



NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF BIOMEDICAL ENGINEERING

EVALUATION OF CARCINOID TUMOR TREATMENT OPTIONS

USING MULTI-CRITERIA DECISION MAKING (MCDM)

M.Sc. THESIS

Declan Ikechukwu EMEGANO

Nicosia

August, 2022

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MASTER THESIS

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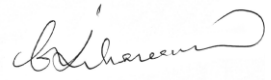


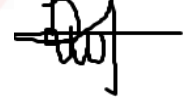

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Approval page

We certify that we have read the thesis submitted by Declan Ikechukwu EMEGANO titled **“EVALUATION OF CARCINOID TUMOR TREATMENT OPTIONS USING MULTI-CRITERIA DECISION MAKING (MCDM)”** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

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Acknowledgments

My special regards go to Assoc. Prof. Dr. Dilber Uzun ÖZŞAHİN and Assist. Prof. Dr. Berna Uzun who devoted their talents and efforts in order for me to acquire excellent skills as supervisors and in writing of this thesis.

My special regards to my wife -Mrs Chinonye Lynda Okpala Emegano and my entire family for their prayers, financial and moral support.

I also thank my course mate Efe Precious, Natacha Usanase, and Dr Mubarak Taiwo as well as Dr Abdullahi Usman for being there for me during this academic pursuit. I also in a special way express my appreciation to Basil Duwa for his incessant cares.

Declan Ikechukwu Emegano

Abstract

Title of the Thesis

Evaluation of Carcinoid Tumor Treatment Options using Multi-Criteria Decision Making (MCDM)

Carcinoid tumor is a neuroendocrine malignancy, which grows from cells of neuroendocrine system. These cells receive and transmit hormonal-mediated information to aid in the biological process. Neuroendocrine cells can be found in all organs of the body and they frequently grow slowly. The objective of this study is to evaluate carcinoid tumors treatment option using fuzzy Preference Ranking Organization Method for Enrichment Evaluation (PROMETHEE)-a multicriteria decision making (MCDM) tool. The PROMETHEE evaluates several alternatives according to multiple criteria. The alternatives were: endoscopic resection, resection, local excision, radiofrequency ablation, radioimmunotherapy, cryosurgery, adjuvant therapy, hormone therapy, embolism, chemo embolism, targeted therapy, radiotherapy, and chemotherapy. The alternatives were evaluated according to these criteria: 5-years survival rate (%), follow-up duration, side effects, cost of treatment, treatment duration, radiation amount (mSv), infection rate, bleeding risk, pain level, and anesthesia usage. Carcinoid tumours are treated according to the severity of the malignancy from very high carcinoid to very low carcinoid. Based on the applied parameters the results show; the high carcinoid treatment alternatives ranked as endoscopic resection, resection, local excision, and cryosurgery with net flows of 0.1730, 0.1280, 0.0811 and -0.3821 respectively. The moderate carcinoid is ranked as radiofrequency ablation, radiotherapy, hormone therapy and targeted therapy with net flows of 0.1943, -0.0216, -0.0601, and -0.1127. However, low carcinoid treatment alternatives are ranked as chemotherapy and embolism with net flow of 0.1126 and -0.1126. Finally, the applied parameters show that very low-grade carcinoids treatment alternative were ranked as adjuvant therapy, radioimmunotherapy, and chemo embolism with 0.1472, 0.1163, and -0.2637 as net flows. The results from this study show that carcinoid tumours treatment option are treated according to the severity of the malignancy from very high carcinoid to very low carcinoid using support from MCDM models.

Emegano, Declan Ikechukwu

MSc, Department of Biomedical Engineering

August,2022, (48) pages

Key Words: carcinoid tumors, treatment options; gastrointestinal; hormones; neuroendocrine neoplasm; fuzzy PROMETHEE, decision making.

Özet

Karsinoid tümör, nöroendokrin sistem hücrelerinden gelişen bir nöroendokrin malignitedir. Bu hücreler, biyolojik sürece yardımcı olmak için hormonal aracılı bilgileri alır ve iletir. Nöroendokrin hücreler vücudun tüm organlarında bulunabilir ve sıklıkla yavaş büyürler. Bu çalışmanın amacı, çok kriterli bir karar verme (ÇKKV) aracı olan Zenginleştirme Değerlendirmesi için Organizasyon Yöntemi Tercih Sıralaması (PROMETHEE) kullanarak karsinoid tümör tedavi seçeneğini değerlendirmektir. ÇKKV, çeşitli alternatifleri birden fazla kritere göre değerlendirmektedir. Alternatifler şunlardır: endoskopik rezeksiyon, rezeksiyon, lokal eksizyon, radyofrekans ablasyon, radyoimmünoterapi, kriyocerrahi, adjuvan tedavi, hormon tedavisi, emboli, kemo emboli, hedefe yönelik tedavi, radyoterapi ve kemoterapi. Alternatifler şu kriterlere göre değerlendirilmiştir: 5 yıllık sağkalım oranı (%), takip süresi, yan etkiler, tedavi maliyeti, tedavi süresi, radyasyon miktarı (mSv), enfeksiyon oranı, kanama riski, ağrı düzeyi ve anestezi kullanımı. Karsinoid tümör, çok yüksek karsinoidden çok düşük karsinoide kadar malignitenin şiddetine göre tedavi edilmektedir. Uygulanan parametrelere dayanarak sonuçlar göstermektedir ki; yüksek karsinoid tedavi alternatifleri sırasıyla 0.1730, 0.1280, 0.0811 ve -0.3821 net akışlarla endoskopik rezeksiyon, rezeksiyon, lokal eksizyon ve kriyocerrahi olarak sıralanmaktadır. Orta dereceli karsinoid tedavisi 0.1943, -0.0216, -0.0601 ve -0.1127 net akış ile radyofrekans ablasyon, radyoterapi, hormon tedavisi ve hedefe yönelik tedavi olarak sıralanmaktadır. Bununla birlikte, düşük karsinoid tedavi alternatifleri 0,1126 ve -0,1126'lık net üstünlük ile kemoterapi ve emboli olarak sıralanmaktadır. Son olarak, uygulanan parametreler çok düşük dereceli karsinoid tedavi alternatiflerinin 0,1472, 0,1163 ve -0,2637 net akış ile adjuvan tedavi, radyoimmünoterapi ve kemo emboli olarak sıralandığını göstermektedir. Bu çalışmadan elde edilen sonuçlar, karsinoid tümörlerin, MCDM modellerinden destek alınarak çok yüksek karsinoidden çok düşük karsinoide kadar malignitenin şiddetine göre tedavi seçeneklerinin değerlendirilebileceğini göstermektedir.

Çok Kriterli Karar Verme (MCDM) kullanılarak Karsinoid Tümör Tedavi Seçeneklerinin Değerlendirilmesi

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Biyomedikal Mühendisliği Yüksek Lisans Bölümü

2022, 4 sayfa

Anahtar Kelimeler: karsinoid tümörler, tedavi seçenekleri; mide-bağırsak; hormonlar; nöroendokrin neoplazmi; bulanık PROMETHEE, karar verme.

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List of Abbreviations

WHO	World health organization
NETs	Neuroendocrine tumours
MEN1	Multiple endocrine neoplasma
ACTH	Adrenocorticotropic Hormone
NEC	Neuroendocrine carcinoma
TRACE	Trance arterial chemo embolism
MSV	Milisieverts
BPNET	Bronchopulmonary neuroendocrine tumours
MCDM	Multi-criteria decision making
PROMETHEE	Preference Ranking Organization Method for Enrichment Evaluation
GIT	Gastrointestinal tract
NENs	Neuroendocrine neoplasm
CAG-A	Chronic atrophic gastritis
G1	Well differentiated
G2	Endocrine carcinoma
G3	Poorly differentiated
ELECTRE	Elimination Choice Expressing Reality
HRQOL	Health related quality of life
ML	Machine learning

SVM	Support vector machine
KNN	Nearest Neighbor
SMART	Simple multi attribute rating technique
DAE	Data envelopment analysis
5HIAA	5hydroxyindoacetic acid
TOPSIS	Technique for order performance by similarity to ideal solution
SCLC	Small cell lung carcinoma
LCNEC	large cell neuroendocrine carcinoma
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumors
G.Fn	Gaussian function
ANP	Analytical Network Process
AHP	Analytical Hierarchy Process
(RBRB)	Relative Benefit Risk balance
IFN	Interferons
5HTP	5hydroxytryptophan
CHD	Carcinoid Heart Disease
PCTS	Polycystic Ovary Syndrome
MCDA	Multicriteria decision Analysis

