PRIMARY TUMOUR LOCATION AS A PROGNOSTIC FACTOR FOR SURVIVAL IN NEUROENDOCRINE TUMOUR IN HUSM : 10 YEARS REVIEW

BY

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Thank you!

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

Neuroendocrine tumour	NET
Gastroenteropancreatic neuroendocrine tumour	GPNET
Histopathological examinations	HPE
Computed tomography	CT
Gastrointestinal tract	GIT
5-hydroxyindoleacetic acid	5-HIAA
Magnetic resonance imaging	MRI
Endoscopic ultrasound	EUS
Somatostatin receptor scintigraphy	SRS
Positron emission tomography	PET
Fluorodeoxyglucose	FDG
Pancreatic polypeptide	PP
Chromogranin A	CgA
Peptide receptor radionuclide therapy	PRRT
Radiofrequency ablation	RFA

Trans-arterial embolization	TAE
Trans-arterial chemo-embolization	TACE
Selective internal radiation therapy	SIRT
World Health Organization	WHO

ABSTRAK

Latar belakang

Kes tumor neuroendocrine semakin meningkat dan jumlahnya berganda jika dibandingkan dengan dekad yang lalu. Tumor neuroendocrine biasanya hadir dengan pelbagai cara dan ini menyebabkan ia amat sukar untuk di diagnos. Pada masa ini, dengan kecanggihan teknologi yang baharu, tumor neuroendocrine lebih mudah untuk dikesan dan dirawat. Tumor neuroendocrine merangkumi spektrum penyakit yang boleh dirawat secara pembedahan atau bukan pembedahan. Ia selalu dikaitkan dengan pelbagai gejala dan tanda-tanda. Antara yang paling penting adalah sindrom 'carcinoid'. Tumor neuroendocrine juga boleh dikesan secara kebetulan semasa pemeriksaan rutin. Kebanyakan pesakit tumor neuroendocrine hadir pada tahap keempat dengan metastasis. Tumor neuroendocrine boleh dikesan dengan menggunakan serum 'chromogranin A'. Lokasi tumor neuroendocrine boleh dikesan menggunakan pengimejan seperti imbas CT, imbas MRI dan imbas PET. Adalah sangat mustahak untuk mengetahui lokasi tumor kerana prognosis dikaitkan dengannya.

Metodology

Rekod-rekod pesakit tumor neuroendocrine di Hospital Universiti Sains Malaysia dari Januari 2005 hingga Disember 2015 akan dikaji semula. Sejumlah 48 pesakit-pesakit yang memenuhi ciri-ciri kemasukan dan ciri-ciri pengecualian akan diambil untuk kajian ini. Senarai pesakit diambil dari pejabat rekod. Rekod pesakit akan dikaji dan data-data akan dimasukkan ke dalam borang koleksi. Data-data seperti umur, jantina, gejala-gejala, lokasi tumor, maklumat pembedahan, maklumat histopatologi, pengimejan, biomarker, tahap penyakit, dan hasil rawatan akan dianalisis.

Keputusan

Analisis kaitan antara data lokasi tumor dan prognosis akan dianalisis. Kaitan jangka masa hidup lima tahun bebas dari penyakit bagi pesakit akan dianggarkan menggunakan analisis Kaplan-Meier. Jangka masa hidup adalah tinggi bagi tumor di lokasi payudara (85 bulan) dan rendah di lokasi paru-paru dan pleura (9.7 bulan). Perbandingan adalah sangat jelas dan penting bagi semua lokasi tumor kecuali lokasi paru-paru, pleura dan pangkal rahim. Masa hidup median adalah tinggi pada lokasi tumor 'other' (30 bulan) dan rendah pada lokasi 'unknown' (7 bulan).

Kesimpulan

Kajian kami menunjukkan bahawa lokasi tumor adalah satu faktor prognosis yang penting bagi menentukan jangka masa hidup bagi pesakit-pesakit tumor neuroendocrine. Lokasi tumor di payudara, appendik dan usus besar mempunyai jangka masa hidup yang tinggi. Namun begitu, tumor di lokasi 'unknown' dan lokasi paru-paru dan pleura mempunyai jangka masa hidup yang rendah.

