ANALYSIS AND ASSESSMENT ON EFFECTS OF DIFFERENT THERAPIES IN CANCER TREATMENT BASED ON FUZZY COGNITIVE MAPS

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Abstract

Cancer is the second leading cause of death worldwide. Even though cancer death rates have slightly decreased in the last decades, the painful experience of cancer diagnosis and treatment still occurs every day globally. It is critically important to develop advanced computing technologies to better understand the effectiveness and management of cancer treatment. Nevertheless, most of the present tools for analysis and assessment therapy effects in cancer treatment are based on immediate relative factors and laboratory reports. The causal relationship of the key factors is not recorded or modelled, thus not analysed and communicated effectively.

Fuzzy cognitive map (FCM), as a medical decision support tool, has been applied in medical practice and overall appreciated in recent decades. In this thesis, clinical cancer cases were analysed and assessed with the help of FCM. It is particularly applied to visualise the knowledge and experience about effects of different types of therapies, including the alternative therapies of sonodynamic and photodynamic therapy and traditional Chinese medicine modalities. Through the cases study with the help of FCM, the model can clearly show that the effects or outcomes of cancer treatments are critically influenced by the causally related factors. The analysis and assessment results demonstrated that FCMs can visually represent the cognitive knowledge, particularly the causal relationship among key factors in the combination of different cancer therapies, while the individuals' causal influence factors showing certain degrees of capability for driving different effective outcomes. This modelling will enable further analysis and communication of the rationales of different intervention or decision makings from different practitioners and specialists.

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Student Declaration

I, Daniel Cheng-Chung Lee, declare that the PhD thesis entitled “Analysis and Assessment on Effects of Different Therapies in Cancer Treatment Based on Fuzzy Cognitive Maps” is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature: 

Date: 29 November 2019

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Chapter 1: Introduction

Cancer is the second leading cause of death globally, with an estimate of 18.1 million incidences and 9.6 million deaths by 2018, while one in five men and one in six women will have cancer in their lifetime, and one in eight men and one in 11 women will die from cancer. Globally, it is estimated that there will be 43.8 million people living with cancer within five years of the prevalence rate, according to Geneva, Switzerland, 12 September 2018 – International Agency for Research on Cancer (IARC). The World Cancer Report 2014 estimates that there will have been more than 20 million cancer incidences every year by 2025 [97].

The number of cancer deaths worldwide is expected to increase by 45% from 2007 to 2030 (from 7.9 million to 11.5 million), in part because of global population growth and aging. The estimated increase is expected to result in a slight decline in the mortality rate of certain cancers in high-resource countries. Cancer new incidences are expected to escalate from 11.3 million in 2007 to 15.5 million in 2030. In most developed countries, following the cardiovascular disease, cancer is the second leading cause of death, and epidemiological evidence suggests that this trend is now happening in less developed countries as well [100].

Unfortunately, curing cancer is even more difficult than getting rid of weeds. Conventional cancer therapies can remove cancer cells by surgery; the use of toxic chemotherapy, targeted therapy, radiation therapy, immunotherapy, hormone therapy and other strategies in the attempt to eliminate cancer cells, but it is difficult to eradicate all of them [1]. Surgery rarely can eliminate every metastatic cancer cell. After Surgery therapy, even if only a few cancer cells survive, they can proliferate, leading to the resurgence of disease [1]. The other above-mentioned therapies may cause many side effects, ranging from mild to very destructive quality of life issues, or even to new diseases which may worsen the cancer burden [1].

There are so many different types of cancer therapies, but the assessment of the side effects, treatment effectiveness and prognosis are mostly based on the conventional data analysis tools. FCM (Fuzzy Cognitive Maps) is based on the dynamic causal relationship for analysis. Using FCM as a medical supportive system

in medical practice has been overall appreciated in recent decades. However, only a few studies have been done on the alternative therapies such as Sonodynamic Photodynamic Therapy (SPDT) and traditional Chinese medicine in cancer treatments. The purpose of this study is an investigation of FCM for Medical Sciences; Application of FCM on overall conventional therapies as well as alternative therapies of SPDT and Chinese medicine in treatment of cancers.

1.1 CANCERS

According to the International Agency for Research on Cancer (IARC), cancer is the leading cause of death globally resulting in 12.7 million cancer incidences and 7.6 million cancer deaths in 2008, and 8.2 million deaths globally in 2012, with an increase of 8% of cancer deaths within four years affecting the population in all countries and regions [3,101].