Chapter 1

Introduction

Carcinoid tumours are slow growing malignancies that arises from different places in the body. Carcinoid tumours grow anywhere in one's body, especially where hormone-producing molecules are present, and they can develop into tumors. Hormones are the natural chemicals that transmit messages. These messages travel via the blood and evaluate the body's functional status. There are a lot of carcinoid tumours that grow in the gastrointestinal tract (Rakha & Tan, 2022), (Dermawan and Farver 2019). Carcinoid tumours are also called neuroendocrine (NETs) tumours, group of malignancies with variety of clinical characteristics. Tumors come from the neuroendocrine cells that are found all over the body. NET is predominant in the lungs and gastrointestinal track (GIT). Most tumours are harmless, but some, particularly those that are not well-differentiated, can be dangerous. A total of 10 percent of sick people have fully functioning tumors, which means they produce hormones, particularly when the illness has spread. NETs have somatostatin receptor sites, which are used to diagnose and treat these tumours (Mathew, Sainulabdeen, and Parameswaran 2022). People with carcinoid tumours often have them for a long time. This tumour is prevalent in the appendix in young adults and children. They are frequently referred to as appendiceal carcinoid tumours or bronchial tumours if they are found in the lungs. In adult humans, carcinoid tumours most often reside in the intestinal tract, but they can be found anywhere. If this tumour grows, its metastasis reaches other body parts. Adults are more likely in risk than children (Sushma, Prasad, and Kumar 2016). United States of America for instance has almost 12,000 people annually with NETs. About 175,000 people are living with this malignancy on a daily basis around the world. The number of people that have this form of tumour are on the rise for ages (Dasari et al., 2017). Carcinoid tumours are the world's most common tumours in the tracheobronchial tree. They make up 2–5% of all lung tumours (Zheng, 2016). When the tumour secretes certain chemicals into the bloodstream, it results in carcinoid syndrome. Carcinoid syndrome may be more common than thought because it can be hard to diagnose and sometimes it is asymptomatic. A few patients display flushing, whizzing sounds during breathing and diarrhoea as major symptoms (Carcinoid Syndrome - National Organization for Rare Disorders (NORD) n.d.) which gets worse during stressful exercises, or allergic reactions to food and drinks (Gade et al., 2020).

1.1. Thesis problem

- In 2021, 48% of cancer deaths were attributed to carcinoids (Derks et al., 2021). This makes it the leading cause of death globally. Therefore, effective management is very vital.
- Cancer has no cure, but treatment alternatives are very necessary, especially to prolong the life span of the patient beyond five years.

1.2. Aim of the study

- To evaluate the carcinoid tumor so as to find the best treatment alternative using multicriteria decision making.
- To simulate the PROMETHEE results in order get the best treatment alternative to support doctors and patients
- To determine the degree of satisfaction over effective and to understand the features of the carcinoid treatment options in detail

1.3. Significance of study

- This study will help clinicians make best clinical decisions for treating patients with carcinoid tumor.
- The study will help the patient and their relatives to choose the effective therapeutic techniques and assure them of a longer life span.
- The findings will provide a net ranking of alternatives based on different criteria and importance weights of the criteria.

1.4. Limitations

- The study utilizes data from the literature review.
- The specialist's opinion on the weight varies.
- The study is limited with the selected criteria but it can simply be updated based on the specific conditions of the patients

1.5. Overview

Chapter 1 has the introductory aspect of the research. Chapter 2 summarizes carcinoid classification, and common symptoms, prevention methods. Chapter 3 contains literature review and its related studies relevant to present study. Chapter 4 discusses treatment techniques of each alternative were analyzed. Chapter 5 discusses result of the analysis carried out. Chapter 6 concludes and discusses the study.

1.6. Overview of carcinoid

Carcinoid tumours are malignancies emanating from neuroendocrine which grows from neuroendocrine cells inside the body (Cives et al. 2019). They are second in number (20-30%) among the most prevalent small intestine cancers (Vusqa et al. 2020). In the 19th century, Lubarsch described the carcinoid tumour (Kabir, Raza, and Kabir 2019) and its incidence increased by more than fourfold between 1973 and 2004 (Bilimoria et al. 2009). This could be as a result of improved diagnostic accuracy in emerging cases. Over the last 30 years, the overall frequency of carcinoid tumours has grown, owing in part to advancements in diagnosis. The incidence has ranged between 2.47 and 4.48 per 100,000 people during the last decade, based on racial category and sex, with black men having the highest rates. The sites of carcinoid tumours (CT) are the small intestine, bronchi,

appendix, rectum, stomach, and appendix. About 68% of carcinoid malignancies are found in the gastrointestinal tract. (Kinney et al. 2020). Carcinoid tumours have no known origin, though genetically certain factors have a vital role. The malignancy lacks the enzyme responsible for the conversion of 5-hydroxytryptophan (5-HTP) to serotone. Tumors of the midgut do not secrete 5-hydroxytryptophan or serotonin, whereas the majority of hindgut tumours do. Different patterns of secretion cause this malignancy to have different clinical symptoms and biochemical traits. According to (Oberndorfer, 1907), GIT neuroendocrine tumours arises from enterochromaffin cells. They are known as amine precursor (apudoma) for uptake as well as decarboxylation (Mattos, Johnson, and Piccione 2021).

Meanwhile, WHO classifies all cancerous tumours from neuroendocrine as neuroendocrine neoplasms (NENs). (Clement et al., 2020a) and neuroendocrine tumours (NETs) (Fottner, Ferrata, and Weber 2017). NETs release several classes of symptomatic physiological active chemicals. Nets start in neuroendocrine cells (Hofland, Zandee, and de Herder 2018) secreting variety of polypeptide proteins. The diagnostic symptoms include increased bowel movements, bronchospasms, and vasoactive flushes. Other symptoms include alteration of the fibrous cells in the mesentery of the heart (Hofland et al. 2019a), (Rubin de Celis Ferrari, Glasberg, and Riechelmann 2018a).

1.7. Incidence of Neuroendocrine Neoplasms (NEN)

Latest report from the United Kingdom reveals a comparable incidence rate of 8.6 per 100,000 people (Clement et al.,2020) . In Asia there are 2.2 cases per 100,000 people (Lim et al. 2017). Australia has 4,228 new cases, 2,252 males and 1,975 females (neuroendocrine tumours statistics and cancer in Australia.). African has a total of 1.5-1.9 person diagnosed with this malignancy per 100,000 persons (carcinoid malignancy: practice e.b.p n.d.). In Turkey, 25 cases detected after 4,642 appendectomies were performed in hospitals, 13 males and 12 females were having carcinoid malignancy (Yavuz and Sentürk, 2020). Recently, NETs were recognized as aggressive tumours. 13% to 34% from the small intestine are benign while 17% to 46% are malignant (Dasari et al. 2017). Using United States of America as a research study, the prevalence was originally predicted to be 1.5 occurrences in 100 000 people but has increased to 3,201 both male and female inclusive. (Ali et al., 2021).

1.8. Carcinoid syndrome

When a rare malignant tumour secretes particular chemicals into the bloodstream, it causes a variety of indications and symptoms (Hameed et al., 2021). The clinical consequences of these bioactive chemicals released by carcinoid tumours create carcinoid syndrome. These symptoms include bronchospasm as a result bradykinin secretion, diarrhoea is caused by serotonin metabolites, cutaneous flushing has several mediators, and valvular abnormalities of the right side are mediated by serotonin (Bardasi et al. 2022; Carcinoid Syndrome - NETRF n.d.; Rubin de Celis Ferrari, Glasberg, and Riechelmann 2018b) (Ratnayake et al. 2022) .