ABSTRACT

Background

Neuroendocrine tumour is on the rise. The incidents doubled compared to last decade. It presents with a variety of manifestations and sometimes become a challenge to diagnose. Currently, with the modern technology, neuroendocrine tumour (NET) can be detected and managed accordingly. Neuroendocrine tumour is a spectrum of disease which can be managed surgically or non-surgically. It is associated with wide range of symptoms and signs. The most important is the carcinoid syndrome. Sometimes, NETs are found incidentally during routine check-up and imaging. Most of the time, patients presented with evidence of metastasis (stage 4 disease). NETs can be detected using serum chromogranin A. Primary tumour localization can be found using imaging such as CT, MRI or PET scan. It is important to know the primary tumour localization as prognosis is associated with it.

Methodology

All patients who are diagnosed with neuroendocrine tumour in Hospital Universiti Sains Malaysia from January 2005 to December 2015 are retrospectively reviewed. A total of 48 patients who met the inclusions and exclusion criteria were enrolled for this study. List of the patients is obtained from record office. The medical records of patients that recruited in the study will be reviewed and the data will be entered into the data collection form. The data (age, gender, patient's symptoms, primary tumour location, surgical information, histopathological examination findings, imaging, biomarkers, stage of disease, and patient's outcome) will be analysed. Descriptive analysis will be done using mean and standard deviation for numerical variables and frequency and proportion for categorical variables.

Result

Association of primary tumour location and survival was analysed. Five-years disease free survival in NET according to primary tumor location estimated by Kaplan-Meier analysis. The survival rate was high in tumor in breast (85 months) and lower in lung and pleura (9.7 months). The comparisons were significant in all tumor location except in lung, pleura and cervix. The median survival time were high in other tumor location (30.0 months) and lower in unknown location (7.0 months).

Conclusion

Our study demonstrated that primary tumour location is a prognostic factor for survival in neuroendocrine tumour. Primary tumour location in breast, appendix and colorectal have better survival while NET with unknown primary tumour location and in lung or pleura have poor survival.

CHAPTER 1.0 – INTRODUCTION

1.1 – INTRODUCTION

Neuroendocrine tumour (NET) is a mass that begins in the parts of the body that produce and release hormones. Neuroendocrine tumours are rare tumours. However, there has been a steady increase in incidence and prevalence of neuroendocrine tumours over the last decade. Studies from United States and Europe have shown the that the disease is on the rise. This is possibly due to improved diagnostic modalities and greater awareness among surgeons.

It represents a group of neoplasms which developed from different endocrines cells in the body. Neuroendocrine tumours arise from enterochromaffin cells located throughout the body. Neuroendocrine tumours exhibit a wide spectrum of clinical behaviour ranging from indolent to highly aggressive and metastatic. Neuroendocrine tumour is always believed to be associated with carcinoid syndrome, but literatures have shown that it is not. Patients with carcinoid syndromes may presented with symptoms such as flushing, diarrhoea and epigastric pain.

Neuroendocrine tumours can be diagnosed clinically and using various methods such as biomarkers, imaging, endoscopy and histopathology. Biomarkers are important as it can give clinicians an index of suspicion in diagnosing neuroendocrine tumours. Histopathological examination is important to see the grading of the tumour as grading of neuroendocrine

tumours is associated with outcome of the patients. Imaging such as CT scan, MRI and PET scan can help determining the primary location of tumour and the location of tumour is thought to be an important prognostic value in NETs.

In general, neuroendocrine tumours are associated with poor outcome as they usually presented late and at late stage of disease. Moreover, there are several prognostic factors associated with the outcomes. Literatures have shown that factors such as age, primary tumour location, grades by histopathological examination, stages based on imaging, level of Chromogranin A and treatment received by patients.

1.2 – LITERATURE REVIEW

Incidence of NETs is increasing today. In United States alone, there has been a five-fold increase in the number of cases over the last 5 years. Modlin reported the incidence to be 2.5-5 per 100,000 per year (Modlin *et al.*, 2007). The prevalence has recently been calculated by Yao to be 35 per 100, 000 per year. In a paper by American Cancer Society in 2014, quoted that each year estimated 8,000 people in the United States are diagnosed with a neuroendocrine tumour (Yao *et al.*, 2008). Study in England demonstrated the incidence for small bowel neuroendocrine tumour is estimated to be from 0.32 per 100,000 per year. Meanwhile in Sweden estimated to be from 1.12 per 100,000 per year. Study by Neiderle done in Austria showed that the overall incidence was 2.39 per 100000 per year (Niederle *et al.*, 2010).