It is estimated that there will be 18.1 million cancer incidences (excluding NMSC's 17 million) and 9.6 million cancer deaths (excluding NMSC's 9.5 million) globally in 2018. Overall, of the total global population, in 2018, it is estimated that nearly half of new cancer cases and more than half of cancer deaths will occur in Asia, partly because nearly 60% of the population lives in Asia. Although Europe accounts for only 9% of the global population, it accounts for 23.4% of the total number of cancer cases worldwide, 20.3% of cancer deaths; followed by 21% in the Americas and 14.4% of the global mortality rate [18].

It is estimated that the incidence of all cancers has increased globally in 2018, and men (age normalization rate, ASR, 218.6 / 100,000 people) are about 20% higher than women (ASR, 182.6 / 100,000 people), varying across different regions. Among men, the incidence rate varies by nearly 6 times higher in all regions, from 571.2 / 100,000 in Australia/New Zealand than 95.6 / 100,000 in West Africa. Among women, the incidence has nearly four times higher, with 362 out of every 100,000 people in Australia/New Zealand, than 96.2 out of every 100,000 people in South and Central Asia.

These differences largely reflect differences in the type of exposure and associated cancer (cancer mix) and the availability and use of screening imaging of diagnostic services. For example, men and women in Australia/New Zealand have the highest overall incidence, partly because of the elevated risk, but also because of the

increased detection rate of skin cancers (especially non-melanoma skin cancers) in these countries; although global cancer incidence is generally significantly increased, but in some areas, the latter part may not be fully captured, and this possibility must be considered as well [18].

Cancer also causes social burden, and the enormous potential of human beings is being lost; the economic impact of treating and caring for more and more cancer patients is escalating. Among the common cancer burden impacts on human beings, there are variations from country to another [2].

The impact of cancer on the economy is significant and escalating. It was estimated that the annual economic loss caused by cancer in 2010 is about 1.16 trillion US dollars [7]. According to the World Cancer Report 2014, the global cancer burden is expected to increase by about 70% in just 20 years, but the poorest economy countries with the least cancer services will be affected the most [98].

To fight against the cancer burden, it is increasingly important to analyse the effectiveness of cancer treatment and cancer prevention. The application of fuzzy cognitive map (FCM) in medical assisted systems can be one of the important solutions [104].

1.2 FUZZY COGNITIVE MAPS

This study aims to reveal the causal relationship among the affecting factors of patients' diseases and their treatments, and the inter-action with the outcome of cancer therapies. In this study, fuzzy cognitive map (FCM) is utilised for data analysis and assessment, rather than using conventional data analysis tools.

FCM is a visual knowledge that has features suitable for direct use by domain experts. It is a soft computing technique that follows the inference methods of human reasoning and human decision-making processes. FCM has two major functions: one is to reason about the causal factors involved in the prediction; the other is the result of the causation analysis. FCM can be a powerful tool to support decision making because expert experience and information in historical data can be combined to form the maps that represents knowledge [67,69,88]. In a word, FCMs are illustrative causal

representations of complex system modellings and operations designed to model the behaviour of any system.

Unlike structure equation modelling or machine learning models, FCMs are based on human expertise. The data driven modelling of FCM expresses a system in a form of very consistent with human perception. Experts in various scientific fields express their knowledge by drawing a weighted causality graph, which usually has a fuzzy weight graph composed of feedback, nodes, and direction of links. FCM can help decision makers consider their representation of a given object to determine its adequacy and possible hints introducing any necessary changes to reflect the reasoning behind the decision. The generated fuzzy model can be used to analyse, simulate, and test the influence of parameters, and predict the behaviour of the system, and well reflect the decision-making process and causes. FCM can strategically generate a more accurate description of a difficult situation [57, 67, 69].

FCM represents and models human knowledge and expertise in decision making [75]. It allows loops to model widely existing feedback; it is not a "rigid" model, consequently allowing multiple experts to contribute their knowledge without compromising to maintain a structure (such as a tree structure in classical logic) [57,69]. Compared with many formal knowledge modelling tools [67], FCMs have been widely used by domain experts due to their ease of use.

