MORDECAI MAISAINI
PROMETHEE ANALYSIS OF RETINOBLASTOMA TREATMENT TECHNIQUES
NEU 2018

PROMETHEE ANALYSIS OF RETINOBLASTOMA TREATMENT TECHNIQUES

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By

MORDECAI MAISAINI

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Engineering

NICOSIA 2018

PROMETHEE ANALYSIS OF RETINOBLASTOMA TREATMENT TECHNIQUES

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By

MORDECAI MAISAINI

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Engineering

NICOSIA 2018

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name:

Signature:

Date

ACKNOWLEDGEMENT

Firstly, my sincere appreciation go to my supervisor Asst. Prof. Dr Ilker Ozsahin and co-supervisor Assoc. Prof. Dr. Dilber Uzun Ozsahin for their support and guidance and corrections on this project, I cannot thank them enough. I cannot fail to thank all my lecturers, without them I will not be here, the HOD of Biomedical Engineering, Near East University, Prof. Dr. Ayse Kibarer, you are a mother to me.

My heroes Mr and Mrs Maisaini, parents like no other, you have always been here for me, I cannot even begin to thank you enough for all you have done for me in this life. Thank you. To my sisters, Miriam, Judith and Jennifer, I love you so much. My nieces, Jojo and Jaydee, my angels your smiles mean the world to me.

To all my friends and my colleagues, to my Swittim, thank you. To all the people that I cannot even begin to mention for lack of space, I really appreciate you all. Thank you.

To God Almighty and my Family

ABSTRACT

Retinoblastoma is one of the most common cancer types that affects children, especially between the ages of 5 and 15 years, it involves an uncontrollable growth and division of cells in the light-sensitive part of the eye (retina). Retinoblastoma is a curable disease with very low mortality rate, early diagnosis can result in a 95% chance of treatment success and survival of the patient, with a likelihood of saving 70 to 80% of vision in the affected eye(s). Despite the promising results of the survival rate of the disease, the jury is still out on the best treatment method to embark upon in order to obtain the best results based on the different parameters that affect the treatment alternatives available. The main objective of this study is to shed more light on the parameters that affect the different treatment alternatives of retinoblastoma and how these parameters affect the preference ranking of each technique. In this study, the most common treatment techniques of retinoblastoma are analyzed based on some parameters that are likely to affect the outcome of the treatment methods. This analysis and ranking was carried using fuzzy PROMETHEE (Preference ranking organization method for enrichment evaluations), a multi-criteria decision-making tool. The results of the analysis suggest that cryotherapy is the most favorable treatment technique for treating retinoblastoma and radiation therapy is the least favorable technique. This ranking is based on the weights, criteria and parameters used for the analysis.

Keywords: Retinoblastoma; fuzzy PROMETHEE; decision-making; therapeutic techniques; eye cancer.

ÖZET

Retinoblastom, özellikle 5 ile 15 yaş arasındaki çocukları etkileyen en yaygın kanser tiplerinden biridir ve gözün ışığa duyarlı kısmında (retina) kontrol edilemeyen bir büyüme ve hücre bölünmesi içerir. Retinoblastom çok düşük mortalite oranına sahip tedavi edilebilir bir hastalıktır, erken tanı, hastanın tedavi başarısı ve sağkalım şansı% 95 ile sonuçlanabilir, etkilenen göz (ler) de% 70 ila% 80 oranında bir oran kazanma olasılığı vardır. Hastalığın hayatta kalma oranının ümit verici sonuçlarına rağmen, jüri hala mevcut tedavi alternatiflerini etkileyen farklı parametrelere dayanarak en iyi sonuçları elde etmek için en iyi tedavi yöntemine sahiptir. Bu çalışmanın temel amacı, retinoblastomanın farklı tedavi alternatiflerini etkileyen parametrelere daha fazla ışık tutmak ve bu parametrelerin her tekniğin tercih sırasını nasıl etkilediğini ortaya koymaktır. Bu çalışmada, retinoblastomun en yaygın tedavi teknikleri, tedavi yöntemlerinin sonucunu etkileyebilecek bazı parametrelere dayanarak analiz edilmiştir. Bu analiz ve sıralama, çok kriterli bir karar verme aracı olan bulanık PROMETHEE (zenginleştirme değerlendirmeleri için tercih sıralama organizasyon yöntemi) kullanılarak gerçekleştirilmiştir. Analiz sonuçları, kriyoterapinin retinoblastomanın tedavisinde en uygun tedavi yöntemi olduğunu ve radyasyon tedavisinin en az tercih edilen yöntem olduğunu düşündürmektedir. Bu sıralama, analiz için kullanılan ağırlıklar, kriterler ve parametrelere dayanmaktadır.

Anahtar Kelimeler: Retinoblastoma; Bulanık PROMETHEE; karar verme; terapötik teknikler; göz kanseri.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AHP	Analytic Hierarchy Process
CT	Computer Tomography
EBRT	External Beam Radiation Therapy
ELECTRE	Elimination and Choice Expressing Reality
FBP	Filtered Back Projection
ICRB	International Classification for Intraocular Retinoblastoma
LM	List Mode
MCDA	Multi-Criteria Decision Analysis
MCDM	Multi-Criteria Decision-Making
MRI	Magnetic Resonance Imaging
MSE	Mean Square Error
MTF	Modulation Transfer Function
OE	Origin Ensemble
OSEM	Ordered Subset Expectation Maximization
PET	Positron Emission Tomography
PROMETHEE	Preference Ranking Organization Method for Enrichment of Evaluations
RC	Resolution Compensation
Rb	Retinoblastoma
SMART	Simple Multi-Attribute Rating Technique
SPECT	Single Positron Emission Tomography

CHAPTER 1

INTRODUCTION

Retinoblastoma is a cancer that affects the retina (a light-sensitive thin layer in the inner part of the eye), it occurs when there is a mutation in both alleles of the Rb1 suppressor gene of the retinoblastoma (Rushlow et al., 2013; Soliman, Racher, Zhang, MacDonald & Gallie, 2017). Retinoblastoma is one of the most common cancer types affecting children mostly below the age of five and fifteen (Bakhshi, Meel & Radhakrishnan, 2012), it is however very rare to detect and diagnose retinoblastoma at the time of birth of a child. The growth of the cancerous cells may only affect one eye (unilateral retinoblastoma), both eyes (bilateral retinoblastoma) or in very rare cases may spread to other parts of the body like the lymph nodes or bones (trilateral retinoblastoma).

Early diagnosis and treatment of retinoblastoma like all cancers greatly increases the chances of survival. Patients who are diagnosed between birth and five years of age generally have a survival chance of 92.3%, while patients diagnosed with retinoblastoma generally have a 95.5% chance of survival (Naseripour, 2012).

Retinoblastoma is viewed as one of the potentially curable cancer types (Chawla, Jain & Azad, 2013), with several therapeutic techniques that are applicable based on the stage of the cancer and effectiveness of the treatment. The treatment options that are frequently explored as regards retinoblastoma include, chemotherapy (systematic or intravitreal), surgery (enucleation), radiation therapy, thermotherapy and cryotherapy, targeted therapy is a treatment technique that is still in the stages of clinical trials and hence is not included in this study. In order to determine the best treatment option to undertake to obtain maximum desirable results, a number of factors have to be put into consideration; these factors are likely to affect the outcome of the treatment option decided upon in one way or the other.

In this thesis study, the most common aforementioned treatment techniques for retinoblastoma are considered and analyzed in order to obtain a ranking of the techniques in relation to treatment time, cost of machine, cost of the treatment, how comfortable the technique is for the patient, radiation dose and the success rate of the technique. The analysis and ranking is done

using fuzzy preference ranking organization method for enrichment evaluations (PROMETHEE).

1.1. Thesis Problem

- Retinoblastoma is the most common form of cancer that affects children with a reported one in every 16,000 to 18,000 children born worldwide affected with the disease (Bowman, 2018).
- Even though retinoblastoma is a curable disease with the success rate of treatment approaching 100% in the United States and other developed countries (Houston, Murray, Wolfe & Fernandes, 2011), the treatment option undertaken plays a very important role in the success of the treatment.
- Some of the treatment options available may not necessarily get rid of all the cancerous cells and a combinational treatment may be required in some cases or a possibility either of the cancer reoccurring in the eye again or in another part of the body.
- Asides the risk of reoccurrence of cancer, some other factors also come into play when considering treatment, such as the cost, radiation dose, treatment period, comfort and other factors.

1.2. Aims of the Study

- To analyse and rank the most common treatment techniques of retinoblastoma using fuzzy-PROMETHEE.
- To simulate and determine the most desirable treatment technique based on some contributing factors that determine the quality of treatment.
- To determine with a degree of confidence the most efficient treatment that results in the least negative effects on the patient.

1.3. Significance of the Study

- The findings of this study will enable the oncologist to give a guided and informed suggestion on the treatment option to be undertaken.
- This study will enable the patients to have at their disposal an information on the factors that may affect the treatment choice to be undertaken.
- The findings of this study will also make it easier to make a decision on the best treatment option to undertake that will result in desirable results with the least negative effects on the patient.

- The findings of this study will provide an outright ranking of the treatment options of retinoblastoma not based on just one factor, but in consideration of a number of factors.

1.4. Limitations of the Study

- All the data used for the research are secondary data, no original data was obtained in order to verify the consistency of the obtained data.
- Different specialists have different opinions about the weight of each parameter.
- No other decision-making software was readily available to make analysis in order to verify the results obtained from the VISUAL PROMETHEE software.
- Some of the treatment techniques of retinoblastoma are better utilized based on the stage of the cancer and size of the tumour.

1.5. Overview of the Thesis

Chapter 1 is an introductory chapter of the whole thesis work, outlining the thesis problem, aim of the study, significance of the research and the limitations of the study. Chapter 2 is a detailed clinical background of the eye, including the common diseases that affect the eyes of children and the disease with details of the most common treatment techniques of retinoblastoma. Chapter 3 is a literature review of previous studies carried out and related to the present research. Chapter 4 outlines the method used for the analysis of the treatment techniques of retinoblastoma. Chapter 5 is the results of the analysis; the conclusion and discussion is contained in chapter 6.