Neuroendocrine tumours can appear at any ages, the highest being from the fifth decade of life onwards. The exception is the carcinoid of the appendix, which occurs with the highest incidence at 40 years of age. Study by Yao in 2007 showed that there is a slight overall higher incidence of NETs for males (5.35) compared with females (4.76) (Yao *et al.*, 2008). In Malaysia, a study done showed that the mean age was 49 years (20–75) (Gunavathy *et al.*, 2014).

Oberndofer first described these tumours and used the term carcinoid (or "karzinoide") in 1907 (Creutzfeldt, 1996). In 1963 Williams and Sandler classified carcinoids according to embryogenetic aspects into: foregut (lung, stomach, duodenum, upper jejunum, and pancreas), midgut (lower jejunum, ileum, appendix, and cecum), hindgut (colon and rectum).

The first WHO classification of endocrine tumours, published in 1980, the term carcinoid was applied to most of the neuroendocrine tumours. The carcinoids were divided into: enterochromaffin (EC cell), gastrin (G cell), other unspecified carcinoids. In the year 2000, WHO came out with a new classification of NETs of the GIT: 1a – well differentiated neuroendocrine tumour, 1b - well differentiated neuroendocrine carcinoma, 2 - poorly differentiated neuroendocrine carcinoma.

Kloppel and Clemens claimed that the stomach as the most frequent location (22.8% of all GEP-NETs) (Klöppel, Perren and Heitz, 2004). This is contrast to studies by Modlin in 2003 describing NETs of the small intestine most frequently. In Malaysia, pancreatic NETs are the most common according to study by Gunavathy in 2014. NETs are characterized by their ability to produce peptides that cause characteristic hormonal syndromes. They are more indolent, however they can be aggressive and resistant to therapy. Kloppel again in 2004 demonstrated NETs in the stomach (67.7%), rectum (65%) and appendix (62.7%) were usually behaved as benign, those in the small intestine (86.4%), pancreas (75.8%) and colon (70.0%) were predominantly malignant (Klöppel, Perren and Heitz, 2004). Yao in 2007 found that disease stage, primary tumour site, histology, age, sex, race, and period of diagnosis were important predictors of outcome. Primary tumour site to be perhaps the most useful predictor of outcome in patients with NETs (Yao *et al.*, 2008).

NETs may present with variants of symptoms. Most patients are asymptomatic and the tumours are incidentally detected. Symptomatic patients may present with hormonal excess, mass effect (e.g. abdominal pain, jaundice, vomiting) due to the primary tumour or metastasis. Some tumours don't overproduce hormones and not causing symptoms. These are known as non-functioning NETs. Diagnosis of NETs is difficult. Some patients are treated

for different diagnosis first before discovering NETs. This is because the variability of presentation and lack of awareness. Clinically “functioning” tumours are detected earlier because the secreted hormones produce recognizable symptoms such as flushing and the carcinoid syndrome. “Non-functioning” tumours are less likely to be detected unless found incidentally or when the primary or metastatic lesion have grown large enough to cause mass effects.

NETs can be diagnosed using various methods such as biomarkers, imaging, endoscopy and histopathology. Pathological diagnosis is based on histo-morphology, aided by immuno-histochemistry. The histo-morphology of the tumour shows uniform cells with a wide range of arrangement, including polygonal cell nests, ribbons, glands and isolated cell clusters. The histological grading is based on mitotic count and Ki-67 activity. Turaga in 2011 stated that the grade of tumour relates to its aggressiveness (Turaga and Kvols, 2011). Study by Rindi, Hotta, Moyana, and Chaudry claimed that Ki-67 proliferative index (Ki-67 index) has been suggested to be useful in predicting the metastatic potential of GI-NETs and survival of patients with GI-NETs (Rindi *et al.*, 1999; Moyana *et al.*, 2000; Hotta *et al.*, 2006).

NETs are a challenge to diagnose, stage and treat. A multidisciplinary expertise is needed. There should be a multidisciplinary collaborative effort involving gastroenterologists, endocrinologists, surgeons, oncologists, pathologists, and interventional radiologists. The challenges in managing NETs are variable and unclear natural history of the disease, inability to determine the behaviour of the tumour and lack of awareness among doctors (Phan *et al.*, 2010). Before treatment can be initiated, the extent of tumour, presence of metastases and secretory profile should be determined.