Cognitive maps have been used to analyse and assist decision making by investigating causal relationships among relevant domain concepts. FCM is an extension of cognitive graphs with the additional ability to represent feedback through weighted causality. As such, FCM can be used to develop decision support systems based on human reasoning, represented by symbolic diagrams to describe and model complex systems. FCMs consist of concepts illustrating different aspects of model and behaviour of the system, and they dynamically interact with each other. The FCM structure can be used to represent qualitative and quantitative models. FCMs integrate accumulated experience and knowledge, and systematically analyse the factors, characteristics, and components of causal relationships based on human experts understanding the system and its behaviour [67, 81].

1.3 FCM FOR MEDICINE

Medical decision system is a complex system, which can be deconstructed into unrelated and related subsystems and elements, among which many factors must be considered, which may be complementary, contradictory and/or competitive. These factors interact each other and determine overall clinical decision making to different degrees [75].

Numbers of studies have been conducted to apply FCM to medical decision-making, in which FCM helps analyse perspectives and events on medical topics in both qualitative and quantitative ways. For example, FCM is an interpretable modelling which has been used in medical diagnosis, long-term prediction of disease, disease risk assessment and disease management including treatment planning, data analysis, and evaluation the effectiveness of treatment and the prognosis of disease [15,30,47,75,76,88]. Our study is focused on the treatment analysis and its effectiveness evaluation.

A study has been conducted to investigate the efficiency of FCM to simulate established knowledge from standard medical literature and accumulated expertise in the specific application of breast cancer risk assessment by clinical oncologists. The conclusion is that the proposed decision support approach can accurately assess breast cancer risk factors and assess the overall risk grade by providing clinical oncologists with useful information to adjust patient intervention procedures accordingly [88].

An enhanced version of the evolutionary learning approach of FCM was studied to apply to the prediction of prostate cancer, considering the parameters that define the long prediction range. The conclusion is that the fitness function of the enhanced learning algorithm can better optimize FCM for the task of long-term prediction of multivariable time series. The calculation and prediction error of FCM-II was small, because the improved optimization of FCM is accomplished by using the exploration approach. The proposed solution has been verified in a pilot study using real medical data [47].

Through application of the computational intelligence training technology activating Hebbian algorithm, the classification ability of the FCM hierarchical model is improved. The main advantage of the proposed FCM grading model is that it has sufficient interpretability and transparency in the decision-making process, which

makes it a convenient consulting tool for characterising the tumour invasiveness in daily clinical practice [76].

Medical decision-making is a complex process that requires a combination of multiple reasons and leads to diagnosis and decision making. For decades, computer systems have been used to help doctors make patient diagnoses and medical decisions. In order to reduce the workload of doctors in making accurate medical decisions, it is important to have a consistent system as support. This must include the processing and evaluation of large amounts of data from multidisciplinary sources, such as patient background information and medical records, medical examinations, laboratory tests, medical device examinations, treatment records, and results; also to clarify unclear information and promptly supplement missing information.

A study on the FCM structure of medical decision support system (MDSS), concludes that FCM, a soft computing technology, can be used for consistent MDSS; and it can achieve better solutions in diagnosis, treatment and prediction. FCM can be a powerful tool because of many experts' experience and knowledge from historical data to be combined and contributing to the formation of FCMs [15].

Based on FCM implemented using the semantic Web approach, the modelling of medical knowledge and the systematic behaviour of decision support for urinary tract infection (UTI) diagnosis have been studied. This work established a decision support tool based on FCM formalism for UTI diagnosis, suggesting an appropriate diagnosis for each case [15]. In conclusion, FCM is suitable for a medical decision support system, which helps analyse views and events on medical subjects through qualitative and quantitative methods [75].

A study has been conducted to investigate the efficiency of FCM to simulate established knowledge in standard medical literature and to accumulate expertise in the specific application of breast cancer risk assessment by clinical oncologists. The conclusion is that the proposed decision support approach can accurately assess breast cancer risk factors and assess the overall risk grade by providing clinical oncologists with useful information to adjust patient intervention procedures accordingly [88]. FCM can process imprecise and uncertain information and can be used as a decision model to determine radiation dose and other related quantities [30].

According to our investigation, FCM can be applied to use as a supportive system in diagnosis decision making and treatment effectiveness assessment for different medical therapies.