CHAPTER 2

CLINICAL BACKGROUND

2.1. Anatomy and Physiology of the External Eye

The eye is an extremely complex and sensitive organ which provides the sense of sight. The eyes are a pair of organs that are structurally separated, but they function as a unit that is often compared to the camera, in that just like the camera, the eyes gather light and try to transform the light input into a picture or signal that can be recognized and processed by the brain. The eye itself is a small organ, measuring about 1 inch in diameter and only a small portion of it is visible, with most of it buried within the surrounding bone structure and skull (The Eyes (Human Anatomy): Diagram, Function, Definition, and Eye Problems, 2018).

The anatomy and structure of the eye is divided into three layers, an outer fibrous layer (sclera, cornea, and conjunctiva), a middle vascular layer (ciliary body, choroid and iris) and an inner layer (retina). Figure 2.1 is a structure of the eye showing some key parts of each of the three layers.

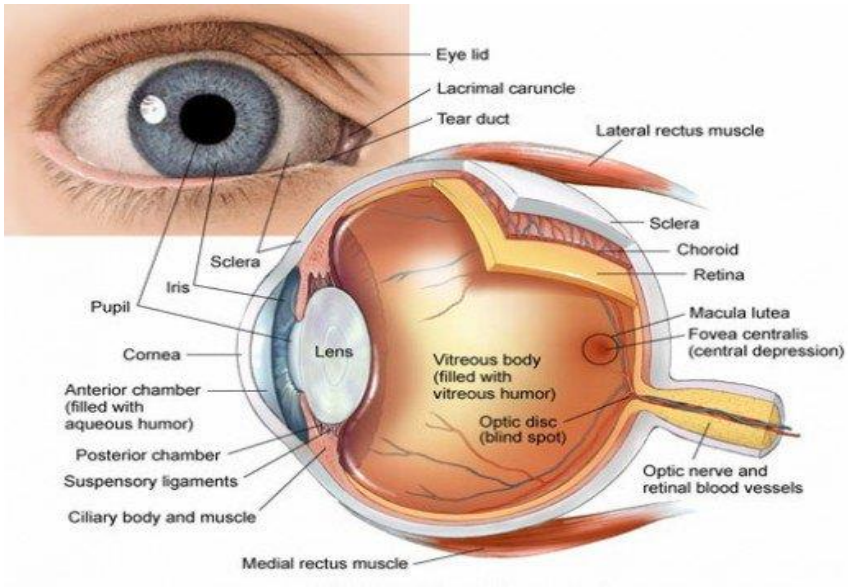


Figure 2.1: Structure of the eye (Human Eye: Anatomy, parts and structure, 2018)

2.1.1. The Outer Fibrous Layer

This layer is made up of three key structures:

- Sclera: the front of the sclera is the visible white part of the eye, and it extends inwards, covering most of the eye, providing the eye with a structural integrity and shape. The

sclera is a tough, leather-like tissue attached to the extrinsic muscles, which enables eye movements when the muscles pull it.

- Cornea: it is a transparent layer on the iris in the front and centre of the eye, covering the anterior part of the sclera. It is responsible for bending light and focusing it on the retina.
- Conjunctiva: this is a thin layer of tissue responsible for protecting the cornea from damage. It covers the inner surface of the eye, including the sclera and inner surface of the eyelids. Another important feature of the conjunctiva is its responsibility in preventing bacteria and infectious substances from getting into the inner eye.

2.1.2. The Middle Vascular Layer

The middle vascular layer consists of the ciliary body, choroid and the visible iris.

- Ciliary body: it is connected to the edge of the iris, close to the eye wall. The ciliary body produces a clear fluid, which fills the eye and is responsible for providing nutrition for the entire structure of the eye. The ciliary body also holds a connection to the lens and is responsible for keeping it in place. Another major function of the ciliary body is the contraction and relaxation of the lens in order to focus on an image.
- Choroid: this is a layer of tissue between the retina and sclera. It is embedded with various blood vessels that supply nourishment to the eye, as such is one of the most highly vascularised structures in humans (Nickla & Wallman, 2010). The choroid has pigmented cells, which absorb light and prevent the light from being reflected.

  The choroid is made up of four layers, a large layer of blood vessel (Haller's layer), a medium sized layer of blood vessels (Sattler's layer), layer of capillaries (Choriocapillaries), and an innermost layer of membrane (Bruch's membrane).
- Iris: this is a visible, muscular, ring shaped, coloured part of the eye. It is situated in front of the lens, and houses the pupil (a hole that serves as a sort of "gateway" to the back of the eye). When the iris contracts, it causes the pupil to become smaller, thereby reducing the amount of light that gets to the back of the eye and when it relaxes, the pupil in turn expands, increasing the amount of light passing through to the back of the eye.

2.1.3. The Inner Layer

The inner layer consists solely of the retina.

- Retina: it is the innermost layer of the eye and an extension of the central nervous system. It has an important function of sending stimulus to the brain through the optic nerve. The retina consists of two sets of specialized photoreceptor cells; rod cells, which are very sensitive to light enabling better vision in low lighting situations but with less colour and cone cells, which enable vision in well-lighted situations, and enable formation of images with colours. There is a part of the retina, that contains neither rod nor cone cells, it is a blind spot, and when light falls on this part of the retina, no image is formed.

2.1.4. Auxiliary Parts of the Eye

These are other parts of the eye with important functions but not necessary in any of the above-mentioned key layers of the eye.

- Orbit: This is the bony structure surrounding the eyes, protecting it from external injuries, it is made up of seven different facial bones. The orbit is surrounded by fatty tissue that cushion the eyes. The optic nerve, which transfers signals back to the brain exits the eyes through an opening behind the orbit.
- Eyelids: they serve the important role of keeping the anterior surface of the eye moist, by spreading the fluid secreted by the lacrimal gland over the surface of the eye and serve as a lid that prevent large particles from entering the eye via reflex actions.
- Eyelashes: these are attached and work in conjunction with the eyelids in protecting the surface of the eyes from foreign materials.
- Extraocular muscles: these refer to the six muscles that are responsible for the movements of the eyes. The rectus muscles (inferior recti, medial recti, lateral recti and superior recti) have their origin from a fibrous ring around the optic nerve situated at the optic foramen. The rectus muscles are attached to the sclera. The oblique muscles (superior and inferior) are attached to the sclera of the eyeballs on opposite ends. The oblique muscles are responsible for the rolling movements of the eyeballs, while the rectus muscle are responsible for the upward, downward and sideways movements of the eyeballs. Figure 2.2 shows the muscles of the eyes and their positions.

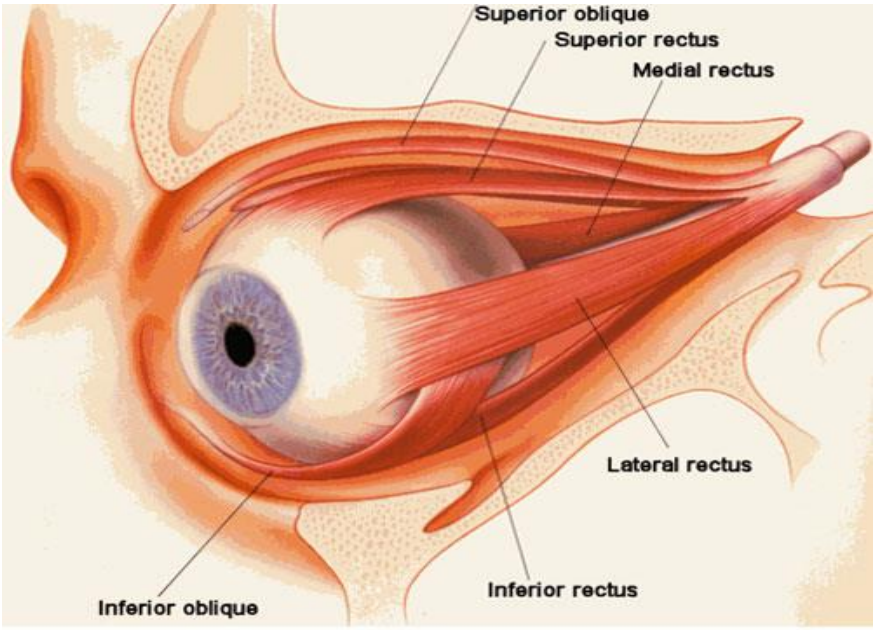


Figure 2.2: Muscles of the Eye (Anatomy of the Eye — AAPOS, 2018)

2.2. Image Formation

In order to form a clear discernable image, the light that reaches the pupil, which diverges in all directions from the source must be focused. The image formed on the retina is determined by the refraction of light by the cornea and lens, but most of the refraction is done by the cornea (Purves & Williams, 2001).

The images we see with our eyes are as a result of the light being reflected by the objects we are looking at. The light gets into the inner eye through the cornea which acts as a sort of window into the eyes, the light entering the eyes is controlled by the pupil, surrounded by the iris. The front of the eye is curved, and the cornea's refractive power is responsible for bending the light that enters the eye so that the light can pass without any inhibitions, this causes the image reaching the retina to be inverted.

The lens is an adjustable part of the eye that is responsible for focusing the incoming light on the retina, using the ciliary muscles. The lens change shape in order to focus on an object based on its distance. This adjustable feature of the lens is not controlled by the brain but rather is an involuntary action.

The retina is responsible for converting the light signals falling on it to signals recognizable by the brain. The impulses are carried to the brain by the optic nerve. The brain is responsible for

decoding these signals and turns the inverted image, making it right side up. Figure 2.3 is an illustration of how images are formed on the eye.