Carcinoid syndrome

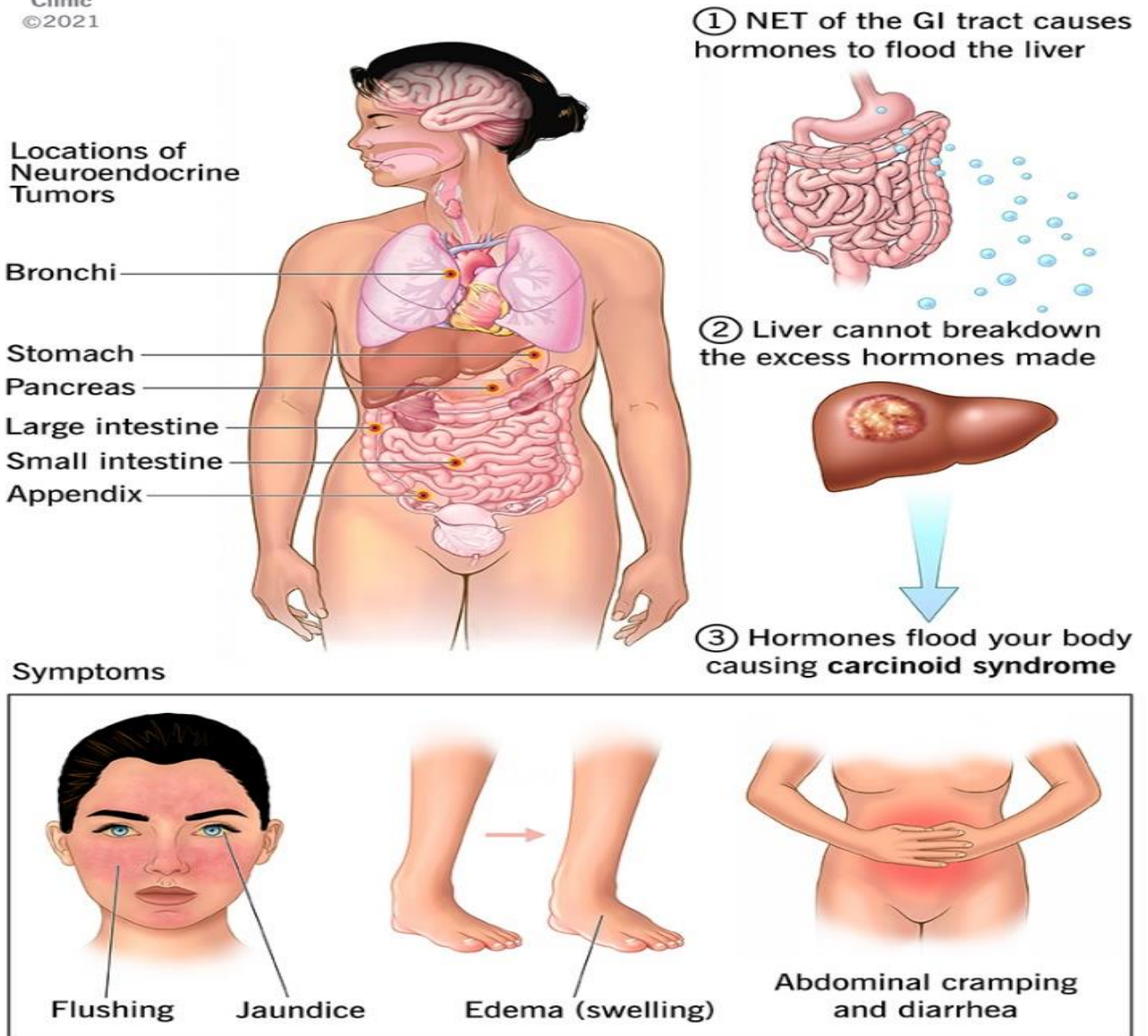


Figure 1: Carcinoid syndrome and organ affected with hormonal secretions. (Carcinoid Syndrome: Symptoms, Treatment & What It Is n.d.)

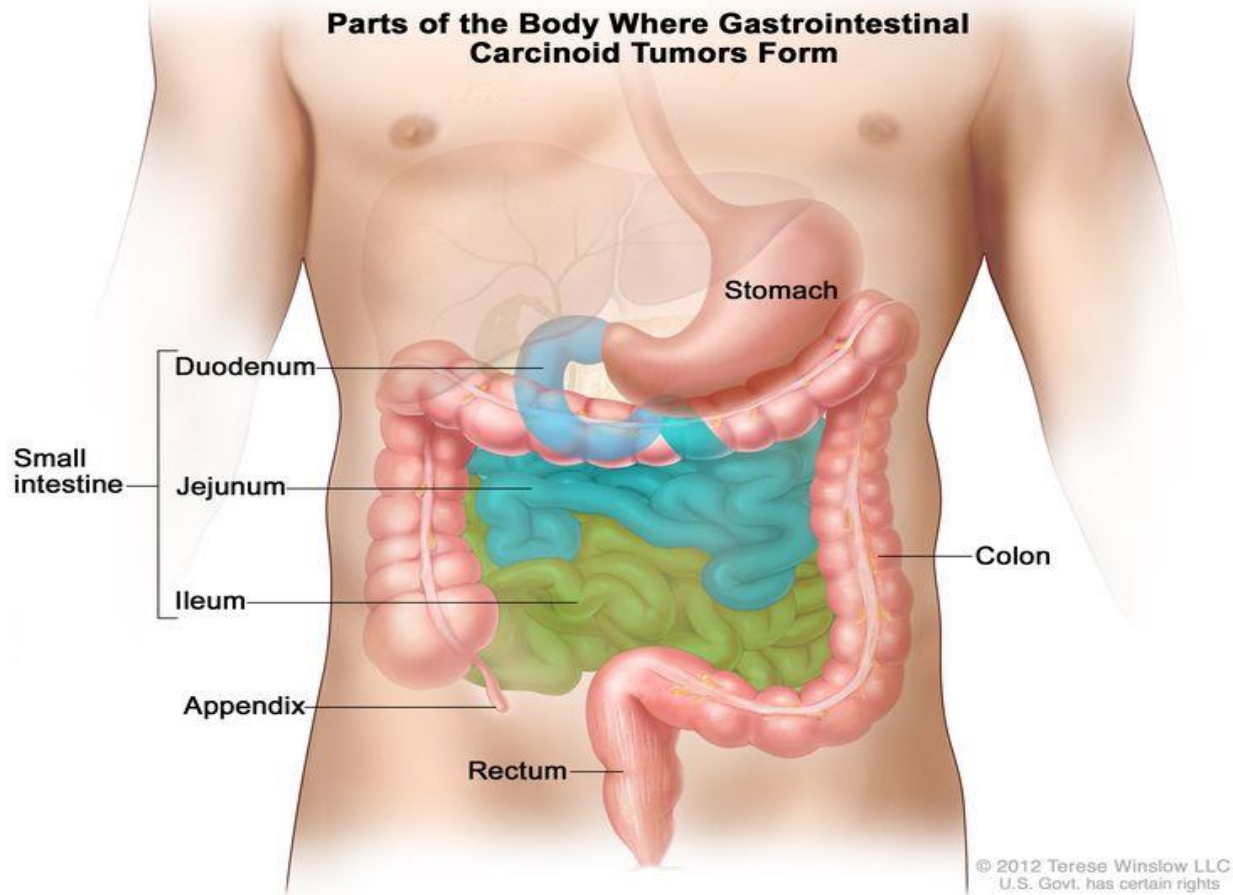


Figure 2 Parts of the body where GI carcinoid are located. (Gastrointestinal Carcinoid Tumors | OSUCCC – James n.d.)

1.9. Classification

For more than two decades now, carcinoids have been classified according to sites of origin, morphological characteristics, and their affinity for silver (Aggarwal, Obideen, and Wehbi 2008) (Carcinoid Tumors n.d.). Williams and Sandler's classification divided carcinoids into foregut, midgut, and hind gut tumours (respiratory tract, thymus, stomach). The foregut tumours are made up of the stomach, the airway, and the thymus. The midgut tumor comprises small intestinal and appendicular tumours. The tumours from foregut have a trabecular pattern, whereas tumours in the midgut are monotonous and polygonal in shape. Historical classification of tumour is based on their silver-stained features. Foregut and rectal tumour are positive to silver deposits (Subash et al. 2022).