The aim of treatment in metastasized disease is to maintain a good quality of life, and at the same time control the symptoms and tumour growth. Liang Tao in 2016 claimed that prognosis depends on mitotic rates and functional status correlates strongly with survival (Ye *et al.*, 2016). According to Yao et al, survival can, however, vary widely across specific types of NETs. Median 5-year survival for patients with GI NETs with distant metastases range from 5 months for colon tumours to 56 months for small bowel tumours. Yao also claimed that metastatic pancreatic NETs are considerably more malignant, with a median 5-year survival of only 23 months among patients with distant metastasis (Yao *et al.*, 2008). Modlin stated that to improve outcome from NETs, a better understanding of their biology is needed, with emphasis on molecular genetics and disease modelling. More-reliable serum markers, better tumour localization and identification of small lesions, and histological grading systems and classifications with prognostic application are needed (Modlin *et al.*, 2007).

1.3 – RATIONALE FOR THE STUDY

Neuroendocrine tumour incidence is rising now with the development of new technology in detecting the disease. New kind of investigations and imaging helped in detecting the disease. The awareness among surgeon also contributed in the rise of the incidence.

The epidemiology of NET in Malaysia are not well documented maybe because it is very rare. There are no local studies was done regarding the prognostic factors for neuroendocrine tumour. Furthermore, there is no epidemiological data regarding neuroendocrine tumour in our institution. The study can tell us the epidemiology of NET in our own institution.

Imaging is needed in finding the primary tumour location. Studies showed that primary tumour location is an important factor determining the prognosis of patients with neuroendocrine tumour. The study will see the association of primary tumour location with the prognosis of patient in term of present of metastasis and disease free survival. We can help to stratify patient and help in term of management and prognosis.

Survival rate, disease free progression and life expectancy can be estimated in all NET patients. From this, we can ideally plan the management and follow up of NET patients. From the study, hopefully we can better treat our neuroendocrine tumour patients. The study will also indirectly help our oncologist in deciding their managements.

CHAPTER 2.0 - STUDY PROTOCOL

2.1 DOCUMENT SUBMITTED FOR ETHICAL APPROVAL

RESEARCH PROPOSAL

Primary Tumour Location As A Prognostic Factor For Survival in Neuroendocrine Tumour in HUSM: 10 Years Review

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1-TITLE:

1-a-Primary Tumour Location As A Prognostic Factor For Survival in Neuroendocrine Tumour in HUSM: 10 Year Review

1-b-This study is a retrospective study to see the association between primary tumour location and prognosis of patient with neuroendocrine tumour. This study involves all patients who are diagnosed with neuroendocrine tumour in Hospital Universiti Sains Malaysia. The patients involving in this study are screened with our inclusions and exclusion criteria. List of patients diagnosed with neuroendocrine tumour from January 2005 to December 2015 is obtained from record office. The medical records of patients that recruited in the study will be reviewed and the data will be entered into the data collection form. The data will be analysed. The study will analysed the association of the primary tumour location with the clinical symptoms and signs, biochemical markers, nodal status, metastasis status, and survival of patient in neuroendocrine tumour. The literature review of studies done before relating to this topic have produced similar results.

2-a-Introduction

Neuroendocrine tumour (NET) is a mass that begins in the parts of the body that produce and release hormones. NETs are rare tumours. However, there has been a steady increase in incidence and prevalence of NETs over the last decade. This is possibly due to improved diagnostic modalities and greater awareness among surgeons. It represents a group of neoplasm which are develop from different endocrines cells in the body. NETs arise from enterochromaffin cells located throughout the body. NETs exhibit a wide spectrum of clinical behaviour ranging from indolent to highly aggressive and metastatic. NETs can be diagnosed clinically and using various methods such as biomarkers, imaging, endoscopy and histopathology. Histopathological diagnosis is important to see the grading of the tumour. Imaging can help determining the primary location of tumour and the location of tumour is thought to be an important prognostic value in NETs.

