECLARATION

I hereby declare that this dissertation is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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This thesis is dedicated to my beloved parents, whom have given me a great foundation from the beginning and seamless support in my life, respected teachers and colleagues whom gave me words of encouragement and valued enlightenment.

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TABLE OF CONTENTS

Abstract	ii
Approval Page.....	iii
Declaration	iv
Acknowledgements	vii
Table of Contents	viii
List of Tables	x
List of Figures	xii
CHAPTER ONE: INTRODUCTION	1
1.1 Background Of The Study	1
1.2 Research Questions.....	2
1.3 Objectives	2
1.3.1 General Objectives	2
1.3.2 Secondary Objectives (Specific).....	2
CHAPTER TWO: LITERATURE REVIEW	3
CHAPTER THREE: METHODOLOGY	9
3.1 Study Design and Sampling.....	9
3.1.1 Study Design	9
3.1.2 Study Period	9
3.1.3 Study Location	9
3.1.4 Inclusion Criteria	9
3.1.5 Exclusion Criteria	10
3.2 Sampling Method	10
3.3 Data Collection	10
3.3 Data Analysis.....	11
3.4 Ethical Consideration.....	11
3.5 Confidentiality	11
CHAPTER FOUR: RESULTS	13
4.1 Age.....	13
4.2 Gender.....	13
4.3 Ethnicity.....	14
4.4 Clinical Characteristic	15
4.4.1 Presenting Symptoms.....	15
4.4.2 Risk Factors & Comorbidities	16
4.5 Peri-Operative Parameters	17
4.5.1 ASA Score	17
4.5.2 Biochemical Markers	17
4.5.3 Pre-Operative Biliary Drainage	19
4.5.4 Types of Surgery	20
4.5.5 Emergency Surgery.....	20
4.5.6 Operative Time	21

4.5.7 Estimated Blood Loss	22
4.5.8 Number of Packed Red Cell Transfusion	23
4.5.9 Postoperative Complication	23
4.5.10 Length of In-Hospital Stay.....	25
4.6 Histo-Pathological Variables	25
4.6.1 Types of Periapillary Tumour	25
4.6.2 Differentiation of Tumours	26
4.6.3 Clinical Stage of Disease	27
4.6.4 Lymphovascular and Perineural Invasion.....	29
4.7 Overall Survival.....	30
4.8 Incidence.....	31
4.9 Affecting Factors	32
4.9.1 Demographic Factors	32
4.9.2 Perioperative Factors.....	32
4.9.3 Histopathological Factors	33
4.10 Univariate Analysis	33
4.11 Multivariate Analysis	35
CHAPTER FIVE: DISCUSSION.....	38
6.1 Limitations	44
CHAPTER: SIX CONCLUSION.....	46
REFERENCES.....	47
APPENDIX I DATA COLLECTION FORM.....	51
APPENDIX II IREC APPROVAL.....	56
APPENDIX III NMRR AND MREC APPROVAL LETTERS	57

LIST OF TABLES

<u>Table No.</u>	<u>Page No.</u>
Table 4.1 Distribution by age group in 56 patients of periampullary cancer underwent pancreaticoduodenectomy in Sarawak General Hospital.	13
Table 4.2 Distribution by risk factors & comorbidities in 56 patients of periampullary cancer underwent pancreaticoduodenectomy in Sarawak General Hospital.	16
Table 4.3 ASA scoring for 56 patients of periampullary cancer underwent pancreaticoduodenectomy in Sarawak General Hospital.	17
Table 4.4 Total bilirubin level in 56 patients of periampullary cancer prior pancreaticoduodenectomy.	18
Table 4.5 AST and ALT levels in 56 patients of periampullary cancer prior pancreaticoduodenectomy.	18
Table 4.6 Albumin levels in 56 patients of periampullary cancer prior pancreaticoduodenectomy.	19
Table 4.7 Pre-operative CA 19-9 in 56 patients of periampullary cancer from Sarawak General Hospital.	19
Table 4.8 Pre-operative biliary drainage in 56 patients of periampullary cancer from Sarawak General Hospital.	20
Table 4.9 Types of surgery in 56 patients of periampullary cancer from Sarawak General Hospital.	20
Table 4.10 Comparison between elective and emergency surgery in 56 patients of periampullary cancer from Sarawak General Hospital.	21
Table 4.11 Estimated blood loss in 56 patients of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	23
Table 4.12 Number of packed red cell transfusion in 56 patients of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	23
Table 4.13 Postoperative complications in 56 patients of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	24