1.4 CONTRIBUTIONS AND THESIS STRUCTURE

The modelling and analysis of the causal factors contributing to the decisions on curative cancer therapies and cancer prevention has become critical while the cancer burdens are keep increasing. The application of FCM in medical decision support systems is an important scheme. It is desirable to widely apply a computing model like FCM in medical systems to model the core decisions and related factors.

In this study, we propose an investigation of applying the FCM for alternative therapies. The FCM-based approach is evaluated through case studies on the assessment effectiveness of treatment in cancers, the prevention of cancer, and particularly the different types of therapies in cancer treatments. It is clearly shown that the FCM-based approach can provide efficient and precise decision making for the relevant health practices.

The structure of the thesis is as follows. Chapter 2 provides a comprehensive literature review on cancers, their treatments and side effects as well as FCM and its usage in medical sciences. Chapter 3 describes the methodology of medical decision making based on FCM, illustrated by a case study on TCM's treatment on different types of cold. Chapter 4 presents the major results, the FCM-based cognitive modelling on the effects of various therapies on different types of cancer. Chapter 5 provides in-depth discussion of the research. Chapter 6 concludes the whole thesis.

Chapter 2: Literature Review

This thesis is a cross-disciplinary research across medical sciences and fuzzy cognitive map (FCM). This chapter introduces the background knowledge of cancers, their treatments and associated side effects, FCM. Also discussed is the related work on FCM-based medical decision making.

The focus of this study is to evaluate the effectiveness of various cancer treatments. The premise of this study relevant to medical science is to understand the incidence rate of cancer, its impact to human beings, the formation of cancer cells, pathogenic risk factors, treatment options and efficacy evaluation, etc.

Although the treatment of traditional Chinese medicine (TCM) is not the major focus of this study, TCM has thousands of years of history in treating cancers effectively. FCM is an Information Technology which can be used as a supportive system in various medical clinic decision making. When people have cancer, treatment approach can be multifaceted, and some patients may use TCM as a primary therapy exclusively or using TCM as part of an integrative treatment combining with Western medicine regimens. This study also did some analysis and evaluation of the curative effect of TCM on cancer.

2.1 CANCERS

2.1.1 Cancer burden

Cancer is an expensive disease that is a disaster for humans. First and foremost is the human cost, including the uncertainty and suffering of individuals, families and friends living in pain. The painful experience of cancer diagnosis is truly universal and occurs every day in the community [99].

The burden of cancer is the second leading cause of death in the world. It is estimated that by 2018, the number of new cases will increase to 18.1 million, and the death toll will reach 9.6 million, while one in five men and one in six women will suffer from cancer in their lifetime. One in eight men and 11 women will die of cancer [57].

More specific measures for the cancer burden are ubiquitous. The number of people who are diagnosed with cancer still live at a given time. Worldwide, the total number of people suffering from cancer within 5 years after diagnosis is a 5-year prevalence rate,

estimated at 43.8 million. Geneva, Switzerland, September 12, 2018 - International Agency for Research on Cancer (IARC) [57]

The survey results show that resource-rich countries have the highest incidence of cancer under the best service for cancer detection, diagnosis and treatment, which can be inferred from mortality and survival data. These countries also have the highest incidence of cancer [57].

The incidences of specific tumours may be relatively low in the countries with low and medium resources, but the associated mortality data often reflects late diagnosis with poor clinical outcomes [99]. Cervical cancer remains the most common cancer among women, according to data from resource-poor countries.

The early onset of some common cancers such as cervical cancer and liver cancer, as well as the low survival rates in low- and middle-income countries, means that these countries have reduced life expectancy due to cancer and are similar to high-income countries.

Late presentation and difficulties in accessing the proper diagnosis and treatment are common. In 2017, only 26% of low-income countries reported that pathological services were widely provided in the public sector. More than 90% of high-income countries provide treatment services, compared with less than 30% in low-income countries [51].

Among the low- and middle-income countries, only one in five have the necessary cancer data to implement their cancer policy [51].

Cancer is increasingly becoming a serious burden among the low-and middle-income countries [99] suffering with 70% of the cancer mortality rate [51].

The increased burden of cancer is due to several factors, including population growth and ageing, as well as changes in the prevalence of certain cancer causes associated with social and economic development. This is especially true in fast-growing economies, from cancers associated with poverty and infection to cancers that are more typical of lifestyles in industrialized countries [51].