Clinically, carcinoids exhibit different cellular characteristics in their embryonic forms. For example, chronic atrophic gastritis type A (CAG-A), multiple endocrine neoplasia (MEN-1) type 1. (Carcinoid Tumors - Endotext - NCBI Bookshelf n.d.) This led to the classification of carcinoid malignancies histologically into typical and atypical carcinoid malignancies. Atypical carcinoid tumours grow slowly, and the majority of carcinoid cases have a low grade of malignancy (Aikharashi et al., 2018). The typical carcinoid is invasive, as already mentioned. This categorization enables clinicians to make comparisons and predictions about patients' clinical outcomes. Tumors are classified into five groups according to severity of malignancy: (a) fully characterize (differentiated) tumor, (b) well

characterize endocrine malignancy (c) poorly characterize endocrine malignancy (d) Mixed tumors of exocrine–endocrine and (e) lesions of tumor (Öberg et al., (2004), (Nagtegaal et al. 2020a) (la Rosa and Bongiovanni 2020)

1.10. Carcinoid tumours with organ-related features

Carcinoid tumours could be seen in some organs at a very minimal rate, but the GIT and bronchopulmonary system are mostly prevalent. Depending on where the main tumour is, there is a wide range of clinical characteristics and prognoses, such as how aggressive or likely it is to spread (Manneh Kopp, Espinosa-Olarte, and Alonso-Gordoa 2022). These organs or sites are the bronchopulmonary which has about 2% of lung cancers and 30% of carcinoid cancers (Araujo-Castro et al., 2022) (Limaïem, Tariq, and Wallen 2021). Carcinoid tumor are also in the gastric and small intestine. The classification is based on MEN-1 (Nagtegaal et al. 2020b) with the small intestine being numerous and characterize with abdominal pains (Pu et al. 2021). The most prevalent is the appendiceal carcinoid though highly curable (Abreu, (2018) . Meanwhile rectal carcinoid is uncommon (Maione et al. 2021) whereas thymic and pancreatic are seen in older people (Bicci et al. 2020) of above 40 years especially smokers (Zaman et al. 2020). Duodenal carcinoid does not metastasize therefore it has a very good prognosis and neurofibromatosis, MEN I, and/or pheochromocytomas, as well as hormone reactivity (Domenech-Ximenes et al. 2020). Other emerging and uncommon (Sanchez-Nadales et al. 2020) carcinoid tumour is from unknown origin (Berner et al. 2020), carcinoid of the heart (Sabet et al. 2020) and carcinoid fibrosis (Hardy & Ghaye, 2020).

Table 1 Summary of different classifications of carcinoid tumor by WHO 2018

Sites	Tumor category	Name	Types	Gradient	Current name
Lungs	Neuroendocrine tumor	NET	Pulmonary	G-1 G-2	Atypical carcinoid
			Lung cell cancer		Small lung cell
		NEC	NEC-Pulmonary		cancer
			Large carcinoma		Large cell NEC
Cervix, uterus			Uterine, Lung cell	G-1	Carcinoid
	NEC	Neuroendocrine tumour		G-2	Atypical (tumour)
				G3	
		NEC	Uterus, larger cell		Small (tumour) cell Larger tumour cell
Pancreas	Neuroendocrine malignancy	Neuroendocrine tumour	Pancreas	G-1	NET G1
				G-2	NET G2
				G-3	NET G3
		Neuroendocrine carcinoma	Large cell form		Small (Tumour) cell
			Pancreatic NEC		Large (Tumour) cell

NECs represent high grade tumors. G3 atypical carcinoid of the lungs is not recognized in WHO 2015 classification. Though in recent times they are known small-cell-lung-carcinoma (SCLC). They can as well be called large cellular neuroendocrine (malignancy) carcinoma-LCNEC. The NET with higher grading has atypical malignant (carcinoid) that resembles pancreatic G-3 tumors. B-not among SCLC (Rindi et al. 2018).

Chapter 2

Literature Review

1. History and origin of Carcinoid

The historical narratives of these tumours dates back to the 18th century. Muller in 1882 named carcinoid tumor bronchial adenoma. Oberndorfer later called it a "Karzinoid" tumour because it looked a lot like lung cancer at that time. The first scientific proof that there were medical conditions with clinical manifestations that turned out to be neuroendocrine tumours came from ancient Egypt. This was the Ebers papyrus (03_Ebers Papyrus: Universitätsbibliothek Leipzig n.d.) that was used to write about these neoplasms when they were first written about. Pathologist and surgeons are interested in these conditions because they have so many different symptoms and signs that make them different from other tumors. They can come from any part of the body, and over the years, many people have tried to classify them histopathologically. Even though they are rare tumors, they have been the subject of many studies, which can be seen in their long history in medicine (Aydin et al. 2011). The year 1944 marked the genesis of differentiation between ordinary neuroendocrine tumours and unusual carcinoids was explained. Arrigoni and his colleagues identified the histomorphological features for this malignancy because they do not exhibit global utilization. World Health Organization (WHO) upgraded these tumors according to stringent guidelines postulated by Travis and coworkers in the year 1999 (Wurtz, Hysi, and Benhamed 2013). During the early months of 2004, carcinoid malignancy has been added among the upper respiratory tumours of bronchopulmonary tumour of the neuro endothelium (BP-NET). The characteristic of the carcinoid tumor is functional, morphological, and also the tumor has immune histochemical property. Carcinoid tumours are usually harmless, although some atypical groups are much aggressive when it comes to treatment and diagnosis (Djordjevic and Mirkovic 2020).

2.1 Literature Review

The health sector is affected on a large extent especially in decision making with a lot of objectives hence it becomes prone to error if adequate decision is not made. Therefore, multicriteria decision making has become a useful tool in the decisions on health sector (Frazão et al. 2018). MCDM can also be applied in theories in healthcare and biomedical engineering as well. The goal of this is to render total support to decisions of uncertainty and conflicting interests. This can be applied severally to solve related issues (Sayan et al. 2021a). Multi-criteria decision-making is one of the fields associated with resolving thoughts and difficulties in respect to the numerous characteristics of the

choices. Decisions are made on a daily basis as part of life, but may be tagged to a personalized interest (Uzun, Uzun Ozsahin, et al., 2021).

Researchers have worked on MCDM methodologies and its utilization in the improvement of quality of life in sectors such as chemistry, engineering, health, and even social sciences. MCDM strategies include the analytical hierarchy process (AHP), Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS), the simple multiple attribute rating technique (SMART), data envelopment analysis (DEA), Elimination Choice Expressing Reality (ELECTRE), analytical network process (ANP), and PROMETHEE, to name only a few of the several accessible methodologies (Weistroffer & Li, 2016) (Zlaugotne et al., 2020).

PROMETHEE is a vital method used in evaluating alternatives in MCDM in accordance with the criteria. This is achieved using different types of preference function assigned to the criteria of the alternatives. This is one of the effective methods among all other MCDM for its development was centered on practical or complete outranks of set of actions (Tsamboulas 2007)(Abdullah, Chan, and Afshari 2019)

According to (Tsamboulas, 2007), each MCDM has its advantages and disadvantages and its selection are all dependent solely on the type and natures of the problem to be solved (Yannis et al. 2020). (Wagner et al. 2018) conducted research using MCDM in managing Gastro-enteropancreatic Neuroendocrine Tumors (GEP-NET) in Spain. The patients were scored using somatostatin analogues (SSA) treatment, shared insights as well as knowledge as the criteria. The weights and scores were combined to get relative benefit–risk balance (RBRB) of an exploratory comparative study (Health-Related Quality of Life Scale | SPARQtools n.d.). The result of this research showed efficacy, patient report, and safety. The overall average of RBRB was ± 0.32 standard deviation (SD) 0.24, the greatest contributions from advancement lifespan ± 0.11 SD of 0.07, severe adverse reactions 0.06 SD 0.08, and health-related quality of life (HRQOL) is 0.04 SD 0.04). Evaluation of moderating variables (treatment advantage category, demand, expenses, proof, and practicality) boosted the RBRB to $+ 0.50$ SD 0.14, with treatment advantage form ($+ 0.10$ SD 0.08) as well as scientific proof performance ($+ 0.08$ SD 0.06) influencing more to therapy. Various weighted schemes produced comparable outcomes. Results correspond to those of a study conducted in the United States (Wagner et al. 2018).

(Mustapha, Ozsahin, et al. 2022a) in their study on Breast Cancer Screening using supervised learning also utilizes MCDM. The study uses Wisconsin dataset which has 569 cases of breast malignancy with over 30 attributes in one file which indicates benign or malignancy. The data fed into the Wisconsin dataset were from fine needle aspirates to breast mass tissues all indicating the cancerous and benign. ML like random forest, support vector machine (SVM), KNearest Neighbor (KNN), and logistic regression were all employed in the study. It was the first approach in breast

cancer combining ML and MCDM in order to have the best diagnostic measure, the study support vector machine was ranked the most effective model in early cancer (malignant) cells K-Nearest Neighbor (KNN). This preferred alternative had 0.0766 as net flow (Mustapha., et al., 2022a). Also, Dilber Uzun Ozsahin et al. 2021 in “Applied Machine Learning and Multi-Criteria Decision-Making in Healthcare” conducted another research on hemorrhoids using MCDM. In the study the cost, efficiency, duration of recovery, survival rates, duration and time of hospitalization were all analyzed and ranked using fuzzy PROMETHEE technique.