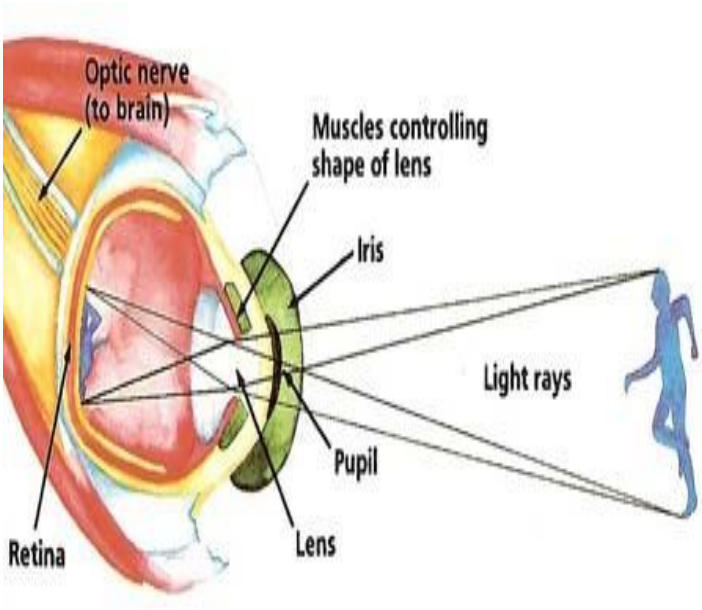


Figure 2.3: Image formation on eye (How the Eye Works - Lessons - Tes Teach, 2018)

2.3. Common Diseases that Affect the Eyes of Children

Due to the delicate state of the immune system of children, they are susceptible to a variety of diseases and infections and the eyes are not an exception. Listed below are some of the most common diseases that affect the eyes of children:

- Amblyopia: This is a defect commonly referred to as “lazy eyes”, where one eye does not transmit recognizable signals for the brain to decode, thereby leading to reduced vision, it rarely occurs in both eyes, but is a possibility. Amblyopia is the limited ability of one eye to focus as well as the other.

  The primary cause of amblyopia is unknown, and can vary from irregular shape of eye, misalignment of the eye to clouding of the lens of the eye.

  The symptoms of amblyopia include, noticeable clouding in the eyes, noticeable favoring of unaffected eye, bumping into objects in the line of sight of affected eye.

  The treatment options available for children with amblyopia include a combination therapy of correction lenses, prisms, and use of an eye patch if necessary. Vision therapy

is an option also available, whereby the patient is taught how to utilize, adjust and use both eyes together.

An early diagnosis of amblyopia increases the chances of complete recovery for affected patient and the later the diagnosis, the longer it will take for the patient to make a complete recovery. If left untreated, amblyopia will not go away on its own (Aoa.org, 2018).

- Astigmatism: This is a condition which causes the vision of the patient to be blurry, as a result of abnormal, irregularly shaped, cornea due to the curvature of the lens in the eye, meaning the eyes are not as roundly shaped as they should be, causing objects at a distance to look blurry.

  Most people are affected with a slight degree of astigmatism, as the shape of the eye is rarely perfect, it is only in chronic cases that it becomes an issue. Astigmatism usually occurs in relation to other eye defects such as myopia and hypermyopia, referred to in combination as refractive defects, due to the inability of the eyes to properly refract light, making only part of the object being viewed to be in focus.

  Astigmatism can be hereditary and is usually first noticed at birth, it can also be caused by an eye injury, eye disease or after eye surgery. Astigmatism is treatable, by using recommended lenses, or a surgery to correct the shape of the cornea.

- Childhood tearing: this condition is also known as "pediatric epiphoria" and causes excessive tearing in the eyes of children. It is a condition that is usually detected soon after birth, and could be due to improper drainage of the tear duct of the infant. When there is a blockage in the tear duct, the eyes of the child become noticeably red and swollen, with a yellowish-green discharge that cause the lids to stay stuck together.

  Pediatric epiphoria is manageable, with a high degree of success in treatment. The most common treatment is constant massage of the lacrimal duct, for the sole purpose of getting rid of any blockage and allow normal drainage of tears, very rarely is a surgical procedure needed to treat the defect. Most cases of pediatric epiphoria get corrected spontaneously, even without any massage, however for cases that persist for over 12 months, a surgical procedure is often necessary (Clarke, 1999).

- Retinitis Pigmentosa: this refers to a group of diseases that cause a breakdown and eventual loss of retina cells. Retinitis pigmentosa is a hereditary disease. It is caused by an inability

of the genes responsible for producing the proteins necessary for the nutrition of the cells to produce the required amount of proteins. The malnutrition and loss of these cells eventually leads to blindness.

The most common and foremost symptoms of Retinitis pigmentosa involve the rods due to their position on the outer part of the eye. These symptoms incluse night blindness, decreased central vision and an inability to distinguish colors.

Generally, Retinitis pigmentosa is not curable, but there are drugs and therapies that can slow the blindness, such as vitamin supplements, use of sunglasses and a retina implant.

2.4. Retinoblastoma

Retinoblastoma is a cancer that affects the retina, a light-sensitive thin layer in the inner part of the eye. It occurs when there is a mutation in both alleles of the Rb1 suppressor gene of the retinoblastoma (Rushlow et al., 2013). Retinoblastoma is one of the most common cancer types affecting children mostly between the ages of five and fifteen (Bakhshi, Meel & Radhakrishnan, 2012), though it is a cancer type that is rarely diagnosed at birth. The growth of theses cancerous cells may only affect one eye (unilateral retinoblastoma), both eyes (bilateral retinoblastoma) or in very rare cases may spread to other parts of the body like the lymph nodes or bones (trilateral retinoblastoma).

2.4.1. Types of Retinoblastoma

There are two types of pediatric retinoblastoma, hereditary retinoblastoma and non-hereditary retinoblastoma. Both types of retinoblastoma could occur in unilateral, bilateral or trilateral form.

- Hereditary Retinoblastoma: constitutes about 30-40% of retinoblastoma cases, it occurs in children whose parents or relatives have a history of the disease. The cancer is caused by a mutation in the RB1 tumor suppressor gene. Mutation occurs in one allele of the RB1 gene, with the other allele having an acquired somatic mutation.

  A main feature of hereditary retinoblastoma is its tendency to affect both eyes, only about 10-15% of unilateral retinoblastoma are hereditary. Hereditary retinoblastoma usually manifests itself in the early age of the infant (12 months).

  Children who survive hereditary retinoblastoma have an increased risk of developing other forms of cancer, which are not eye related. (Kleinerman, Schonfeld & Tucker, 2012).

- Non-hereditary Retinoblastoma: it is also known as “sporadic retinoblastoma”, most cases of non-hereditary retinoblastoma are unilateral. 60% of cases of retinoblastoma are usually non-hereditary and manifest later in life (within first 5 years of a child’s life) as compared to hereditary retinoblastoma that can be diagnosed much earlier.

  Non-hereditary retinoblastoma rarely spreads beyond the point of origin, and children with non-hereditary retinoblastoma are not at a higher risk than a normal child or person of developing other types of cancer later in life.

  Children who survive non-hereditary cancer and grow to adulthood are not at higher risk of passing the mutated gene to their children and making it hereditary.

2.4.2. Stages of Retinoblastoma

The International Classification for Intraocular Retinoblastoma (ICRB) is currently the preferred classification method of retinoblastoma by most physicians for the fact that recent advancements in treatment techniques have been considered in this classification method (How Is Retinoblastoma Staged? 2018). The classification is done based on five groups lettered A to E;

- Group A: the tumours that fall in this group are small, less than 3mm in size and are not in close proximity to any key structures of the eye.
- Group B: all other tumours greater than or less than 3mm but close to a key structure such as the fovea or optic disc fall in this group.
- Group C: the tumours in this group are distinguishable in shape and have spread to the area beneath the retina.
- Group D: in this group, the large tumours could be distinguishable or non-distinguishable in shape, and have spread extensively under the retina. The retina may have also become detached from the back of the eye.
- Group E: the tumours that fall in this group are very large and have spread to the front of the eye, causing either bleeding or glaucoma or other symptoms that cause low chances of saving the eye.

2.4.3. Common Signs and Symptoms of Retinoblastoma

1. Amblyopia: when the eyes do not appear to be looking in the same direction.
2. Painful eyes.
3. Enlarged Pupil

4. White pupillary reflex: when the pupil appears white or pink instead of red when a bright light is shone on it.
5. Differing color of iris.
6. Unchanging size of pupil when exposed to light.

2.4.4. Common Diagnostic Tests of Retinoblastoma

1. MRI or CT scan of brain: This scan is carried out in order to find out if the pineal gland, which is responsible for response to light is functioning properly as it should.
2. Biopsy: This is most probably the most dependable test for diagnosis of most cancer types. It involves takin a small sample of tissue for laboratory testing in order to determine if there is any abnormalities in the cells. However, a biopsy test is rarely done in retinoblastoma cases unless absolutely necessary, this is to avoid damaging the cells of the eye in the process of harvesting the cells, or causing the tumor cells to spread.
3. Ultrasound Scan: It involves the use of sound waves to create an image of tissues in the body and determine if there is the presence of a tumor and its location. Ultrasound scans are generally the most preferred and utilized method for diagnosing retinoblastoma because it is a painless procedure and does not have any risk associated with radiation.

2.4.5. Factors to Consider in Relation to Retinoblastoma

After diagnosis and before any treatment plan is embarked on, there are certain factors that should be considered which might in some way affect the decision of the therapeutic technique that will be considered regarding the patient.

1. How far the tumor has spread.
2. Age of the patient.
3. If the cancer is hereditary or non-hereditary.

2.4.6. Treatment Techniques of Retinoblastoma

As stated earlier, retinoblastoma has a high success rate when it comes to treatment, especially if it is diagnosed in its early stages. The most common treatment techniques of retinoblastoma are discussed below.

1. Chemotherapy: This is a treatment technique that involves the use of drugs to eliminate cancerous cells. This treatment technique involves the use of one or more drugs singularly or in combination, usually given in cycles over a period of time. Most times, chemotherapy alone is not enough to completely get rid of the cancerous cells but is instead utilized

before a treatment technique to shrink the tumor (chemoreduction) or after a treatment technique to completely get rid of the residue cells. One of the indications that usually necessitates the use of chemotherapy is when the tumors are too large to be gotten rid of by the use of local therapies alone, recurrent and relapsed tumors, for cases of high-risk histopathologic characteristics it is used as adjuvant treatment to enucleation (Chawla, Jain and Azad, 2013).