2.1.2 Impact of cancer

Cancer is the leading cause of death worldwide, with an estimated 8.2 million deaths worldwide in 2012. The World Health Organization (WHO) estimates that about 30 percent

of cancer deaths are due to smoking, overweight, obesity, and lack of physical factors exercise, diet, and alcohol consumption.

The global cancer burden was studied using GLOBOCAN, a 2018 estimate of global cancer incidence and mortality compiled by the International Agency for Cancer Research, focusing on geographic differences in 20 regions of the world.

It is estimated that there will be 18.1 million new cancer incidences in 2018 (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer).

According to the "World Cancer Report" published by the World Health Organization and the International Agency for Research on Cancer on April 3, 2003, by 2020, the incidence of cancer may increase by 50%, reaching 15 million new cases each year. The projected sharp increase is mainly due to longer life expectancy in developing and industrialized countries, current smoking trends, and an increasing number of people adopting unhealthy lifestyles.

However, the report also provides clear evidence that healthy lifestyles and public health actions taken by governments and health practitioners can contain this trend and prevent up to one third of cancers globally. The World Cancer Report 2014 estimates that by 2025, there will be more than 20 million cancer incidences each year.

According to Australian Institute of Health and Welfare, in 2019, the rate of new cancer cases in Australia is expected to reach 483 new cases per 100,000 people, while cancer-related deaths are expected to decrease to 159 per 100,000 people.

The number of new cancer cases is increasing each year, with an estimated 150,000 cases in Australia by 2020.

The most common cancers in Australia are prostate, bowel, breast, skin melanoma and lung cancer, accounting for an estimated 60 per cent of all cases diagnosed in 2015.There are estimated to be nearly 46,600 cancer deaths, accounting for 3 out of every 10 deaths in Australia in 2015. Lung, bowel, prostate, breast, and pancreatic cancer will be the most common causes of cancer deaths, accounting for nearly half of all cancer deaths in Australia in 2015 [10].

2.1.3 How cancer starts

Cancer occurs when healthy cells go through a multistage transformation into tumorous cells. These changes are due to human genetic and physical interactions and cells mutations, with the four most common external factors, including:

- Physical carcinogens such as ultraviolet light and ionizing radiation;
- Chemical carcinogens such as asbestos, smoking tobacco ingredients, aflatoxins contamination in food, and arsenic contamination in drinking water.
- Tobacco use is the most important risk factor for cancer, with about 22 percent of cancer deaths linked to tobacco use.
- Biological carcinogens, such as certain viral, bacterial or parasitic infections.

According to statistics, one-third of cancer deaths are caused by five major behavioural and dietary risks: high body mass index, low fruit and vegetable intake, lack of activity, smoking, and alcohol consumption. Smoking is the most important risk factor for cancer. In low- and middle-income countries, about 22% of cancer deaths result in cancers such as hepatitis and human papillomavirus (HPV), and up to 25% of cancer cases in low-and-middle-income countries [51].

Ageing is also a key factor leading to cancer. The incidence of cancer increases significantly with age, probably because the risk of certain cancers increases with age. Cell repair mechanisms become less effective as they are getting aged, which is related to the establishment of overall risk [51].

2.1.4 Origination of cancer cells

Our bodies are made up of more than 30 trillion cells [13]. All cancers originate in cells. Cancer begins with changes in a cell or group of cells. In general, the number of cells per type is correct. This is because cells produce signals that control the number and frequency of cell division. If any of these signals are wrong or absent, the cells may begin to overgrow and multiply, forming a mass called a tumour. However, cancer cells accumulate in the blood, sometimes in the bone marrow. When certain changes occur in the genes of a cell or group of cells, cancer development may begin, especially when the abnormal changes of cell growth and division occur. [26,71,91]

Changes in certain gene mutations can cause healthy cells to disrupt normal growth control and become cancerous. For example, some changes in oncogenes increase the

production of proteins that cause cell growth. Others can lead to malformations, which become non-functional proteins that normally repair cell damage. [71,91]

A cancer begins when one or more genes in a cell are mutated. It produces abnormal proteins. Or it may prevent the formation of proteins. Abnormal proteins provide different information from normal proteins [71,91].

Beginning of Cancer

When such mutation happens, it can cause cells to multiply uncontrollably and become cancerous [71,90]. Genetic mutations are permanent abnormalities in the DNA (Deoxyribonucleic acid) sequences that make up genes, making them different from what most people found. The sequence of DNA structural units determines genes and their functions. A change in just one of the thousands of structural units that make up a gene makes a big impact. Mutations vary in size; they can affect a wide range of functions, from a single DNA gene to most chromosomes that contain multiple genes [4,50].