Hofland et al., 2019 conducted a study on severe condition associated with NET with a functional purpose. Patients were treated with chemotherapy, interferons (IFN), Somatostatin Analogs (SSA)(Somatostatin Analogs (SSA) - Carcinoid Syndrome n.d.), liver therapy, serotonin pathway inhibitor and radionuclide therapy. Patient's response included general symptoms, diarrhea and flushing. The biomarker was tested using urinary 5-hydroxyindoleacetic acid (HIAA), chromogranin-A and gastrin. Various therapeutic approaches exist to ease the hormonal effects, but the effectiveness of these hormone is yet to be determined (Hofland et al. 2019b). The use of somatostatin and lanreotide caused improvement its symptomatic effects in 65% – 72% of patients and using biochemical responses gives about 45% – 46% percent. In 72% – 84% percent of the patients, the dose and frequency were increased which reduces the interclass transition to flushing diarrhea (Herrera-Martínez et al. 2019). Again, research has shown that patients with neuroendocrine tumors often develops CS with various symptoms such as flushing, diarrhea and abdominal cramps. These secret vasoactive substances that induce fibrogenic signals in the tissues which cause complications like carcinoid heart diseases (CHD) and often cognitive retardations. The scholarly reviews suggested they are best managed surgically especially the CHD and fibrosis of the abdomen (Mota, Sousa, and Riechelmann 2016).

(Turla et al., 2022) using ovarian strumal carcinoid, a rare tumor characterised by the coexistence of thyroid (struma) and carcinoid components. The experiment was carried at oncology department of Spedali Civili (Brescia) where a systematic review of the histological samples of positive cases of strumal carcinoid was tested. Kaplan-Meier methology was used in the statistical analysis, the graph indicates a survival rate when compared by log-rank testing. The regression models of the hazards, exploration analysis was also performed to get the prognostic significance of medical characteristics and treatment approaches. A database of demographs, different sizes of tumor, histological properties, disease recurrence and treatments. The results show that out of the 88 patients with these symptomatic effects. 37 of them had distention of the abdomen, the tumor growth causes 49 of the total patients to have pain in the lower abdomen. Therapeutically surgery had 99% success rate. Among these 3 patients' carcinoid had metastasized and 5 of the patients had a reoccurrence of the disease after the surgery. These metastases affected the thyroid glands according to the histological report (Contin et al. 2021; Turla et al. 2022).

According to Jedrych and Pulitzer (2014) revised papers on the primary carcinoid of the skin whereby patients who have polycystic ovary syndrome (PCTS) have features that are indicative of a low-grade tumour with neuroendocrine differentiation. From the result, the traits include structural, cytomorphologic, ultra - structural, and immunohistochemistry features. This is because PCTS often have a benign clinical history that must be differentiated from cutaneous metastases of visceral carcinoid tumours in order to avoid misdiagnosis (Jedrych and Pulitzer 2014). These papers typically show that the tumor is benign and named to be differentiated from the metastatic carcinoid of visceral origins. The articles were revised based on the histological features and how these tumors could be managed (Goto et al. 2017).

Silas and Rajsingh (2016) analyzed the application several multi-criteria decision approaches, including ELECTRE, PROMETHEE, and AHP in pervasive environmental computing of adverse effects of neuroendocrine disorder. The study was based on cost of accessing medical services, the duration of time, personnel involvement, and feedback experience. About 95% choose PROMETHEE in the analysis of the result.

Chapter 3

Methodology

3.1. Fuzzy Logic

In order to obtain crisp values in data processes that suits real life scenario, the process is indeed a challenging approach. More so, it is much difficult to have information that is devoid of errors. In this regard Boolean logic defines these two extremes i.e. a true or a false situation designated by 1 and 0. Fuzzy logic treats uncertainties for example Boolean logic could define room temperature as either hot or cold without stating the exact degrees. Fuzzy logic on the other hand provides the degree of coldness thus very hot, moderate cold, very cold etc. Fuzzy methodology is therefore applied in this study because of its great merits (advantages) compared to methods like Bayesian controls, probability and classical theories because according to (Zadeh, 1996) logic could be utilized in representing numerical computation and reasoning.

3.2. Multicriteria decision Making (MCDM)

According to (Huang et al.,2011), Multicriteria Decision Making (MCDM) are procedures geared towards finding the best favored solution and ranks all the ones remaining. MCDM allows one to combine values from different assessment criteria to an easy and interpreted format. This is done whenever these assessment criteria contradict each other. Invariably, MCDM ranks all possible alternative according to it preferences. We chose Multicriteria Decision Analysis (MCDA) as an evaluation tool because it has been shown to work successfully in Engineering. MCDM were applied in comparison of test parameters using semiautomatic analyzer (Castro and Silv Parreiras 2018; Kumari et al. 2020).

MCDM is a very important factor in utilize by decision makers for it the overall complexity is increased. As a result, error reduction becomes a necessity and this is achieved by incorporating techniques, processes and criteria which will reduce these errors. Often it is not an easy task to perform these decisions, the criteria are challenging making it very difficult resulting in ambiguity of the end result (Albarwary et al. 2021; Castro and Silv Parreiras 2018; Kumari et al. 2020; Mustapha, Ozsahin, et al. 2022b; Mustapha, Uzun Ozsahin, et al. 2022; Sayan et al. 2021b; Torres and Nieto 2006; B. Uzun et al. 2021; Uzun Ozsahin et al. 2021). According to (Köksalan, Wallenius, and Zionts 2011; Marsh et al. 2017) there was great improvement in MCDM in terms of its credibility in decision making since its emergence. Alternatively, MCDM can also be termed multiple-criteria-decision analysis (MCDA), an area of research that analyses variable options or different research areas of our daily life, social sciences. engineering and medical departments' makes a parameter favorable and sometimes unfavourable in specific applications. This multicriteria decision making goal is to help in making decisions, which thus reduces the responsibilities of the authorities and

ensuring solutions are attributed to them. In health sector the application of this method is quite complex. It involves a lot of techno economic considerations as well as human effects which creates conflict and hinders final choices (Marsh et al. 2017). This made researchers who are using MCDM to improve whole health systems (Marsh et al. 2016; Ozsahin et al. 2018).

PROMETHE technique is of great importance in multiple criteria decision makings. Among the advantages of these are its ease in usage. Applications to real life scenarios, complete ranking processes as well as the ability to recognize both discrete and indiscrete information's (Wu and Abdul-Nour 2020). As a result of this, this article uses PROMETHEE methodology.

3.3 Fuzzy PROMETHEE

The Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE) as Multi-Criteria Decision Making (MCDM) platform allowing users examine critically as well as ranking of alternatives according to specific criteria. PROMETHEE lets users look at and rank available options based on their own criteria. Brans and Vince came up with the PROMETHEE method in the year 1985 (A Preference Ranking Organisation Method: (The PROMETHEE Method for Multiple Criteria Decision-Making) on JSTOR n.d.) to compare different options based on the chosen criteria (Goswami 2020). It is better than other MCDM methods for instance the analytical hierarchy processes (AHP) and the method for ranking performance based on how close it is to the ideal solution (S. Uzun and Kazan 2016). It gives the user full control over how the criteria's preference values are set. PROMETHEE is among most widely used MCDM for making decision in many areas of life. (Macharis et al. 2004a). It only needs a few things from the policy makers: the weights assigned to these criteria and their preference function in other to figure out which option is better on each criterion (Yildirim et al. 2021) . Fuzzy-based MCDM works better in many situations where numbers are not available. Again, decision-makers (authorities) look at linguistic information to compare different options (Yildirim et al. 2021).

PROMETHEE MCDM allows the analysis and ranking of the alternatives according to individual criteria. Also, it compares the alternatives criteria selected. As a result, PROMETHEE is mostly preferred MCDM tool because

1. PROMETHEE handles both quantitative and qualitative criteria at the same time.
2. PROMETHEE methodology handles vagueness and uncertainties
3. PROMETHEE offer the user full control over the assigned criterion weight.