Table 4.14 Length of in-hospital stay in 56 patients of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	25
Table 4.15 Tumour differentiation in 56 patients of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	27
Table 4.16 TNM staging of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	28
Table 4.17 Histopathological factors of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	30
Table 4.18 1- year and 3-year survival of 56 patients underwent pancreaticoduodenectomy in Sarawak General Hospital.	31
Table 4.19 Univariate Analysis of characteristic, perioperative and histopathological factors of 56 periampullary cancers patient in Sarawak General Hospital	33
Table 4.20 Multivariate Analysis of characteristic, perioperative and histopathological factors of 56 periampullary cancers patient in Sarawak General Hospital	35

LIST OF FIGURES

<u>Figure No.</u>	<u>Page No.</u>
Figure 4.1 Distribution by Gender	14
Figure 4.2 Distribution by Ethics	15
Figure 4.3 Average operating time for pancreaticoduodenectomy in	22
Figure 4.4 Types of periampullary tumour for pancreaticoduodenectomy in	26
Figure 4.5 Staging distribution of periampullary cancer underwent pancreaticoduodenectomy from Sarawak General Hospital.	29
Figure 4.6 Overall survival of 56 patients underwent pancreaticoduodenectomy in Sarawak General Hospital.	31
Figure 5.1 Overall survival of 56 patients in comparison of tumour types in pancreaticoduodenectomy in Sarawak General Hospital	43

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Periampullary tumours are described as those tumour arises within 2 centimetre from the major papilla in the duodenum in which that they encircle tumours of the ampulla of Vater, distal common bile duct, head of pancreas tumours and duodenal tumours involving the papilla (Rattner & Warshaw, 1997). The compound anatomy of that region often subjects to a common operative procedure; pancreaticoduodenectomy. However, these tumours from different type of entities carry different prognosis (Fernandez-Cruz L, 2001).

In the North America, the overall median survival for periampullary cancers following pancreaticoduodenectomy is 21.9 months with ampullary having the best survival, 44.3 months. Head of the pancreas cancers has the worst survival outcome with 17.1 months (Hatzaras I et al, 2010). Even though periampullary cancers represent about 0.2% of all gastrointestinal tract tumours (Yeo CJ et al, 1998), however there is an increasing numbers of occurrence particularly in Asia. In the latest study from China, it is reported the overall median survival is 533 days and 3- years overall survival rates is 66% (He et al, 2018)

Data on survival on periampullary cancers in Malaysia are limited and mainly carried out as an audit in hospital level. There have been no data collection and investigation on survival of periampullary cancers in Sarawak yet; hence, the writing of this thesis will hopefully create a foundation basis for the future research on periampullary cancers in Sarawak.

1.2 RESEARCH QUESTIONS

- i. What is the overall survival rate of periampullary cancer in Sarawak?
- ii. What is the incident of periampullary cancer in Sarawak?
- iii. What are the factors affecting the survival of periampullary cancer in Sarawak?

1.3 OBJECTIVES

1.3.1 General Objectives

- i. To determine the overall and 3 years' survival of periampullary adenocarcinoma following pancreaticoduodenectomy in Sarawak.

1.3.2 Secondary Objectives (Specific)

- i. To study the incidence of periampullary cancer in Sarawak.
- ii. To identify the factors (socio-demographic, peri-operative and hist-pathological) affecting the overall survival of periampullary adenocarcinoma in Sarawak.