Mutations often occur. Mutations can be beneficial, harmful, or neutral. It depends on where the gene changes. Usually, the body corrects most of the mutations. Individual mutations may not cause cancer. A cell usually needs a lot of mutations before it can cause cells to become cancerous. These mutations may affect different genes that control cell growth and division. Some of these genes are called tumour suppressors. Mutations can also cause some normal genes to become oncogenes [4,50]. We have two copies of most genes, one from each chromosome in the pair. To completely make a gene dysfunctional that has the potential to cause cancer, both copies must be eliminated by mutations. This means that for most genes, two mutations are needed to shut down the gene completely [4,50].

Cancer usually develops as a result of multiple mutations over a lifetime. Therefore, cancer is more common in the elderly. They have more opportunities to build mutations [4,50].

Genetic mutations may affect cells in a variety of ways.

By completely blocking protein production:

• change the proteins produced, and causing them to no longer function as required, or they may not even work any longer at all;

• activate genes to make more proteins than usual;

• no obvious effect, but others may cause illness. For example, certain mutations in the haemoglobin gene may cause sickle-cell anaemia [4,50];

These mutations may affect different genes that control cell growth and division. Some of these genes are called tumour suppressors. Mutations may also cause some normal genes to become oncogenes [50].

Mutations can be genetic or somatic

There are two main types of genetic mutations, germline mutations and somatic mutations. They are two different types of mutations that occur in somatic cells at different life stages of a multicellular organism [96]. Germline mutations occur at different stages of gametogenesis. Somatic mutations occur in normal somatic cells, such as hepatocytes, muscle cells, and skin cells [96].

The main difference between germline mutations and somatic mutations is that germline mutations are inheritable, whereas somatic mutations cannot be inherited by offspring [96]. Germline mutations are inherited from parents and are present in almost every cell of the body throughout life, and they can be passed on to offspring. These mutations are also known as germline mutations because they are present in the parent's egg or sperm cells, which are also known as germ cells [50]. Cancers caused by germline mutations are known as hereditary cancers. It accounts for 5 to 10 percent of all cancers [50].

The Endogenous factors

Germline mutations usually occur due to endogenous factors such as errors in cell duplication and oxidative damage. The damage is rarely imperfectly repaired but may occur frequently because of the high rate of germ cell division.

The Exogenous factors

Somatic mutation is a major factor in transforming normal cells into cancerous cells. There are no somatic mutations present in fertilized eggs. They occur at certain times in later life and are found only in certain cells, not in every cell in the body. It occurs in a cell and is then transferred to any new cells that are descendants of the original cell. These changes may be caused by environmental factors, such as ultraviolet radiation from the sun, diet, smoking, viruses, environment, ageing, etc. Problems may also occur with DNA replication during cell division.

For example, it might be that a breast cell or colon cell continues to divide multiple times to form a tumour. The tumour is an abnormal mass. A cancer caused by an acquired mutation is called a sporadic cancer. Mutations obtained in somatic cells are not from the eggs or sperm of the parents and cannot be passed on to the next generation. Acquired mutations are more common than hereditary types. Most cancers are caused by acquired mutations. This type of mutation is also known as a scattered mutation or a somatic mutation [4,5,86,91].

Somatic mutation refers to the mutation of the genetic material of an organism after conception. They are called somatic because they do not occur in the germ cells; they only occur in the somatic cells of the organism and cannot inherit from their parents or pass on to future generations [72].

Although somatic mutations are not inheritable, their risk increases in the presence of other genetic factors and mutations. They are mainly caused by environmental factors such as UV radiation, viral and bacterial infections, ingestion of toxic substances, DNA repair defects and unhealthy lifestyle choices. When somatic mutations alter the genetic material of the cell and all the cells produced by its division, there is a resultant formation of a group of cells that have a genetic composition different from other cells in the organism [72,91].

The characteristics of somatic mutation are:

• they occur in normal somatic cells, such as liver cells, muscle cells, and skin cells;

• they can occur at any time in an organism's life;

• they can be found in certain parts or tissues of the body;

• they cannot be passed on to future generations;

• the effects on the body are local;

• they usually affect a single tissue;

• it has no effect on the evolution;

• the mutated proto-oncogenes produce cancer tumours in the body [77].