Some side effects that can arise from chemotherapy of retinoblastoma include, kidney problems, hearing problems, swelling of tissues around the eye, drooping eyelid, drop in vision quality of the affected eye.

Chemotherapy can be used in the following ways;

a) Systematic Chemotherapy: This is when chemotherapy drugs are administered into the bloodstream either intravenously or orally using drugs.

b) Periocular Chemotherapy: This technique involves injecting some of the drugs into the tissues surrounding the eye. This is usually practiced in combination with systematic chemotherapy when it is suspected that the tissues around the eye are not absorbing as much of the drugs from the bloodstream as needed.

c) Intra-arterial Chemotherapy: This technique involves injecting the drugs directly into the artery that supplies blood to the eye. Since, the drugs are injected directly into the ophthalmic artery in this case, lower doses are used as compared to the dose used in systematic chemotherapy.

2. Radiotherapy: In this treatment technique, high energy x-ray particles are used to bombard the cancerous cells.

Radiation therapy is considered advantageous over surgery because if successful, the eye and vision is saved, but there are also some disadvantages associated with this technique, such as loss of hair, dental problems, slowing and affecting proper growth of facial bones, dry eye, fatigue, drowsiness, nausea, cataract and risk of developing another cancer.

There are two types of radiation therapy that are used in treating retinoblastoma;

a) External beam radiotherapy (EBRT): In this procedure, an external x-ray source is focused on the site of the tumor. The technique is similar to getting a routine x-ray exam, but with higher dose of x-ray focused on the area of interest. Due to the high

risk side effects associated with this technique of radiotherapy, such as damage to the ocular structures and increased risk of a secondary tumor, EBRT has been replaced with other more suitable treatment techniques and is only utilized when the preferred techniques fail or if there are multiple or very large tumors (Bakhshi, Meel & Radhakrishnan, 2012).

b) Brachytherapy (plaque radiotherapy): In this technique, a small radioactive material is placed on the affected eye and held in place by a holder and left in place for several days. The place holder or plaque is made up of materials that shield nearby tissues from damage due to radiation and is held in place by small sutures. The use of this therapeutic technique is limited to small tumors and is advantageous because the radiation exposure is limited to the area of interest.

3. Cryotherapy: Also referred to as "cryosurgery", is a treatment technique that involves rapid freezing of cancerous cells using a low temperature probe. Cryotherapy is more efficient for use on small tumors that are close to the front of the eye, it is rarely used on large tumors or multiple tumor cells.

   The whole procedure of cryotherapy is carried out in two or three sessions, with a monthly break in between sessions. Cryotherapy administered a couple of hours before a chemotherapy treatment increases the delivery of the drug across the system (Pandey, 2014).

   Cryotherapy is associated with low side effects which include, temporary swelling of the eye, blind spots and temporary detachment of the retina from the eyeball, it also results in a scar which is usually larger than the tumor.

4. Surgery (Enucleation): This treatment technique is utilized when there is a very large tumor which cannot be gotten rid of using other treatment techniques and removal of the eye and some part of the optic nerve surrounding it becomes necessary in other to prevent the tumor from spreading.

   Enucleation is usually not considered in bilateral retinoblastoma in order to preserve vision in one eye unless absolutely necessary. Enucleation has a high success rate in eliminating cancerous cells albeit with loss of vision in the affected eye, though in most cases where enucleation is used, vision in the affected eye has been lost already due to the advanced stage of the tumor.

5. Thermotherapy: This technique involves the application of heat with temperature between 45℃ to 60℃ directly on the tumor, using infrared rays, ultrasound or microwave. The threshold temperature is suitable and does not cause coagulation of the retinal vessels (Chintagumpala, Chevez-Barrios, Paysse, Plon & Hurwitz, 2007).

   Thermotherapy is suitable for small tumors, but can be used as a combination therapy with chemotherapy or radiation therapy if thermotherapy alone is insufficient to eliminate all the cancerous cells. The side effects associated with this technique include, shrinkage of the iris, clouding of the lens, scarring of the eye, swelling of eyelid and damage to the retina.

6. Laser therapy (Photocoagulation): In this technique, a laser beam is aimed through the pupil to eliminate with heat the blood vessels that feed the cancerous cells. This is carried out by coagulating the blood in the blood vessels that feed the tumor and blocking, this will in turn block the flow of blood and cause the vessels to shrink, thereby starving the tumor. Photocoagulation is effective and mostly utilized on small tumors that are situated towards the back of the eye.

   The procedure of photocoagulation is mostly done with the patient under anesthesia, this is to ensure that the patient does not move during the procedure. The procedure is usually carried out about three times with a month in between treatments.

   Side effects of the laser therapy include retinal detachment, blind spots, red eyes and swelling.

CHAPTER 3

LITERATURE REVIEW

Many researchers have carried out studies on multi-criteria decision-making (MCDM) techniques and how they can be applied in various fields such as chemistry, engineering, medicine and even social studies to improve the quality of life. Such MCDM techniques include, Analytic hierarchy process (AHP), Simple Multi-Attribute Rating Technique (SMART), ELECTRE (Outranking), PROMETHEE (Outranking) to mention but a very few of the numerous techniques that are available (Weistroffer, Smith & Narula, n.d.).

PROMETHEE ranking is one of the most common of these decision-making tools, which was developed as an outranking method to obtain either a partial or complete outranking of a defined set of practical actions (Brans, Vincke & Mareschal, 1986).

Ozsahin et al. (2017) conducted a study, which evaluated cancer treatment alternatives using fuzzy PROMETHEE. They applied the principle of multi-criteria decision-making theories on various cancer treatment techniques. Their study was focused on comparing the treatment techniques of chemotherapy, radiation therapy, hadron therapy, immune-therapy, hormone therapy and surgery with regards to some primary factors that could affect the outcome of a chosen treatment technique, such as treatment duration, cost of treatment, side effects and survival rate. Their results concluded that hadron therapy, which emerged with the highest survival percentage, shortest treatment time and combined net-flow value of 0.4931 was the most suitable treatment technique for a cancer patient.

Ozsahin et al. (2017) carried out a research to evaluate and compare the most common nuclear medicine imaging devices available, using a multi-criteria decision-making technique. In this study, they made comparisons between Positron Emission Tomography (PET), Single Positron Emission Computed Tomography (SPECT), PET/CT, SPECT/CT and PET/MRI using cost of treatment, average radiation dose, spatial resolution, sensitivity and specificity of the device, energy resolution and average scan time as parameters for the comparison. In their analysis, they used Yager Index to find the magnitude of the triangular fuzzy numbers. Finally, they utilized Visual PROMETHEE Decision Lab Program with the Gaussian preference function to

arrive at their results. Their analysis concluded that PET with a net-flow of 0.0005 is a more beneficial and advisable imaging device based on the parameters used.

Ozsahin et al. (2018) carried out a study that examined and compared the most commonly employed techniques of image construction algorithms in nuclear medicine, using the method of fuzzy PROMETHEE. In their study, they compared Ordered Subset Expectation Maximization (OSEM), Origin Ensemble (OE), List Mode-OSEM (LM-OSEM) and Filtered Back Propagation (FBP), which are the most commonly used image construction algorithms to decide on the most effective technique which would likely produce a higher quality image, an important and desirable feature in nuclear imaging. The parameters they used to make the comparison in the study are, Modulation Transfer Function (MTF), Mean Square Error (MSE), Bias, Run Time, Variance, Resolution Compensation (RC) and Uniformity. The results of their study show that according to the parameters used, FBP is a superior algorithm for higher quality images, with a net-flow of 0.0031.

Ozsahin et al. (2018) used Fuzzy Preference Ranking Method for Enrichment Evaluations to evaluate x-ray based medical imaging devices. They used Fuzzy PROMETHEE to assess the image quality parameters of these x-ray based devices in order to portray the efficiency, potentiality and negativity of each device. The parameters utilized in their studies to make these analysis were, sensitivity, specificity, radiation dose, cost of treatment and the cost of the machine. The parameters were chosen and analyzed based on the effects they have on the patient as well as the hospital. The devices that were put into consideration for these analyses are conventional x-ray machine, angiography, Computed Tomography (CT), fluoroscopy and mammography. They used Yager index to view the magnitude of the parameters of the alternatives. Their results rank the conventional x-ray machine as a suitable imaging device when the cost of machine is not put into consideration with a net flow of 0.0017. While mammography outranked the other medical imaging devices when the cost of machine is put into consideration with a net flow of 0.0015.

Ozsahin and Ozsahin (2018) made a fuzzy PROMETHEE approach for breast cancer treatment techniques to analyze and rank the most suitable treatment technique for patients diagnosed with breast cancer. In their research, they made analysis on surgery, radiotherapy, chemotherapy and hormone therapy treatment techniques for breast cancer, using parameters such as treatment time, cost of treatment, side effects and overall survival rate of each technique. They applied Yager index to defuzzify the triangular fuzzy numbers and calculate

the weight of each criterion. The conclusion of their studies ranked surgery as the most suitable treatment technique for patients with breast cancer, amounting a net flow of 0.5156, based on the parameters that they used.

Silas and Rajsingh (2016) used different multi-criteria decision methods such as ELECTRE, PROMETHEE and AHP to analyze healthcare services application. The analysis was done based on certain criteria such as, the average overhead incurred in selection of the health care services, the time taken to select the health care services, degree of human intervention and patient satisfaction based on the overall performance. The results of their analysis indicate that PROMETHEE is a suitable MCDM tool for application in healthcare service analysis with 95% of users preferring PROMETHEE algorithm for the selection of a healthcare service.