This methodology (Fuzzy PROMETHEE) requires the opinion makers to make decisions on the weight assigned to these criteria and preference functions used in comparing these alternatives (Borovička 2014; Macharis et al. 2004b)

3.4. Application of Fuzzy PROMETHEE in Evaluation of Carcinoid Tumour

The weights of the criteria are determined using fuzzy triangular numbers the Yager index for the defuzzification process. The alternative used as can be seen in the triangular fuzzy scaling. The individual weight was assigned based on the opinion of the experts. These features support the patients get the best therapeutic measure from the treatment alternative. The weight in future can be modified based on the decisions from the analyst, patients' medical conditions and experts' discretion.

Table 3.1: showing the triangular fuzzy linguistic scale

Linguistic fuzzy scale	Triangular fuzzy numbers	Criteria
Very High [VH]	[0.75, 0.92, 1]	5-years survival rate (%), side effects, cost of treatment, infection rate
High [H]	[0.50, 0.75, 1]	Follow up, radiation amount (mSv), pain level
Medium [M]	[0.25, 0.50, 0.75]	Bleeding risk, anesthesia usage
Low [L]	[0, 0.25, 0.50]	
Very Low [VL]	[0, 0, 0.25]	

Subsequently, we evaluate treatment alternatives by considering the important criteria. Gaussian preference function was assigned to each criterion. The reason of using Gaussian function over preferences is because the deviation of the criteria are considered by (Macharis et al. 2004b; Petropoulos et al. 2022)

Table 3.2 Data of the carcinoid tumor treatment options

Treatment alternatives /criteria	5year survival rate (%)	Follow up duration	Side effects	Cost of treatment \$	Treatment duration (hrs.)	Radiation Amount (mSv)	Infection rate (%)	Bleeding involved	Anesthesia used
Endoscopic resection	89%(Ortiz and Ragunath 2015)	46months(Kwon et al. 2013)	sedative effects, vomiting, cramps, sore throat, excessive gas	15,264	25-35 mins	1.97	6.8%	yes	yes

Local excision	72-95% (Zhao et al. 2009)	43 months (Ferguson et al. 2000)	Blood clots, bleeding, infection, stiffness, nerve pain, inflammation	15,152	30-90 mins	2.00	8.95% (Lilani et al. 2005)	yes	yes
Resection	58.6% (Fernandez et al. 2004)	6 months (He et al. 2018)	Bowel obstruction, fatigue, bleeding, diarrhea	5,315	2-3 hrs.	2.97	13.0%.	yes	yes
Cryosurgery	28% (153303460400300212 n.d.)	31 months (Vergnon et al. 2006)	Blisters, ulcer, skin discoloration, scarring, burn, eye injury	500	7-10 days	3,7	30% (Lilani et al. 2005)	yes	yes
Radiofrequency ablation	44-48% (Sucandy et al. 2016)	12.5 months (Meij et al. 2005)	discomfort, nausea, temperature rise.	3,982	15min-2hrs	7.2	0.32%	no	GA
Radiotherapy	10.4% (Hanna et al. 2018)	14 months (Hudson et al. 2022)	Hair loss, tiredness, eating/drinking problem, skin burns, joint pains, diarrhea, stiffness	3,683	10-30 min	8.3	0.038% (Maeda et al. 2020)	no	yes
Radioimmunotherapy	93% (Primary Carcinoid Tumors of the Lung: A Role for Radiot	53 months (Hudson et al. 2022)	nausea, vomiting, belly pain, temporary hair loss (Chau et al. 2020)	117.82	840min	20.0	0.038% (Maeda et al. 2020)	no	no

	herapy n.d.)								
Chemothe rapy	70.6% (Foste r et al. 2019)	48 months (Lou et al. 2013)	nausea vomiting loss of appetite. low wbc hair loss. mouth sores. Diarrhea ,bleeding , fatigue (Pavel et al. 2018)	12,000	3-6 month s	6.5	2.7% (Bud hatho ki et al. 2021)	no	no
Adjuvant therapy	81% (Rami rez et al. 2021)	24mont hs(Man soor et al. 2020)	hair loss, fatigue, weight loss, loss of appetite, vomiting , nausea. mounth, neuropat hy,infect ion cognitive disorder (Kannar katt et al. 2017)	36,028	3-6 month s (What to expect on your first day of chemo therap y MD Anders on Cancer Center n.d.)	21.7	1%(Gosai n et al. 2018)	no	yes
Hormone therapy	20% (Ayeni and Robins on 2009)	22.6 months (Manso or et al. 2020)	nausea, abdomin al bloating, steatorrh ea(Carcin oid Syndrom e Treatmen t - NETRF n.d.)	2,440	18-24 month	1.9	2.6% (Batu r et al. 2006)	yes	no
Embolizat ion	24% (Ayeni and Robins	35mont hs (Schell et al. 2002)	abdomin al pain, fever, nausea, vomiting	18,000	2-3 month s	1.7	1.2%	yes	yes

	on 2009)								
Chemo embolism	33% (Ruuti ainen et al. 2007)	51.5 months (Diaco et al. 1995)	fevers, pain, leukocyt osis, nausea, malaise, fatigue (Pearson et al. 2008)	22,000	90 minute s	0.96	2.4% (From Chem other apy to Targe ted Thera pies: Curre nt Treat ment of Carcin oid Tumo rs and Pancr eatic Neuro endoc rine Tumo rs n.d.)	yes	no
Targeted therapy	69% (Kulke 2007)	14.9 months (Diaco et al. 1995)	nausea, diarrhea, skin discolora tion, mouth sores, weaknes s, low wbc,tire dness, BP,bleed ing, hand- foot syndrom e, pain, low thyroid hormone	19,023	3- 4years	27.0	2.73 %	no	no

CHAPTER IV

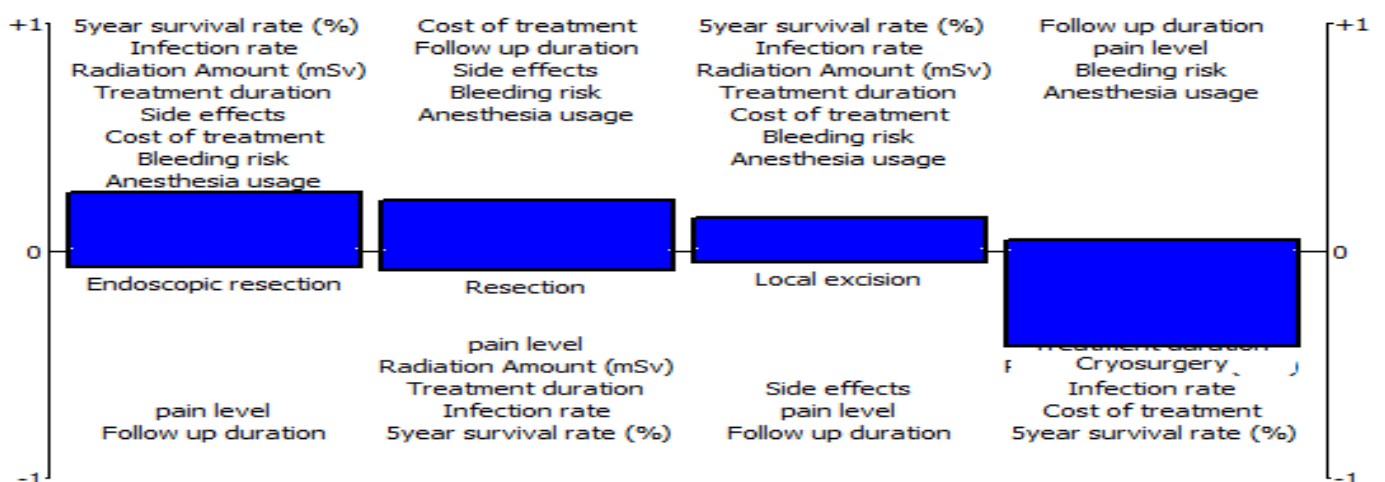
4.0. Result and discussion

The treatment options of the carcinoid tumours are selected based on severity or grades of the malignancy. The very high grades of carcinoid are treated using endoscopic resection, resection, local excision, and cryosurgery. The results showed the first ranked is endoscopic resection, with 0.1730 net flow value, the second is resection with 0.1280 net flow value, the third is local excision with 0.0811 net flow value, and cryosurgery with -0.3821 net flow value respectively as can be seen in Table 4.1. Also Figure 4.1 is the PROMETHEE evaluation of the very high carcinoid tumour treatment options. From the Figure 4.1, endoscopic resection is the first treatment option based on 5year survival rate (%), infection rate, radiation amount (mSv), treatment duration, side effects, cost of treatment, bleeding risk, anesthesia usage, follow up duration, and pain level. The criteria above the alternatives shows the strengths of the alternative while the criteria below show the weaknesses of them (see in Fig.4.1, Fig4.2, Fig.4.3, and Fig. 4.4).