2-b-Literature review

Incidence of NETs is increasing today. In United States alone, there has been a five-fold increase in the number of cases over the last 5 years. Modlin reported the incidence to be 2.5-5 per 100,000 per year (Modlin, 2007). The prevalence has recently been calculated by Yao to be 35 per 100, 000 per year (Yao *et al.,* 2008). In a paper by American Cancer Society in 2014, quoted that each year estimated 8,000 people in the United States are diagnosed with a neuroendocrine tumour. Study in England demonstrated the incidence for small bowel neuroendocrine tumour is estimated to be from 0.32 per 100,000 per year. Meanwhile in Sweden estimated to be from 1.12 per 100,000 per year (Hemminki and Li, 2001). Study by Neiderle done in Austria showed that the overall incidence was 2.39 per 100000 per year (Niederle *et al*., 2010). Neuroendocrine tumours can appear at any ages, the highest being from the fifth decade of life onwards. The exception is the carcinoid of the appendix, which occurs with the highest incidence at 40 years of age. Study by Yao in 2007 showed that there is a slight overall higher incidence of NETs for males (5.35) compared with females (4.76). In Malaysia, a study done showed that the mean age was 49 years (20–75) (Gunavathy et al., 2014). Oberndofer first described these tumours and used the term carcinoid (or "karzinoide") in 1907 (Oberndorfer, 1907). In 1963 Williams and Sandler classified carcinoids according to embryogenetic aspects into: foregut (lung, stomach, duodenum, upper jejunum, and pancreas), midgut (lower jejunum, ileum, appendix, and cecum), hindgut (colon and rectum) (Williams and Sandler, 2017). The first WHO classification of endocrine tumours, published in 1980, the term carcinoid was applied to most of the neuroendocrine tumours. The carcinoids were divided into: enterochromaffin (EC cell), gastrin (G cell), other unspecified carcinoids. In the year 2000, WHO came out with a new classification of NETs of the GIT: 1a – well differentiated neuroendocrine tumour, 1b - well differentiated neuroendocrine carcinoma, 2 - poorly differentiated neuroendocrine carcinoma. Kloppel claimed that the stomach as the most frequent location (22.8% of all GEP-NETs) (Klöppel, Perren and Heitz, 2004). This is contrast to studies by Modlin in 2003 describing NETs of the small intestine most frequently. In Malaysia, pancreatic NETs are the most common according to study by Gunavathy in 2014. NETs are characterized by their ability to produce peptides that cause characteristic hormonal syndromes. They are more indolent, however they can be aggressive and resistant to therapy. Kloppel again in 2004 demonstrated NETs in the stomach (67.7%), rectum (65%) and appendix (62.7%) were usually behaved as benign, those in the small intestine (86.4%), pancreas (75.8%) and colon (70.0%) were predominantly

malignant. Yao in 2008 found that disease stage, primary tumour site, histology, age, sex, race, and period of diagnosis were important predictors of outcome. Primary tumour site to be perhaps the most useful predictor of outcome in patients with NETs (Yao *et al.,* 2008). NETs may present with variants of symptoms. Most patients are asymptomatic and the tumours are incidentally detected (de Miguel Novoa *et al.*, 2014). Symptomatic patients may present with hormonal excess, mass effect (e.g. abdominal pain, jaundice, vomiting) due to the primary tumour or metastasis. Some tumours don't overproduce hormones and not causing symptoms. These are known as non-functioning NETs. Diagnosis of NETs is difficult. Some patients are treated for different diagnosis first before discovering NETs. This is because the variability of presentation and lack of awareness. Clinically "functioning" tumours are detected earlier because the secreted hormones produce recognizable symptoms such as flushing and the carcinoid syndrome. "Non-functioning" tumours are less likely to be detected unless found incidentally or when the primary or metastatic lesion have grown large enough to cause mass effects. NETs can be diagnosed using various methods such as biomarkers, imaging, endoscopy and histopathology. Pathological diagnosis is based on histo-morphology, aided by immune-histochemistry. The histo-morphology of the tumour shows uniform cells with a wide range of arrangement, including polygonal cell nests, ribbons, glands and isolated cell clusters. The histological grading is based on mitotic count and Ki-67 activity. Turaga in 2011 stated that the grade of tumour relates to its aggressiveness (Turaga, 2011).