Amaral and Costa (2014) applied PROMETHEE II in a research to analyze and support decision-making and resource management in an emergency department. The method of their analysis was validated using experimental data from a public hospital in Brazil. Six months after implementing the solution of the analysis obtained from their research the waiting time during overcrowding periods in the waiting room had been reduced by about 70%. Using PROMETHEE enables the decision maker to choose the best option to solve problems that result in overcrowding in the emergency departments of hospitals and can also be extended to other departments.

CHAPTER 4

METHODOLOGY

4.1. Fuzzy Logic

Obtaining crisp data that accurately defines real life situations is a very challenging feat. Additional to this challenge is the description of imprecise data or information that is not completely true or false. Boolean logic has a system of extremities, a situation is either true (1) or false (0), no room for in-betweens or uncertainties is allowed. In fuzzy logic however, a machine can treat situations with a degree of uncertainty attached. For instance, Boolean logic in treating the temperature of a room will either state that the room is hot or cold, but at what point does the temperature cross over from being cold to being hot? Fuzzy logic however provides an alternative of very cold, cold, warm, hot, very hot and so on in order to solve the problem associated with uncertainty.

Fuzzy logic is preferred and has an advantage over other methods such as predictable logic, Bayesian control, probability theory, classical theory and so many such systems because on fuzzy logic provides a system of computing with words, meaning words are used to represent numbers in computing and reasoning (Zadeh, 1996).

4.2. Multi-criteria Decision-Making

Multi-criteria decision-making (MCDM) also referred to as multiple-criteria decision analysis (MCDA) is a research area that makes analysis of various available choices in a situation or research area which spans daily life, social sciences, engineering, medicine and many other areas. (Zionts, 1979) defined the term as solving a problem with multiple conflicting objectives. MCDM is one of the most popular decision-making tool utilized in various fields (Mardani et al., 2015).

MCDM analyses the criteria involved in a parameter that makes the parameter a favorable or unfavorable choice for a particular application and attempts to compare this parameter based on the selected criteria, against every other available option in an attempt to assist the decision maker in selecting an option with the minimal compromise and maximum advantages. The criteria used in the analyses of these parameters can be either qualitative or quantitative parameters.

Division of MCDM can be made into two categories based on the method used to determine the weight of each alternative (Majumder, 2015):

i. Compensatory decision-making: involves evaluating the criteria of the parameters including the weak points and strong points of the parameters and allowing the strong points of each parameter to make up for the weak points, thereby putting all the criteria of the parameters into consideration. An example of compensatory decision-making tool is the Analytical Hierarchy Process (AHP) a technique mostly used when the environment for the analysis is complex, it is used in the comparison of parameters that are difficult to quantify.

ii. Outranking decision-making: this method compares the criteria of the parameters in couples in order to determine which parameter ranks higher than the others based on the comparisons (Yang, Wang & Wang, 2012). A popular example of an outranking decision-making method is Elimination and Choice Expressing Reality (ELECTRE) a method that is used to choose, rank and sort out alternatives to solve a problem.

4.3. Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE)

PROMETHEE is a multi-criteria decision-making tool that allows a user to analyze and rank available alternatives based on the criteria of each alternative. PROMETHEE compares the available alternatives based on the selected criteria.

PROMETHEE is preferred over other multi-criteria decision methods for reasons such as;

- PROMETHEE can be used to handle qualitative and quantitative criteria simultaneously.
- PROMETHEE deals with fuzzy relations, vagueness and uncertainties.
- PROMETHEE is easy to handle and provides the user maximum control over the weights of the criteria.

Using PROMETHEE requires only a couple of information from the decision maker, an information regarding the weights of the selected criteria and the preference function to be used in comparing the alternatives' contribution as regards each criterion (Macharis, Springael, De Brucker & Verbeke, 2004).

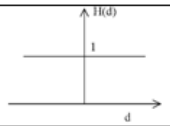
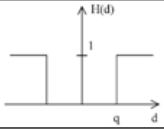
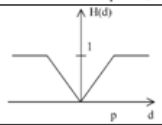
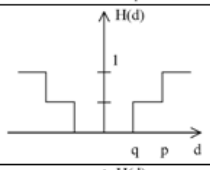
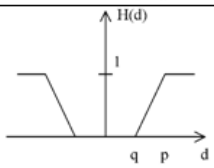
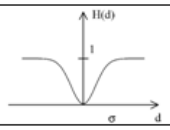
Different preference functions (P_j) are available on PROMETHEE for the definition of different criteria. The preference function defines the difference between the evaluations with

two alternatives (a and a_t) in relation to a specific criterion and a preference degree ranging between 0 and 1. The preference functions for practical purposes that can be used at the discretion of the decision maker include; usual function, v-shape function, level function, u-shape function, linear function and Gaussian function. A detailed description of the preference functions used, their ranking and how to make a decision on which function best suits a scenario was discussed by J. P. Brans et al. a quick summary of the preference functions is shown in Table 4.1 (Brans, Vincke & Mareschal, 1986). Generally, type III (v-shape) and type V (linear) preference functions are mostly used for data with quantitative measures, while type I (usual shape) and type IV (level) preference functions are mostly used for qualitative data.

The significance of the parameters to be defined are as follows;

- q indicates a threshold of indifference.
- p is a threshold that indicates strict preference.
- σ is an intermediate point between q and p.

Table 4.1: Types of Generalised Criteria

Type of genera- lazed criteria	Analytical definition	Shape	Parameters to define
Type I. Usual criterion	$H(d)=\begin{cases}0, & d=0;\\ 1, & \lvert d\rvert>0.\end{cases}$		--
Type II. Quasi-criterion	$H(d)=\begin{cases}0, & \lvert d\rvert\le q;\\ 1, & otherwise.\end{cases}$		q
Type III. Criterion with linear preference	$H(d)=\begin{cases}\frac{\lvert d\rvert}{p}, & \lvert d\rvert\le p;\\ 1, & \lvert d\rvert>0.\end{cases}$		p
Type IV. Level-criterion	$H(d)=\begin{cases}1, & \lvert d\rvert\le q;\\ 1/2, & q<\lvert d\rvert\le p;\\ 1, & otherwise.\end{cases}$		q, p
Type V. Criterion with linear preference and indifference area	$H(d)=\begin{cases}1, & \lvert d\rvert\le q;\\ \frac{\lvert d\rvert-q}{p-q}, & q<\lvert d\rvert\le p;\\ 1, & otherwise.\end{cases}$		q, p
Type VI. Guassian criterion	$H(d)=1-\exp\{-\frac{d^2}{2\sigma^2}\}$		σ

4.3.1. The Steps of the PROMETHEE Method

The creators of the technique (Brans, Vincke & Mareschal, 1986) have discussed the complete steps of the PROMETHEE method, this method has not been altered in any way for this research.

1. Define a specific preference function p_j (d) for each criterion j.
2. Determine the weight of each criterion $w_t = (w_1, w_2, \ldots, w_k)$. Normalization of weights or equality of weights can be decided at the discretion of the decision maker based on the application.
3. For every alternative $a_t, a_{t'} \in A$, determine the outranking relation π.

$$\pi(a_t, a_{t'}) = \sum_{k=1}^{K} w_k . \left[p_k\left(f_k(a_t) - f_k(a_{t'})\right)\right], \qquad AXA \rightarrow [0,1]$$

4. Determine the positive and negative outranking flows;

   - Positive outranking flow for a_t: $\Phi^+(a_t) = \frac{1}{n-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_t, a_{t'})$
   - Negative outranking flow for a_t: $\Phi^-(a_t) = \frac{1}{n-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_{t'}, a_t)$

   n refers to the number of alternatives, and each alternative is compared to an n-1 number of alternatives.

   The positive outranking flow is an expression of how a particular alternative bests the other alternatives. The higher the positive outranking value of a particular alternative is, the better the alternative.

   The negative outranking flows is an expression of how a particular alternative is bested by other alternatives. The lower the negative outranking value is, the better the alternative.

5. Define the partial preorder on the alternatives of A. In PROMETHEE I alternative a_t is preferred to alternative $a_{t'}$ $(a_t P a_{t'})$ if it satisfies the one of the following conditions:

$(a_t P a_{t'})\ if;$

$$\begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'})\ and\ \Phi^-(a_t) < \Phi^-(a_{t'}) \\ \Phi^+(a_t) > \Phi^+(a_{t'})\ and\ \Phi^-(a_t) = \Phi^-(a_{t'}) \\ \Phi^+(a_t) = \Phi^+(a_{t'})\ and\ \Phi^-(a_t) < \Phi^-(a_{t,}a_{t'}) \end{cases}$$

If there are two alternatives (a_t and $a_{t'}$), with similar or equal leaving and entering flows, a_t is indifferent to $a_{t'}$ ($a_t I a_{t'}$):

$$(a_t I a_{t'}) \text{ if: } \Phi^+(a_t) = \Phi^+(a_{t'}) \ and \ \Phi^-(a_t) = \Phi^-(a_{t'}).$$

a_t is incomparable to $a_{t'}$ ($a_t R a_{t'}$) if;

$$\begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'}) \ and \ \Phi^-(a_t) > \Phi^-(a_{t'}) \\ \Phi^+(a_t) < \Phi^+(a_{t'}) \quad and \ \Phi^-(a_t) < \Phi^-(a_{t'}) \end{cases}$$

6. Determine the net outranking flow for each alternative

$$\Phi^{net}(a_t) = \Phi^+(a_t) - \Phi^-(a_t)$$

Using PROMETHEE II, the complete preorder can be obtained by the net flow and defined by:

a_t is preferred to $a_{t'}$ ($a_t P a_{t'}$) if $\Phi^{net}(a_t) > \Phi^{net}(a_{t'})$

a is indifferent to $a_{t'}$ ($a_t I a_{t'}$) if $\Phi^{net}(a_t) = \Phi^{net}(a_{t'})$.

In other words, the better alternative is the one having the higher $\Phi^{net}(a_t)$ value.

4.4. Application of PROMETHEE to the Project

To determine the weight of each criterion, Yager index was used to defuzzify the triangular fuzzy numbers. The use of Yager index was preferred over other methods because it puts into consideration all the points and is not hugely affected by extreme values or weights.