Table 4.1 Ranking of very high carcinoid tumour treatment option

Ranking	Alternative	Net flow	Positive outranking value	Negative outranking value
1	Endoscopic resection	0.1730	0.2798	0.1068
2	Resection	0.1280	0.2975	0.1695
3	Local excision	0.0811	0.2280	0.1469
4	Cryosurgery	-0.3821	0.0565	0.4386

Fig 4.1 PROMETHEE evaluation of very high carcinoid



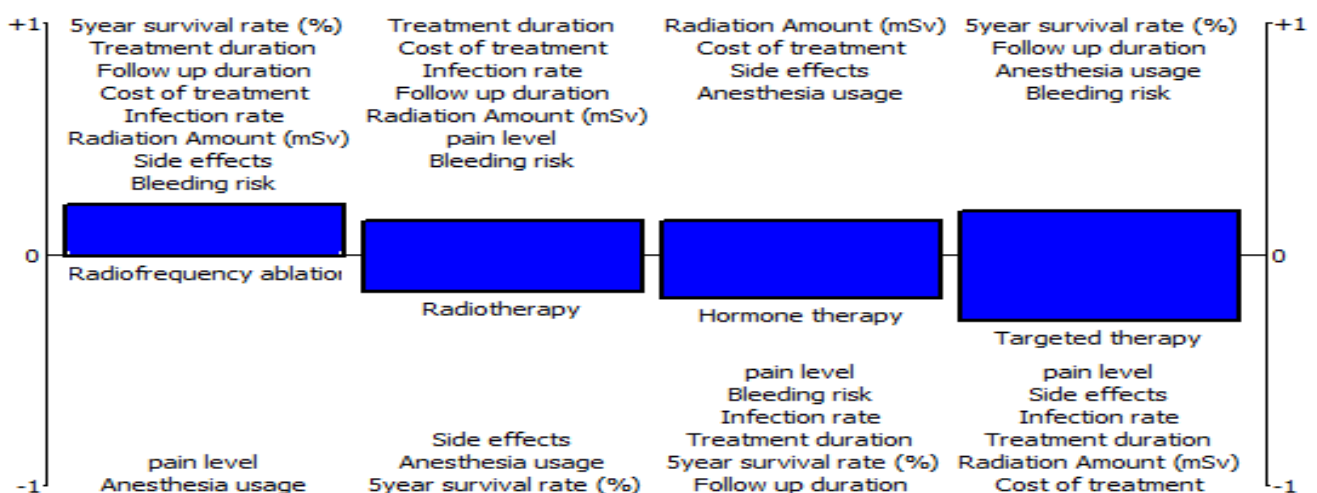
The moderate carcinoid treatment options ranked with mild invasive techniques like radio frequency ablation, radiotherapy, hormone therapy and targeted therapy with 0.1943, -0.0216, -0.0601, -0.1127 as net flows. Table 4.2 is the comprehensive display of positive outranking flows and the net ranking flows of each alternative. Radiofrequency ablation is the first treatment option followed by radiotherapy, hormone therapy and targeted therapy sequentially.

Table 4.2 Ranking of moderate carcinoid tumour treatment option

Ranking	Alternative	Net flow	Positive outranking value	Negative outranking value
1	Radiofrequency ablation	0.1943	0.2735	0.0792
2	Radiotherapy	-0.0216	0.1650	0.1866
3	Hormone therapy	-0.0601	0.1788	0.2389
4	Targeted therapy	-0.1127	0.1796	0.2923

Also, in Figure 4.2 the PROMETHEE evaluation of moderate carcinoid tumour treatment options ranked radiofrequency ablation having the highest impact on the moderate malignant tumours. Radiotherapy, hormone therapy and targeted therapy are also used in treatment of moderately malignant carcinoid tumour but usually as substitute for they are not optimally utilized with selected parameters.

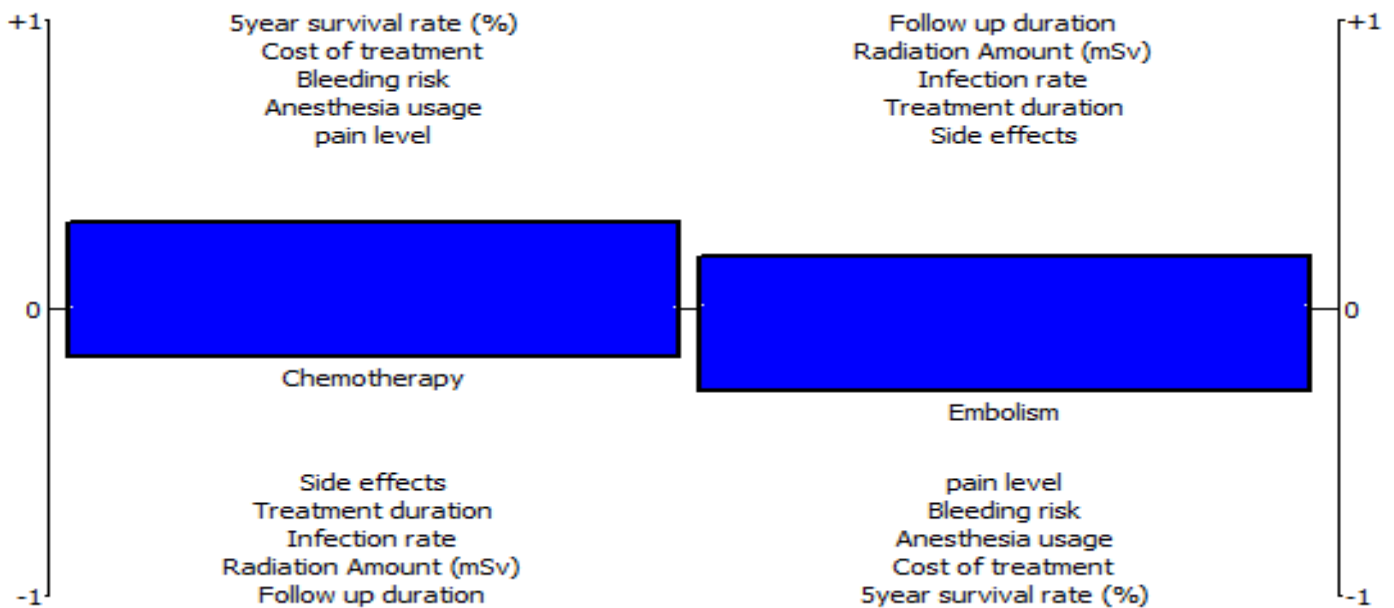
Figure 4.2 PROMETHEE evaluation of moderate carcinoid tumour



Low grade carcinoid tumours ranked chemotherapy and embolism which targets the tumor factor of the carcinoid especially 5-hydroxytryptamine secreted by these tumors. The Table in 4.3 show a net flow of 0.1126 and -0.1126 for chemotherapy and embolism respectively.