Grade	Mitotic count per 10hpf	Ki-67 index
G1	<2	<2%
G2	2-20	3-20%
G3	>20	>20%

Study by Rindi, Hotta and Moyana claimed that Ki-67 proliferative index (Ki-67 index) has been suggested to be useful in predicting the metastatic potential of GI-NETs and survival of patients with GI-NETs (Rindi,1999; Hotta, 2006; Moyana, 2000). NETs are a challenge to diagnose, stage and treat. A multidisciplinary expertise is needed. There should be a multidisciplinary collaborative effort involving gastroenterologists, endocrinologists, surgeons, oncologists, pathologists, and interventional radiologists. The challenges in

managing NETs are variable and unclear natural history of the disease, inability to determine the behaviour of the tumour and lack of awareness among doctors. Before treatment can be initiated, the extent of tumour, presence of metastases and secretory profile should be determined. The aim of treatment in metastasized disease is to maintain a good quality of life, and at the same time control the symptoms and tumour growth. Ye in 2016 claimed that prognosis depends on mitotic rates and functional status correlates strongly with survival (Ye et al., 2016). According to Yao et al, survival can, however, vary widely across specific types of NETs. Median 5-year survival for patients with GI NETs with distant metastases range from 5 months for colon tumours to 56 months for small bowel tumours. Yao also claimed that metastatic pancreatic NETs are considerably more malignant, with a median 5-year survival of only 23 months among patients with distant metastasis (Yao *et al.*, 2008). Modlin stated that to improve outcome from NETs, a better understanding of their biology is needed, with emphasis on molecular genetics and disease modelling. More-reliable serum markers, better tumour localization and identification of small lesions, and histological grading systems and classifications with prognostic application are needed.

2-c-Problem statement & rationale of studies.

Incidence NETs is increasing today even it is still a rare disease. However, the disease is difficult to detect. Surgeons and physicians having the difficulties to diagnose and even to treat the disease. These are due to the variable way of presentation of NETs. Most of the patient presented late and presented with a metastasized disease. The epidemiology of NET in Malaysia are not well documented maybe because it is very rare. So far in Kelantan, there is no paper or article about the epidemiology of NET in this region. By performing this study, we can obtain the epidemiology for our own institution. Neuroendocrine tumour can occur in anywhere in the body. Imaging are required to locate the primary tumour location in most of the cases. Several studies have showed that primary tumour location is an important factor determining the prognosis of patients with neuroendocrine tumour. The study will see the association of primary tumour location with the prognosis of patient in term of present of metastasis and disease free survival. From this study, we can help to stratify patient and help in term of management and prognosis. Survival rate, disease free progression and life expectancy can be estimated in all NET patients. From this, we can ideally plan the

management and follow up of NET patients. Hopefully, this study will also help the oncology team in deciding their managements.

2-d-Objectives

General objective

- To study the correlation of the primary tumor location with the prognosis in neuroendocrine tumors in Hospital University Sains Malaysia (HUSM).

Specific objectives

- First specific objective: To determine the epidemiology of neuroendocrine tumor in HUSM.
- Second specific objective: To determine the association of primary tumor location with the present of metastasis.
- Third specific objective: To determine the relation of primary tumor location with 5years disease free survival in NETs.

3-Research Methodology

3-a Trial Design

- This is a retrospective record review involving patient diagnosed with neuroendocrine tumour in HUSM.

4-a Study population

4-a-i Reference population

- All patients in Hospital Universiti Sains Malaysia

4-a-ii Source population

- All patients diagnosed to have Neuroendocrine Tumor in Hospital Universiti Sains Malaysia.

4-a-iii Inclusion criteria

- All patients who have been diagnosed neuroendocrine tumor with established primary tumor location in Hospital University Sains Malaysia.

4-a-iv Exclusion criteria

- All patients who have been diagnosed neuroendocrine tumor but without known histopathological examination result
- Incomplete documentation of patient's case note
- Patient with NET with concomitant other malignancy

4-b Study settings

4-b-i Study Location

- Hospital Universiti Sains Malaysia

4-b-ii Study Duration

- The study includes all patients who diagnosed with NET from January 2005 to December 2015. The data collection will be started after ethical approval.

5-Sampling size.