Table 4.2 shows the importance of the parameters on a linguistic scale, using a triangular fuzzy scale, the weights of these parameters are based on an expert opinion, arrived upon from experience with cancer patients and the factors that contribute the most in ensuring the patients get the maximum results from a treatment alternative. These weights can also be altered depending on the decision maker, condition of the patient and most importantly discretion of an expert.

Table 4.2: Linguistic scale of importance

Linguistic scale for evaluation	Triangular fuzzy scale	Importance ratings of criteria
Very high (VH)	(0.75, 1, 1)	Chance of blindness

Important (H)	(0.50, 0.75, 1)	Radiation dose
Medium (M)	(0.25, 0.50, 0.75)	Cost of treatment, side effects
Low (L)	(0, 0.25, 0.50)	Treatment period
Very low (VL)	(0, 0, 0.25)	

After all the parameters of the lung cancer treatment techniques were collected, Gaussian preference function was applied for each criterion using visual PROMETHEE decision lab program. Table 4.3 is shows the parameters and weights of the criteria including the values of the parameters as used for the analysis. Gaussian preference function has been preferred over the other preference functions due to the fact that it does not take into account and is not affected by minute and inconsequential deviations in the input values of the parameters (Parreiras & Vasconcelos, 2007).

Table 4.3: Visual PROMETHEE Application for Retinoblastoma Treatment Alternatives

Criteria	**Treatment Period**	**Chances of Blindness**	**Cost of Treatment**	**Radiation Dose**	**Side Effects**
Unit	*months*	*%*	*$*	*mSv*	
Preferences					
(min/max)	*min*	*Min*	*min*	*min*	*min*
Weight	*0.25*	*0.92*	*0.50*	*0.75*	*0.50*
PreferencFn.	*Gaussian*	*Gaussian*	*Gaussian*	*Gaussian*	*Gaussian*
Evaluations					
Cryotherapy	3	12.5	5,500	0	low
Thermotherapy	3	10	14,000	0	moderate
Enucleation	1	100	26,400	0	low
Radiation Therapy	1	20	30,210	40000	high

Chemotherapy	7	18	12,000	0	high
Photocoagulation	3	50	7,500	0	Moderate

CHAPTER 5

RESULTS

The results of the analysis show that with the set treatment period, the chance of survival, cost of treatment radiation dose and side effects, cryotherapy is a favorable treatment technique for retinoblastoma.

Table 5.1 shows a complete ranking of the treatment techniques, showing the positive, negative and net outranking flow values.

Table 5.1: Complete Ranking of Retinoblastoma Treatment Techniques

Complete Ranking	Alternative	Positive outranking flow	Negative outranking flow	Net Flow
1	Cryotherapy	0.4876	0.0253	0.4623
2	Thermotherapy	0.4021	0.1133	0,2889
3	Chemotherapy	0.2927	0.2582	0.0345
4	Photocoagulation	0.2652	0.2968	-0.0317
5	Enucleation	0.1280	0.4521	-0.3240
6	Radiation Therapy	0.1511	0.5810	-0.4299

Figure 5.1 shows the ranking of each treatment technique on a net flow-ranking pole of -1 to +1, with cryotherapy the most favorable technique lying at a net flow point value of 0.4623 and Radiation therapy lying at net flow point value of -0.4299 as the least favorable technique.

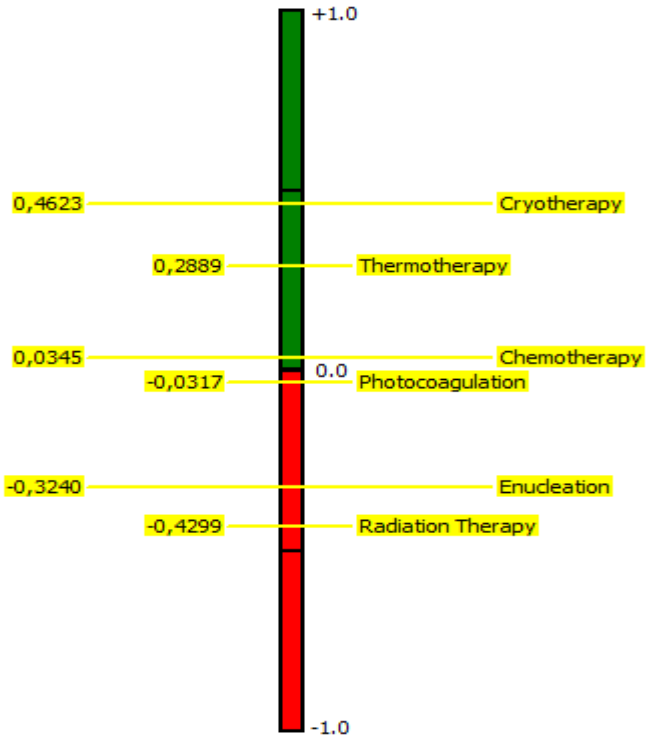


Figure 5.1: Flow-ranking Pole of Retinoblastoma Treatment Techniques

Figure 5.2 shows an action profile of the strong points and weak points for cryotherapy, having a high positive ranking in the chances of blindness and cost of treatment but showing a low ranking in radiation dose, side effects and treatment period.

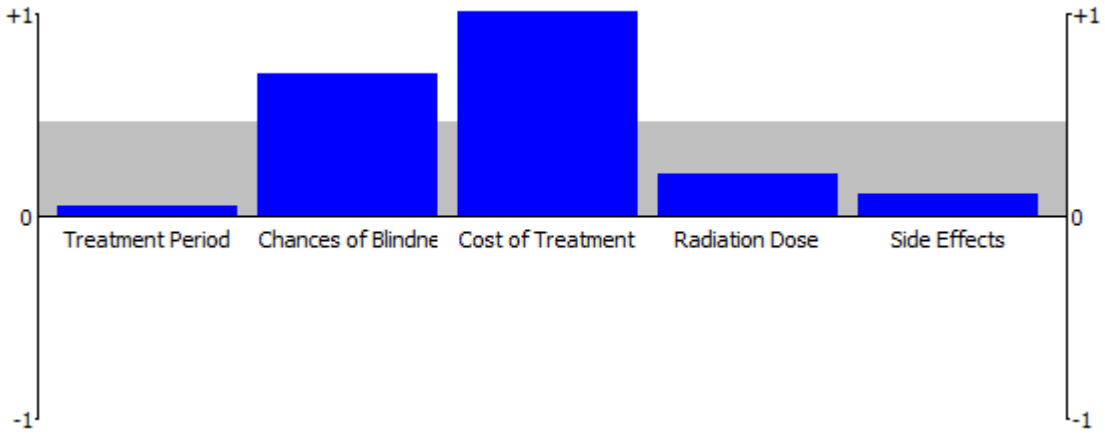


Figure 5.2: Action Profile for Cryotherapy

Figure 5.3 shows very strong point for the chances of blindness in relation to thermotherapy treatment technique for retinoblastoma, but a negative ranking as regards the cost of treatment, with treatment period and radiation dose at very low points. Side effects of thermotherapy however is on an average overall rating, as it lies on the zero mark.

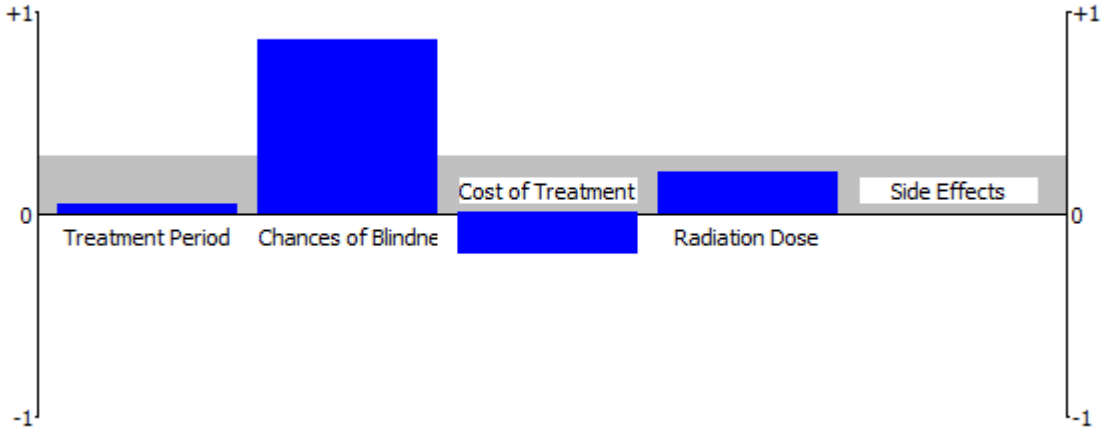


Figure 5.3: Action Profile for Thermotherapy

Figure 5.1 shows the action profile for enucleation shows low ranking of treatment period, radiation dose and side effects, but negative ranking of chances of blindness and cos of treatment. The very low ranking and negative rankings obviously accounts for the negative net-flow ranking of enucleation in the treatment techniques of retinoblastoma.