A genetic type associated with cancer:

Many genes that contribute to the development of cancer can be divided into the following categories [91]:

Tumour suppressor genes are protective genes.

Typically, they limit cell growth by:

• monitoring the rate at which cells divide into new cells

• repairing mismatched DNA

• controlling when a cell died

When the tumour suppressor gene is mutated, the cell cannot control its growth. They eventually form tumours.

The challenges of cancer genetics

Researchers have learned how cancer genes work, but many cancers are not related to specific genes. Cancer may involve multiple genetic mutations. Nevertheless, some evidence suggests that genes interact with the environment, which makes it more complicated for us to understand the role of genes in the causes of cancer.

Researchers continue to study how genetic changes affect the development of cancer. This understanding has led to improvements in cancer treatment, including early detection, risk reduction, use of targeted therapies and survival [91].

Many studies have concluded that more than one mutation is required for a cancer to develop in a cell. However, when a person inherits an abnormal copy of the gene at birth, their cells have already begun mutation once. It makes the gene mutate fast enough and is more likely to cause cancer. Therefore, hereditary cancers usually occur earlier than non-hereditary cancers. [91]

Even if one was born with healthy genes, some of them could change over the course of life. Mutations are the acquired causes of most cancers. These mutations may be due to the individual's exposure to the environment, such as diet, hormones, radiation and smoking. However, the cause of other mutations is unclear, and these mutations may occur randomly during cell division. Cell reproduction begins with cell division, which begins by splitting all the DNA of a cell into two new cells. However, in the process of copying DNA, errors (such as typing errors) may occur because the cells contain too much DNA. This change in DNA in new cells is called mutation and can possibly occur at any time during cell division. The number of genetic mutations increases over time, that explains why our risk of developing cancer increases with age [4].

It is important to realize that even if genetic mutations have been occurring in our cells, they do not always lead to cancer. Under normal conditions, cells detect changes in DNA

and repair them. When it can't be repaired, the cell receives a signal telling it to die under apoptosis. But if the cell is neither dead nor able to repair the mutation, it can lead to cancer. This is more likely to occur if the mutation affects genes involved in cell division, or genes that normally cause defective cell death. People with inherited genetic mutations are at higher risk of developing cancer [4].

Penetrance

For dominant genes and mutations, the term penetrance refers to the proportion of people with mutations that have this characteristic, syndrome, or disease. If all people who inherit this mutation have this disease, this is called complete penetrance. If not all people with mutations get the disease, it is called incomplete penetrance.

In general, inherited mutations that causes cancer have incomplete penetrance, meaning not all people carrying mutations will develop cancer. This is partly because, although a person's copy of a gene has been mutated, he or she needs at least one more mutation to stop the gene from completely working and then cancer may occur.

Since not everyone has the second mutation, not everyone gets cancer. Incomplete penetrance may also be evident since even if the mutation makes the gene ineffective, the occurrence of cancer may require other factors. Gene mutations can cause major changes in gene function. They may even cause the copies of the gene to completely stop working. This mutation is called "high penetrance" when it affects the function of the gene, and enough to cause disease or obvious problems in most people with the disease [4].

High penetrance mutations in cancer susceptibility genes can cause many people in the family to develop certain types of cancer, known as the family cancer syndrome, resulting in a small fraction of cancers occurring in a single household. For example, only about one-fifth of breast cancers in the family are thought to be caused by high penetrance mutations in genes such as BRCA1 and BRCA2 [4]. Hereditary breast cancer accounts for 5-10% of all cases and has distinctive clinical features compared with sporadic breast cancer. The recently identified genes BRCA1 and BRCA2 appear to be the cause of most hereditary breast cancer in the US and European populations [55,111]. Specific genetic mutations in BRCA1 and BRCA2 most significantly increase the risk of breast and ovarian cancer in women, but they are also associated with an increased risk of several other types of cancer. People who have inherited BRCA1 and BRCA2 mutations are more likely to develop breast and ovarian cancer at a younger age than those without these mutations. [19]

The low penetrance mutations appear to have little effect on gene function and usually do not cause significant problems. Nevertheless, they can affect cancer risk by tenuously affecting hormone levels, metabolism, or other factors that interact with cancer risk factors [4]. Sometimes cancers caused by mutations in non-hereditary genes also show "familiarity". For example, a shared environment or lifestyle, such as smoking, eating certain foods, and exposure to chemicals in the same environment, can lead to similar cancers among family members. However, certain patterns in the family, such as the type of cancer development, other non-cancer conditions, and the age at which the cancer develops, may indicate the presence of hereditary cancer syndrome [71].