5-a-i Sample size determination

The sample size was determined by Two Mean formula by using PS Power and Sample Size Calculation software Version 3.0.10 according to study by Schoenfeld & Richter (1982)

Type 1 error (a)	0.05
Power	0.8
Median survival time on control in months (m1)	15
Median survival time on experimental in months (m2)	6
Accrual time in which patient are recruited in months (A)	120
Additional follow up time after end of recruitment in months (F)	60
Ratio of control to experiment patient (m)	1

Sample size experiment: 19

Sample size control: 19

Total sample size: 38

6-Research Tool

After ethical approval, a list of patients who diagnosed with Neuroendocrine Tumor in between January 2005 to December 2015 will be obtained from the record in the record office. Patients who fulfilled the inclusion and exclusion criteria will be recruited in the study. The data of patients will be obtained by retrospective review of patient's medical records. The data will be entered in a data collection form.

7-Data collection

Data collection will be recorded in a data collection form. The following information was recorded: patient's demographic, patient's presentations, primary tumour location, operative information, histopathological examinations (HPE) reports, patient's grading and staging, and patient's current status**.**

8-Proposed data analysis

Data entry and analysis will be done by using SPSS version 22. Descriptive analysis will be done using mean and standard deviation for numerical variables and frequency and proportion for categorical variables.

Each specific objective will be analysed using different methods: Sample Size Calculation v1.7.1 by Dr Wan Nor Arifin, available at medic.usm.my.

. Kaplan-Meier plot

. Log rank test

. Cox proportional hazard regression

9-Ethical Issues

1. **Declaration of Conflict of Interest**.

   There is no conflict of interest in this study.

2. **Handling Privacy and Confidentiality Issues**

   Throughout this study, all personal information and data will not be disclosed unless required by law. Subject's confidentiality will be protected; no name or identifiable information will be collected. Data will be protected through password setting to access the database and securely locked. The data is only accessible by researchers involve in this study. The data will be used and remain directly available up to completion of the study. Thereafter, the data will be compressed with encryption and archived in a flash drive after proper documentation. This is to be destroyed by formatting the flash drive after a 5- years maintenance period determined by the date of its formal closure. We define the formal 15 closure as the submission of a closure report to the National Medical Research Registry of Malaysia. Subject's data and information will be kept confidential and will be known by research team only. Only aggregated (grouped) results will be presented and submitted to local or international peer-reviewed medical journals and relevant government ministries.

3. **Publication and Presentation**

   The data and results from this study will be presented either in poster format or published in any upcoming conference without revealing any subjects' private information.

4. **Community Benefits**

   Hopefully the information and the result from this study can be beneficial for the researcher to evaluate regarding management of neuroendocrine tumor and will enable us to formulate steps that can enhance the quality of service given by health

facilities in the future.

10-Flow chart

List of patients diagnosed with NETs from January 2005 to December 2015 is obtained from record office.

↓

Recruitment of patients who fulfilling the inclusion and exclusion criteria

↓

Review of medical records of patients that recruited in the study

↓

Data from medical records entered in the data collection form

↓

Data collection and statistical analysis

↓

Report and manuscript write up

↓

Submission

11-Gantt chart

	Task	S	O	N	D	J	F	M	A	M	J	J	A	S	0	N	D
1	Department presentation	✓															
2	Research Proposal	✓	✓														
3	Ethical Meeting			✓	✓	✓											
4	Discussion with supervisor	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5	Data Collection						✓	✓	✓	✓							
6	Data Analysis								✓	✓	✓	✓					
7	Report Preparation									✓	✓	✓	✓	✓			
8	Submission of draft													✓	✓		
9	Research Revision														✓	✓	
10	Submission of final research														✓	✓	✓

Data Collection Form Sample No:____

Demographic :

Age :_____ Sex: M/ F Ethnic:_____

Patients first presentation :

Patient's symptoms : Carcinoid/Mass effect/Incidental

Duration of symptoms : _____

Surgery : Yes / No

Date of surgery: _____

Surgeon : _____

Indication for surgery: _____

Surgical procedure :_____

Biopsy/HPE: Yes / No

Tumour Size : ___

Type : _____

Tumour location : _____

Histopathological diagnosis: _____

Imaging : Yes / No

Type of Imaging : _____

Site of Tumour: _____

Lymph node involvement : Yes / No

Metastasis: Regional/Distant

Stage : 1 / 2/ 3/ 4

Biomarkers : Yes /No

Serum CgA : _____

Others : _____

Final Diagnosis :_____

Patient status : Alive/ Death

Date of death : _____

Disease recurrence: Yes/ No

Complications : Yes / No

Chemotherapy : Yes / No

Radiotherapy : Yes / No

Follow up : Yes/No

Follow up duration : _____

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