CHAPTER TWO

LITERATURE REVIEW

Biliary drainage conjoint at the point where the dilated junction of pancreatic duct and the bile duct, *ampulla of Vater*, in which they entered to the duodenum to major duodenal papilla. The released of the bile and pancreatic juices are controlled by the *sphincter of Oddi* which surrounded the ampulla (Horiguchi S et al, 2010). The major duodenal papilla is seen as a hemispherical or oval elevation on the duodenal mucosa. It is a circular fold describe like a hooding covers the duodenal papilla on the oral side, where the frenulum runs vertically at the anal side of duodenal papilla. The vertical fold is a landmark during endoscopic identification according to the author (Horiguchi S et al, 2010). It is occasionally located about 8cm distal to the pylorus at the second part of the duodenum (Dowdy et al, 1962). Lindner et al had described the course of common bile duct into the duodenum in 1,000 patients where the major duodenal papilla is mainly located at the descending part of duodenum (82%), and occasionally in the transition between the descending duodenum and horizontal part (12%). Only 6% of major duodenal papilla are located in the horizontal part, in which that the lower portion of the bile duct ran vertically. The major duodenal papilla projected <10mm into the duodenum in which it varied individually (Dowdy et al, 1962).

There are multiple anatomic variation of pancreatic and biliary duct at the major papilla. It can be divided to multiple duodenal papillae in which that the pancreatic duct and bile duct are separated, or joined together with a partition or those that form a common duct. Dowdy et al described that 70% of the pancreatic and bile duct are located at the duodenal papilla along the choledochal duct and form an ampulla with an

average length of the ampulla is 4.4mm. Rienhoff and Rickrell described that the length of the common duct was <2mm in 53% of the patients. Moreover, the angle of the common duct entered the duodenum determined the length of the common duct.

The *sphincter of Oddi* comprised of thin smooth muscle in which they functioned independently from the muscular proprietary of the duodenum. It is located at the distal part of the bile and pancreatic duct. According to Boyden et al, the *sphincter of Oddi* divided into the sphincter of pancreaticus, sphincter of choledochus and sphincter of ampullae. The *sphincter of Oddi* maintained a basal pressure of 4-5mg Hg higher than bile duct. It regulated the bile flow from the bile duct to the duodenum by peristalsis contraction. It also prevented pancreatic fluids from reflux back to the bile duct.

Rattner & Warshaw defined that periampullary tumours are a group of heterogenous neoplasm with distinct entities arises within 2 centimetres from the major papilla in the duodenum. These group of tumour has different tissue origin. However, they are classified together by their anatomical close proximity with each other.

Yeo CJ et al reported more than 30,000 cancer-related deaths per year in United Stated are due to periampullary adenocarcinoma. Ampullary cancer was reported with incidence about 2.9 cases for minion population. About 6% of periampullary malignancies derived from ampullary cancer. Pancreatic cancers are fourth most common cancers cause of death in United State. It is reported that about 25,000 new cases occur annually in North America. 10-15 per 100,000 persons were diagnosed with pancreatic cancer in Europe (Fernandez-Cruz et al, 2001). Cholangiocarcinoma accounted roughly 5,000 new cases per year in North America. (Shaib Y et al, 2004) Distal common bile duct is classified under extra-hepatic bile cholangiocarcinoma particularly in the intrapancreatic portion of bile duct. Shin et al reported korean had

the highest incidence of extrahepatic cholangiocarcinoma. Age-standardized incidence rate among the Korean is 1.5.

Periampullary tumours presented with painless and progressive obstructive jaundice in 80% of the case. However, only 20% of the patients will presented with fluctuating jaundice (Phatak PS, 1974). Abdominal pain with significant weight loss are often seen in advanced stages of disease. Unlike pancreatic head cancer, the constitutional symptoms of abdominal pain, anaemia, vomiting and weight loss usually preceded before jaundice (Jagannath P et al, 2003).

The most common neoplasm in the pancreas is pancreatic ductal adenocarcinoma and it tends to infiltrate rapidly to the neighbouring organs especially the common bile duct (Blumgarts Surgery of Hepatobiliary, 5th edition). Hence, it is difficult to differentiate pancreatic cancer from other cancer originate from distal common bile duct in view of identical microscopic features. furthermore, pancreatic ductal adenocarcinomas might invade and ulcerate the duodenum or ampulla of Vater, imitating a primary duodenal or ampullary cancer.