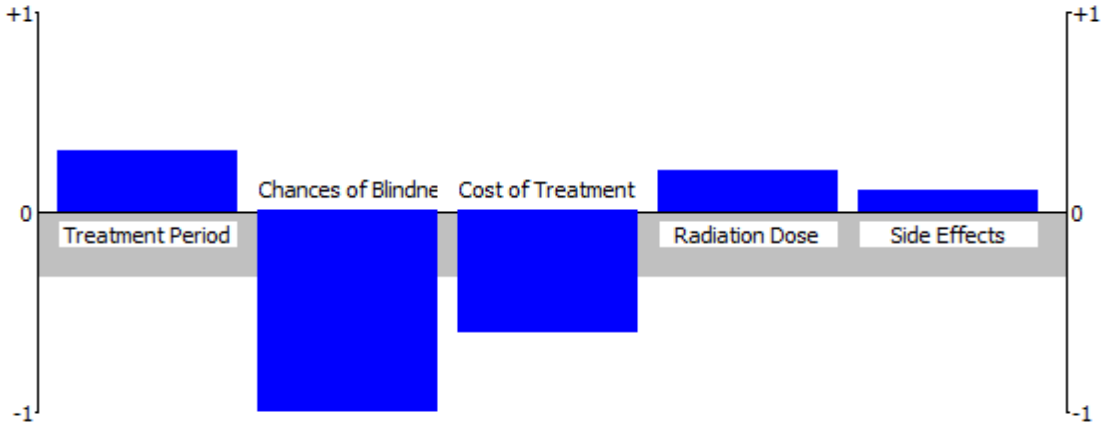


Figure 5.4: Action Profile for Enucleation

Figure 5.5 shows the action profile of radiation therapy indicates very high negative ranking of cost of treatment and radiation dose. The side effects and chances of blindness of radiation therapy for retinoblastoma is also on a negative rank, albeit less than that of the cost of treatment and radiation therapy. Only the treatment period is ranked positively and not even very highly. These rankings indicate why the net-flow of radiation therapy is on 0.4299, resulting in it being the least ranked treatment technique for retinoblastoma in this analysis.

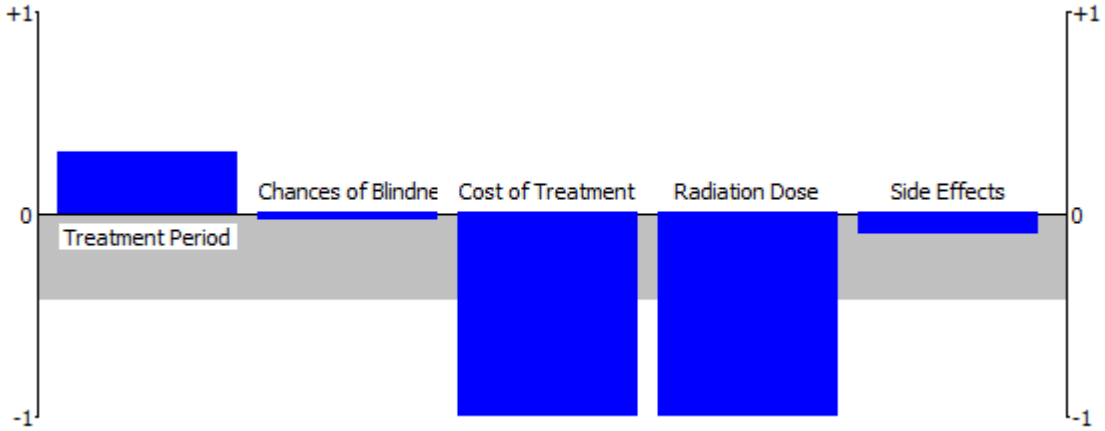


Figure 5.5: Action Profile for Radiation therapy

Figure 5.6 is the net-flow for chemotherapy as regards retinoblastoma is 0.0345 this is backed by the fact that the chances of blindness, cost of treatment and radiation dose have very low positive ranking, the side effects of chemotherapy is also low on the negative rank. The treatment period of chemotherapy as regards retinoblastoma however, is very high.

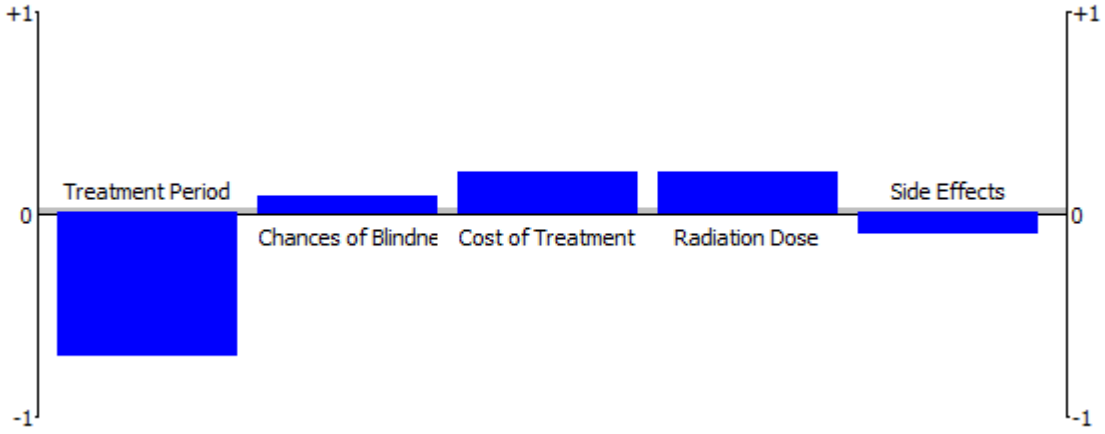


Figure 5.6: Action Profile for Chemotherapy

Figure 5.7 is an action profile for Photocoagulation treatment technique of retinoblastoma it shows a very low positive ranking of treatment period, a low positive ranking on radiation dose and a relatively high positive ranking on cost of treatment and a zero mark ranking of side effects. The ranking of the chance of blindness is very high on the negative side.

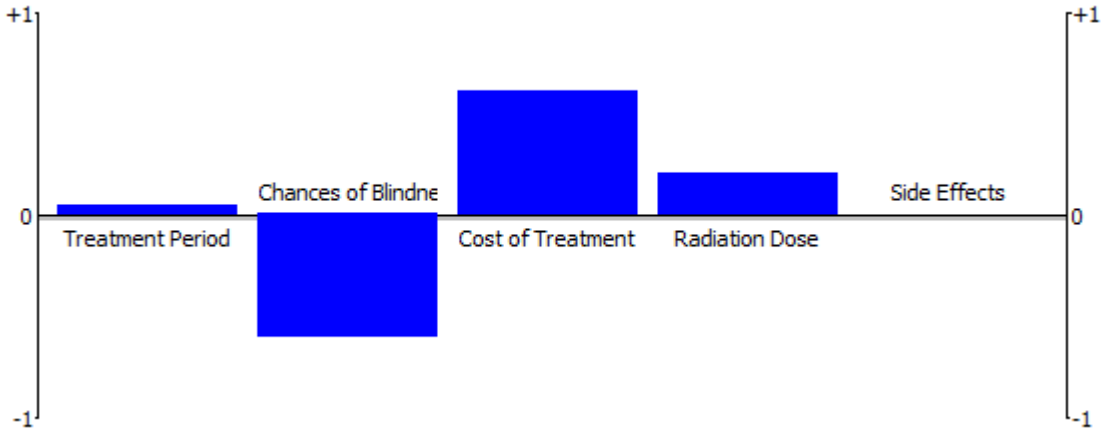


Figure 5.7: Action Profile for Photocoagulation

Figure 5.8 shows a comprehensive rainbow ranking of the treatment techniques and the criteria that make a technique favorable and the criteria that make it unfavorable.

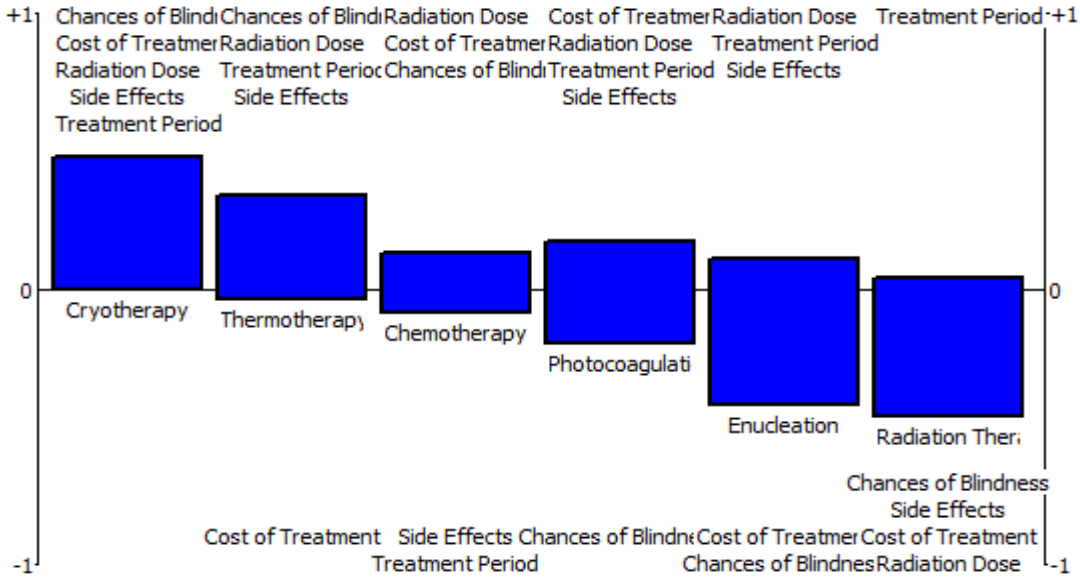


Figure 5.8: Rainbow Ranking of Retinoblastoma Treatment Techniques

Figure 5.9 is a network ranking view of the treatment alternatives with the negative and positive outranking values. This network view can be used to clearly outline how the treatment

alternatives are ranked and the order in which they can be undertaken, from the most favorable, to the least favorable.