Table 4.3 Ranking of low grade of carcinoid tumour treatment option

Ranking	Alternative	Net flow	Positive outranking value	Negative outranking value
1	Chemotherapy	0.1126	0.2788	0.1662
2	Embolism	-0.1126	0.1662	0.2788

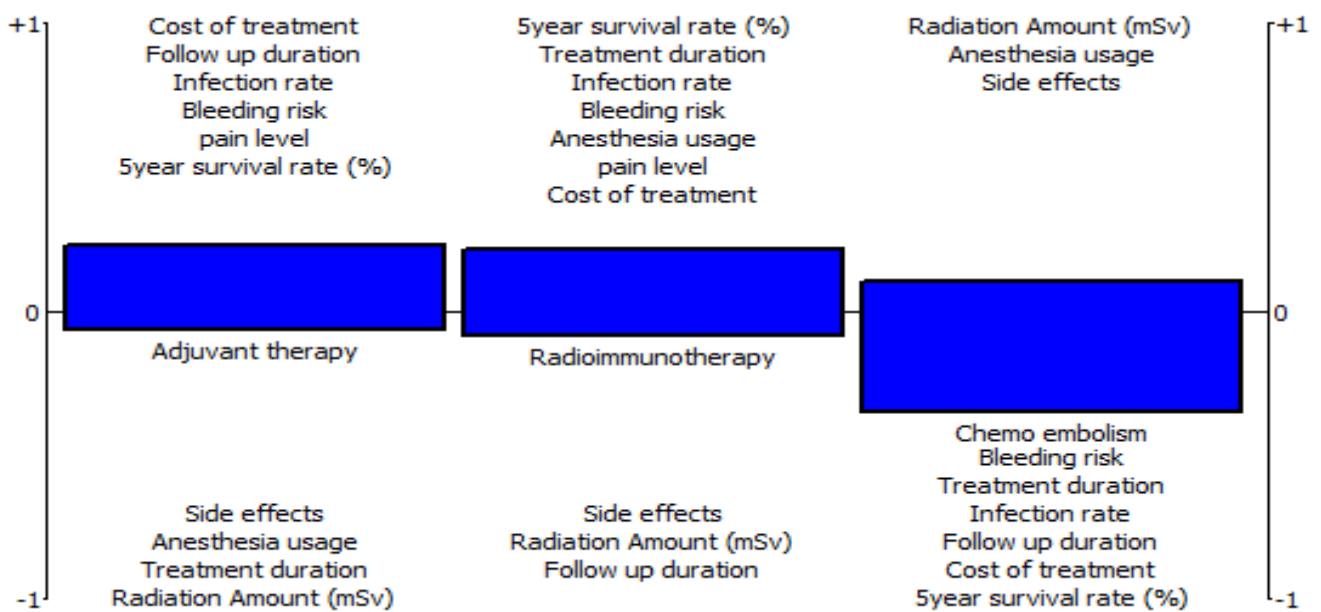
Figure 4.3 PROMETHEE evaluation of low carcinoid tumour

From the Figure 4.3, chemotherapy outranked the embolism treatment options based on 5year survival (%), cost of treatment, bleeding risk, anesthesia usage and pain level. The criteria above the alternatives shows the strengths of the alternative while the criteria below show the weaknesses of them as can be seen from Figure 4.3.

The very low-grade carcinoid tumours treatment option ranked adjuvant therapy, radioimmunotherapy, chemo embolism with net flows of 0.1472, 0.1163, 0.2637 respectively. Adjuvant therapy has the highest net flow followed by radioimmunotherapy and finally chemo embolism as can see from Table 4.4.

Table 4.4 Ranking of very low-grade carcinoid tumour treatment option

Ranking	Alternative	Net flow	Positive outranking value	Negative outranking value
1	Adjuvant therapy	0.1472	0.2883	0.1411
2	Radioimmunotherapy	0.1163	0.2651	0.1488
3	Chemo embolism	0.2637	0.0890	0.3527

Figure 4.4 PROMETHEE evaluation of very-low carcinoid tumour

In Figure 4.4, very low-grade carcinoid tumours ranked adjuvant therapy, radioimmunotherapy, and chemo embolism with cost of treatment, follow-up duration, infection rate, bleeding risk, pain level, 5year survival rate (%), treatment duration, anesthesia usage, radiation amount (mSv) and side effects as criteria.

CHAPTER V

Conclusion

This study includes the evaluation of carcinoid tumor treatment option using MCDM has played a vital role in making decisions concerning the best alternative to this complex situation. MCDM has made analyzing the data used in this study for evaluating therapeutic alternative effectively. As a result, the detailed information of which best treatment to render to carcinoid patients over series of other therapies were determined. These treatment options were categorized into four- very high grades of carcinoid, moderately graded carcinoid, low grade and very low-grade carcinoid tumours. The results ranked endoscopic resection, local excision, resection, cryosurgery as treatment alternative to very high-grade carcinoid tumours. Radiofrequency ablation, radiotherapy, hormone therapy, and targeted therapy are the treatment options for moderately graded carcinoid tumours. However, chemotherapy and embolism ranked low grade carcinoid while adjuvant therapy, radioimmunotherapy, and chemo embolism were the ranking result for very low-grade carcinoid malignancy. The results obtained based on the selected parameters and can be updated simply based on different conditions of the patients. The results of the study will highly be beneficial to the health sector especially to the medical oncologist groups, the patients, relatives, policy makers and society at large in the therapeutic management of carcinoid tumours.

5.1. Limitations

The study is attributed to limitations majorly in time constraints, organizing, typing, editing and reading the manuscript. It is limited with selected parameters. In future more alternatives could be integrated.

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CURRICULUM VITAE

PERSONAL DETAILS

Surname, Name : Emegano, Declan Ikechukwu
 Nationality : Nigerian
 Date and Place of Birth : 1st may, 1984, Orlu
 Marital Status : Married



EDUCATIONAL INSTITUTION

Degree	Institution	Year of Graduation
M.Sc.	NEU, Department of Biomedical Engineering	2022
M.Sc.	National Open University of Nigeria (NOUN) Educational Technology	2020
B.Sc.	Imo State University Owerri, Nigeria	2010

WORK EXPERIENCES

Year	Place	Enrollment
Jan, 2022-present	Operational Research Centre NEU	Research Assistance
Oct-Dec2021	Cyprus International University	Field Lab Sct for Antigen
Jan 2020-2021	Medical Laboratory Scientist	Rock and Garden Clinic Lokoja
Nov, 2017-2021	Medical Laboratory Scientist	FMC Lokoja Nigeria
Dec 2015-2017	Medical laboratory Scientist	Niger Hospital Lokoja Nigeria
2014 -2015	Intern Med.Lab. Scientist	FMC Lokoja Nigeria
2012-2013	NYSC Scientist	Gen. Hospital Omuo Ekiti Nig.

FOREIGN LANGUAGES

English, fluently spoken and written

MEMBER OF PROFESSIONAL ORGANIZATION

- Medical Laboratory Science Council of Nigeria (MLSCN)
- Association of Medical Laboratory Scientists of Nigeria (AMLSN)

TRAINING/SEMINAR ATTENDED

- Medical laboratory Quality Management System (ISO 15189) 23-28th Nov,2020
- Project ECHO Tele ECHO Session. WHO/AFRO IDSR Training courses 8th Oct,2020
- FMOH National Training of Trainers on Management of Patients with Covid for health care workers. 4th August,2020
- ASLM'S Covid 19 ECHO session 8th June,2020
- Introduction to Biostatistics. <http://ccghe.net> 23rd May,2020
- Research Methods by Helix Biogen consult.
- Molecular and Serological Testing for Covid 19 by BIOMERIENX
- GSK Antibiotics and overcoming the challenges to good laboratory Practice in limited setting.2016.

MY HOBBIES

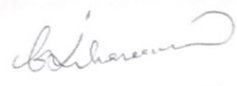




- Reading, Adventure, Traveling

INTERESTS

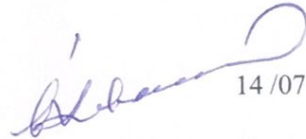
Programming Languages, Information Technologies, Algorithm, and Information Systems, Forensics.

Approval page

We certify that we have read the thesis submitted by Declan Ikechukwu EMEGANO titled “EVALUATION OF CARCINOID TUMOR TREATMENT OPTIONS USING MULTI-CRITERIA DECISION MAKING (MCDM)” and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Prof. Ayse Gunay KIBARER	
Committee Member*:	Prof. Dr. Karem Cankocak	
Committee Member*:	Assoc. Prof. Dr. Doga Kavaz	
Supervisor:	Assoc. Prof. Dr. Dilber Uzun ÖZŞAHİN	
Co-supervisor	Assist. Prof. Dr. Berna Uzun	

Approved by the Head of the Department



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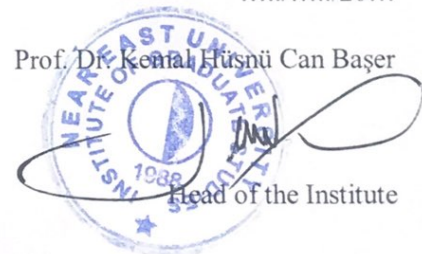
Prof. Ayse Gunay Kibarere

Head of Department

Approved by the Institute of Graduate Studies

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Prof. Dr. Kemal Hüsnü Can Başer



Head of the Institute