The latest periampullary cancer pathological staging are staged based on AJCC 8th edition. It is defined that all the carcinoma of the ampulla of *Vaters* or duodenal papilla, including poorly differentiated neuroendocrine carcinomas are covered using this system of staging. T1a defined as tumour limited to Ampulla of *Vater* of sphincter of *Oddi*. T1b defined as tumour invaded beyond to duodenal submucosa with perisphincteric invasion. T2 defined as invasion of tumour to the muscularis propria of the duodenum. T3a defined as invasion to the pancreas up to 0.5cm. Invasion beyond 0.5cm into pancreas or extended into peripancreatic tissue or duodenal serosa are defined as T3b. T4 means tumour invaded celiac axis, superior mesenteric artery or common hepatic artery. The minimal numbers of regional lymph nodes (peri-

pancreatic, hepatic artery and portal nodes) needed for accurate staging are 12 lymph nodes. N0 defined as no regional lymph node involvement. N1 specified one to three lymph nodes involvement and N2 stated four or more regional lymph nodes involvement. M1 clearly defined as presence of distant metastasis. However, in instance of pancreatic head carcinoma for staging, there are differences in T staging system in AJCC 8th edition. T1 pancreatic tumour is defined as tumour <2cm. T2 stated the maximum tumour diameter >2, but less or equal to 4cm. T3 is defined as tumour diameter more than 4cm while T4 invaded the celiac axis, common hepatic artery or superior mesenteric artery. There are no differences in nodal staging (N).

In terms of socio-demographic factors, Lim JE et al had mentioned that there were no significant differences in survival in comparison of age and gender. However, the prognosis of african american race has significant diminish as compared to non-african american races. Furthermore, abdominal pain was seldom described in patients with ampullary origin but according to Hatzaras I et al, pancreatic type were more likely to present with abdominal pain.

Lim JE et al also analysed that in univariate or multivariate analysis, there were no significant differences in survival for those who did not require blood transfusion intraoperatively, and those who received any packed red blood cell transfusion, in particular, less than or equal to two units compared to three or more units required.

Tumor size and histological grading were often described to be strong predicting factors with survival of periampullary cancers. Tumour size less than 3cm survive better in 3-year survival than and had significant median survival rate than tumour size more than 3cm. Patients with well-differentiated tumours had better survival rates than those with moderately or poorly differentiated tumours. Patients with resected specimen

positive lymph nodes for carcinoma had poorer median survivals than negative lymph nodes (Lim JE, 2003).

Periampullary cancers had lesser lymphatic spreads as compared to pancreatic cancer. Pancreatic cancers often presented with lymph node involvement in 56-79% of the patient while periampullary cancers corresponds about 30-50% of lymph node metastasis (Monson et al, 1991).

Perineural invasion in which indicated a poorer prognosis, often present in most of all pancreatic cancers. It is known that only 5-17 % patients in ampullary cancers associated with perineurial invasion (Nakai et al, 1997). The author also described that presence of perineurial invasion in ampullary cancer is the most important prognostic factor.

Pancreaticoduodenectomy is the best treatment option to improve survival in periampullary cancer (Jagannath P et al, 2003). *Whipple's* Procedure was first described by Kausch in 1909, later which is popularised by Whipple and colleagues, a single stage pancreaticoduodenectomy in 1935 (Cameron JL et al ,2006). Classical *Whipple's* Procedure required a distal gastrectomy with *en-bloc* removal of the pancreatic head, duodenum, first 15 cm of the jejunum and common bile duct. The gallbladder is often removed as separated specimen.

Kenneth Watson described pylorus-preserving pancreaticoduodenectomy in 1943 with preservation of the gastric antrum, pylorus and the proximal part of the duodenum, which is anastomosed to the jejunum. Diener et al compared that preservation of the pylorus to the conventional *Whipple* procedure in periampullary and pancreatic carcinoma showed significant reduction in intra-operative blood loss and operating time. However, there were no differences in term of in hospital mortality and overall survival.

Postoperative pancreatic fistula (POPF) was defined based on the International Study Group on Pancreatic Fistula (ISGPF). It was described as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper limit of the normal serum amylase with association of clinically condition related to pancreatic fistula. Delayed gastric emptying (DGE) and post-pancreatectomy hemorrhage (PPH) and were also defined based on the International Study Group of Pancreatic Surgery (ISGPS) definitions.