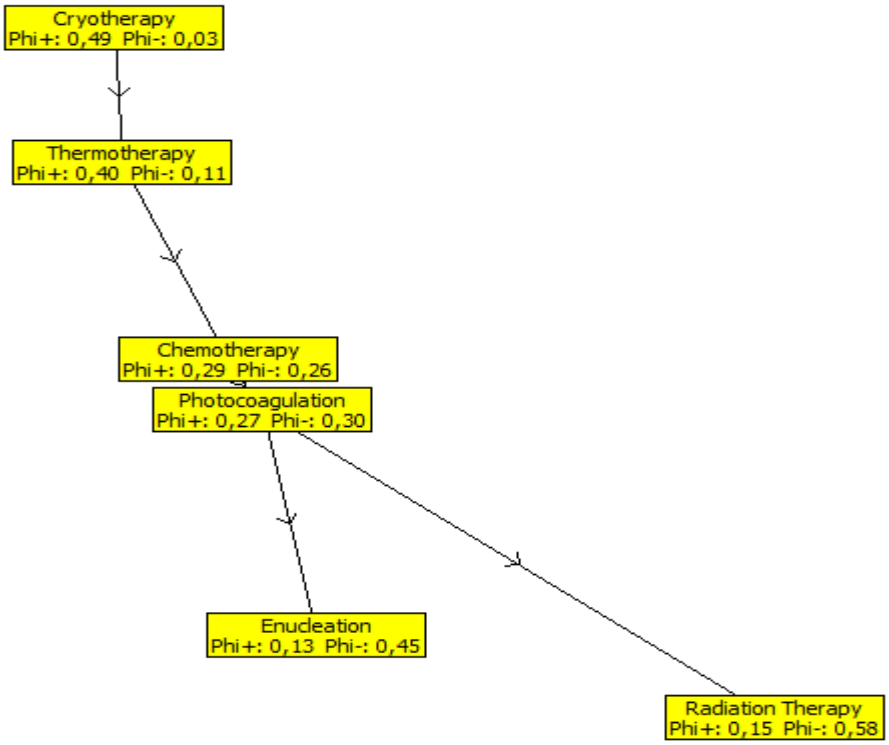


Figure 5.9: Network Ranking View of Retinoblastoma Treatment Alternatives

CHAPTER 6

DISCUSSION AND CONCLUSION

6.1. Discussion

The analysis of these results show that Cryotherapy clearly outclasses other treatments methods of retinoblastoma with a net flow ranking of 0.4623. This is due largely to the fact that cryotherapy treatments involve relatively low chance of blindness, lowest treatment cost, no radiation dose, and low side effects compared to the other treatments alternatives of retinoblastoma. Thermotherapy comes next with a net-flow ranking of 0.2889, followed by chemotherapy with a net-flow ranking of 0.0345. The negative net-flow ranking of -0.0317 gained by photocoagulation places it above Enucleation, which has a net-flow ranking of -0.3240. Radiation therapy on the other hand had only an advantage over the others with low treatment period but high chances of blindness, side effects and treatment cost and has a net-flow ranking of -0.4299.

Fuzzy PROMETHEE is an effective method to employ in decision-making situations. It gives the user complete control over the parameters and their importance, fuzzy PROMETHEE weighs these parameters against each other to determine the combination of parameters that make an option better than other available options.

Changing the weights of any of the criteria in the analysis will likely result in different ranking of the treatment techniques, the weights used in this analyses is a generalized weights based on expert opinion of most likely and commonly seen scenarios. However, the weights can be changed based on the desires and health condition of the patient or the discretion of the oncologist in order to arrive at a different ranking that will best suit the patient.

6.2. Conclusions

It is of utmost importance that it should be noted that preferential ranking methods are solely to be used in assisting a specialist or decision maker in coming up with a decision and is not to be relied upon solely. As can be seen from this project, enucleation is ranked before radiation therapy even though enucleation will result in the total loss of vision. It is widely known and accepted that enucleation is only used as a last treatment resort and only when there is no hope of recovering the vision in the affected eye(s). Therefore in this case like most cases, care

should be taken when using preferential ranking methods, for now they should be accepted for aiding in decision-making and not just accepted blindly without an expert opinion. The results of a preferential ranking analysis may not be as accurate due to some factors such as the fact that data meant to affect the output of the analysis may not have been available at the time analyses were made.

REFERENCES

Amaral, T., & Costa, A. (2014). Improving decision-making and management of hospital resources: An application of the PROMETHEE II method in an Emergency Department. *Operations Research For Health Care*, *3*(1), 1-6.

Anatomy of the Eye — AAPOS. (2018). Retrieved from https://www.aapos.org/terms/conditions/22

Aoa.org. (2018). Amblyopia (Lazy Eye). [online] Available at: https://www.aoa.org/patients-and-public/eye-and-vision-problems/glossary-of-eye-and-vision-conditions/amblyopia [Accessed 8 Aug. 2018].

Bakhshi, S., Meel, R., &Radhakrishnan, V. (2012). Current therapy and recent advances in the management of retinoblastoma. *Indian Journal Of Medical And Paediatric Oncology*, *33*(2), 80.

Bowman, R. (2018). Retinoblastoma: a curable, rare and deadly blinding disease. *Community Eye Health Journal*.

Brans, J., Vincke, P., & Mareschal, B. (1986). How to select and how to rank projects: The Promethee method. *European Journal Of Operational Research*, *24*(2), 228-238.

Chawla, B., Jain, A., & Azad, R. (2013). Conservative treatment modalities in retinoblastoma. *Indian Journal Of Ophthalmology*, *61*(9), 479.

Clarke, W. (1999). The child with epiphora. *Paediatrics & Child Health*, *4*(5), 325-326.

Chintagumpala, M., Chevez-Barrios, P., Paysse, E., Plon, S., & Hurwitz, R. (2007). Retinoblastoma: Review of Current Management. *The Oncologist*, *12*(10), 1237-1246.

Houston, S., Murray, T., Wolfe, S., & Fernandes, C. (2011). Current Update on Retinoblastoma. *International Ophthalmology Clinics*, *51*(1), 77-91.

How Is Retinoblastoma Staged? (2018). Retrieved from https://www.cancer.org/cancer/retinoblastoma/detection-diagnosis-staging/staging.html.

How The Eye Works - Lessons - Tes Teach. (2018). Retrieved from https://www.tes.com/lessons/-2DXocxhvkrGkQ/how-the-eye-works.

Human Eye: Anatomy, parts and structure -. (2018). Retrieved from http://www.onlinebiologynotes.com/human-eye-anatomy-parts-structure/

Kleinerman, R., Schonfeld, S., & Tucker, M. (2012). Sarcomas in hereditary retinoblastoma. *Clinical Sarcoma Research*, *2*(1), 15.

Macharis, C., Springael, J., De Brucker, K., & Verbeke, A. (2004). PROMETHEE and AHP: The design of operational synergies in multicriteria analysis. *European Journal Of Operational Research, 153*(2), 307-317.

Majumder, M. (2015). Multi Criteria Decision Making. *Impact Of Urbanization On Water Shortage In Face Of Climatic Aberrations*, 35-47.

Mardani, A., Jusoh, A., MD Nor, K., Khalifah, Z., Zakwan, N., & Valipour, A. (2015). Multiple criteria decision-making techniques and their applications – a review of the literature from 2000 to 2014. *Economic Research-Ekonomska Istraživanja, 28*(1), 516-571.

Naseripour, M. (2012). "Retinoblastoma survival disparity": The expanding horizon in developing countries. *Saudi Journal Of Ophthalmology*, *26*(2), 157-161.

Nickla, D., & Wallman, J. (2010). The multifunctional choroid. *Progress In Retinal And Eye Research*, *29*(2), 144-168.

Ozsahin, D., & Ozsahin, I. (2018). A Fuzzy PROMETHEE Approach for Breast Cancer Treatment Techniques. *International Journal Of Medical Research And Health Sciences*, *7*(5), 29-32.

Ozsahin, D., Isa, N., Uzun, B., &Ozsahin, I. (2018). Effective analysis of image reconstruction algorithms in nuclear medicine using fuzzy PROMETHEE.

Ozsahin, D., Uzun, B., Musa, M., Şentürk, N., Nurçin, F., &Ozsahin, I. (2017). Evaluating nuclear medicine imaging devices using fuzzy PROMETHEE method. *Procedia Computer Science*, *120*, 699-705.

Pandey, A. (2014). Retinoblastoma: An overview. *Saudi Journal Of Ophthalmology*, *28*(4), 310-315.

Parreiras, R., & Vasconcelos, J. (2007). A multiplicative version of Promethee II applied to multiobjective optimization problems. *European Journal Of Operational Research*, *183*(2), 729-740.

Purves, D., & Williams, S. (2001). *Neuroscience. 2nd edition*. Sinauer Associates.

Rushlow, D., Mol, B., Kennett, J., Yee, S., Pajovic, S., &Thériault, B. et al. (2013). Characterisation of retinoblastomas without RB1 mutations: genomic, gene expression, and clinical studies. *The Lancet Oncology*, *14*(4), 327-334.

Siegel, R., Miller, K., &Jemal, A. (2017). Cancer statistics, 2017. *CA: A Cancer Journal For Clinicians*, *67*(1), 7-30.

Silas, S., & Rajsingh, E. (2016). Performance analysis on algorithms for selection of desired healthcare services. *Perspectives In Science*, *8*, 107-109.

Soliman, S., Racher, H., Zhang, C., MacDonald, H., & Gallie, B. (2017). Genetics and Molecular Diagnostics in Retinoblastoma—An Update. *Asia-Pacific Journal Of Ophthalmology*, *6*(2), 197-207.

The Eyes (Human Anatomy): Diagram, Function, Definition, and Eye Problems. (2018). Retrieved from https://www.webmd.com/eye-health/picture-of-the-eyes#1.

Uzun, D., Uzun, B., Sani, M., & Ozsahin, I. (2018). Evaluating X-Ray based Medical Imaging Devices with Fuzzy Preference Ranking Organization Method for Enrichment Evaluations.

Uzun, D., Uzun, B., Sani, M., Helwan, A., Nwekwo, C., &Veysel, F. et al. (2017). Evaluating Cancer Treatment Alternatives using Fuzzy PROMETHEE Method. *International Journal Of Advanced Computer Science And Applications*, *8*(10).

Weistroffer, H., Smith, C., & Narula, S. Multiple Criteria Decision Support Software. *International Series In Operations Research & Management Science*, 989-1009.

Yang, W., Wang, J., & Wang, X. (2012). An outranking method for multi-criteria decision making with duplex linguistic information. *Fuzzy Sets And Systems*, 198, 20-33.

Zadeh, L. (1996). Fuzzy logic = computing with words. *IEEE Transactions On Fuzzy Systems*, 4(2), 103-111.

Zionts, S. (1979). MCDM—If Not a Roman Numeral, Then What?. *Interfaces*, 9(4), 94-101.