Inability to return to normal diet first week after surgery with nasogastric tube is defined as delayed gastric emptying (DGE). ISGPS further categorized the situation into A, unable to tolerate solid diet by day 7 post-operatively or reinsertion of nasogastric tube at post-op day 3. B and C are defined as inability to tolerate solid diet by day 14 and day 21 post-operatively with reinsertion of nasogastric tube at day 7 and day 14 post-operative day respectively. Post-pancreatectomy hemorrhage (PPH) is classify by ISGPS based on the time of onset, location (intraluminal or extraluminal) and severity of the bleeding.

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN AND SAMPLING

3.1.1 Study Design

Retrospective cohort study.

3.1.2 Study Period

Five and a half years duration from 1st January 2013 until 30th June 2018 as accrual time with follow up time from 1st July 2018 to 30th September 2019.

3.1.3 Study Location

Sarawak General Hospital (SGH), Kuching. Sarawak.

3.1.4 Inclusion Criteria

- i. All patient diagnosed with periampullary adenocarcinoma who under pancreaticoduodenectomy with curative intent in Sarawak General Hospital from the date January 2013 through June 2018.
- ii. Periampullary adenocarcinoma includes four tumor types: tumor originating from head, neck, or uncinata process of the pancreas; ampulla of Vater; distal common bile duct; and the tumors originating from the duodenum.

3.1.5 Exclusion Criteria

- i. Suspected periampullary carcinoma undergo pancreaticoduodenectomy with benign disease on histopathological diagnosis.
- ii. Tumors including cystic tumor such as cystadenocarcinoma and solid and papillary neoplasms, neuroendocrine tumor and tumors metastasized to periampullary region.

3.2 SAMPLING METHOD

All eligible subjects were selected. No sampling was applied.

3.3 DATA COLLECTION

Subject cases were selected by reviewing the archives of Sarawak General Hospital (SGH) operation theatre registry for patient who underwent pancreaticoduodenectomy. Data collection were then taken from Surgical Outpatient Department (SOPD), Sarawak General Hospital, Kuching. The demographic, pre-operative presentation, co-morbidities, radiological findings, intra-operative and post-operative data were collected the data collection form (Appendix A).

Further collection of data was compiled from Pathology Unit and Radio-Oncology Unit, Sarawak General Hospital with permission in order to complete the necessary information on histopathological data and oncological follows up. Patients were staged according to the American Joint Commission on Cancer (AJCC), 7th edition criteria on pancreatic, distal bile duct and ampulla of Vater. The date and cause of death were taken. The survival time of a patient will be taken as the number of months from the day the subject was diagnosed with histo-pathological confirmation until the date she passed away or was last known to be alive.

3.3 DATA ANALYSIS

Data was collected using Microsoft Excel and was converted to Statistical Package for Social Science (SPSS) software version 22 for analysis. Socio-demographic, peri-operative and histo-pathological parameters were analysed. Overall survival estimation were determined using Kaplan-Meier curves and the differences in survival were compared by the log-rank test.

The affecting factors were determined using the Cox's regression models. Multivariate logistic analysis was performed to determine the factors affecting the prevalence of periampullary cancer in Sarawak. All variables (socio-demographic, intra-operative and histo-pathological parameters) were entered for multivariate analysis. The final model included all variables of $p < 0.05$ with adjusted odds ratio and 95% confidence interval reported.

3.4 ETHICAL CONSIDERATION

Ethical approval was obtained from IIUM Research Ethics Committee (IREC) and Malaysian Register of Ethics Committee (MREC). MREC approval number : NMR-18-3354-44577 was obtained on 4th March, 2019.

3.5 CONFIDENTIALITY

The information collected from this thesis project was kept with confidentiality. Subject's name was not shown in the data collection. Instead, identification numbers were used in data collection. Only the primary investigator and researchers who collected the data knew the ID numbers and information of each subject. Subjects were not be allowed to view their personal data, as the data were consolidated into database.

Publication of the study results will be done without revealing the personal information of the subject.