Even if there is a mutation in a family that is prone to cancer, not everyone who inherits this mutation will get cancer. Several factors influence the prognosis of people with genetic mutations, including the genetic pattern of cancer syndrome [79].

Cancer cells usually have more genetic changes than normal cells. But everyone's cancer has a distinct combination of genetic variations. Some of these changes may be the result of cancer, not the cause. As cancer continues to grow, other changes will occur. Even within the same tumour, cancer cells may have different genetic changes as well [71].

Genetic variation

People may also have different versions of non-mutated genes. The common difference in genes is called variants. These versions are inherited and are present in every cell of the body.

The key characteristics and difference of variations are as below:

- The most common genetic variation involves only one base nucleotide change of a gene. These are called single nucleotide polymorphisms (SNP). It is estimated that there are millions of SNP in everyone's DNA [4].
- Other types of variations are less common. Many genes contain repeating base sequences. A common variant involves a change in the number of repetitions [4].
- Some variations have no significant effect on the function of the gene.
- Others tend to influence the function of genes in subtle ways, such as making them slightly more active or less [4].

- These changes do not directly develop cancer but make people more susceptible to cancer by affecting factors such as hormone levels and metabolism. For example, some genetic variants can affect the levels of estrogen and progesterone that may increase the risk of breast and endometrial cancer [4].
- Others may affect the breakdown of toxins in tobacco smoking, causing people to become more susceptible to lung cancer and other cancers. Genetic variation may also play a role in diseases that increase cancer risk, such as diabetes and obesity.

Variations and low penetrance mutations may be similar. The main difference is how common they are. This mutation is rare, and genetic variation is more common [4].

However, since the variation is common, it may make some people have many variations, so their effects can be superimposed. Studies have shown that these variations can affect cancer risk together with low penetrance mutations that can become a large part of the risk of familial cancer [4].

DNA methylation:

In this epigenetic change, a molecule called a methyl group is attached to a specific nucleotide. This changes the structure of the DNA disabling the gene to begin the process of encoding the protein, known as transcription. This basically shuts down the gene. It may happen in some people when a copy of a cancer-susceptible gene is mutated, and a copy of the other gene becomes inactive, not because of a mutation, but because the methylation causes the cell to become cancerous [4].

According to the British "Daily Telegraph" reported on September 28, 2019 [38], American scientists are looking for abnormal patterns of methylation in DNA, which can indicate different types of cancer. The study found that this new method can even pinpoint the source of cancer, including the most difficult to detect ovarian and pancreatic diseases, in nearly 90% of the time. The lead author of the study, Dr. Jeffrey Oxnard, from the Dana-Farber Cancer Institute in Boston (part of Harvard Medical School), said methylation-based assays are used to detect multiple cancers in blood samples. The aspect is superior to the traditional DNA sequencing method. From this finding, it further firmly confirmed that the DNA methylation can lead to development of cancer [38].

2.1.5 Cancer incidence and death rates by world region

Globally, the incidence rate of all cancers, the age standard rate (ASR), in men (218.6 per 100,000) about 20% higher than women (182.6 per 100,000), of which the incidence rates in both male and female vary across regions. Among men, the incidence rates vary by nearly 6-fold across regions, from 571.2 / 100000 in Australia/New Zealand to 95.6 / 100000 in West Africa. Among women, the incidence rate is nearly 4-fold, from 362 / 100000 in Australia / New Zealand to 96.2 / 100000 in South Asia / Central Asia [52,98].

These variations greatly reflect differences in the type of exposure and associated cancer (cancer mix) and the availability and use of screening services and diagnostic imaging. For example, in Australia/New Zealand, the overall incidence of men and women is highest, in part because of the elevated risk, but also because of the increased detection of skin cancer, especially NMSC, in these countries; it must also be considered, despite the global overall cancer morbidity burden has increased significantly, but in some areas, the latter part may not be adequately captured. The 2014 World Cancer Report estimates that by 2025, more than 20 million new cancer cases will be diagnosed every year [8,9,59,98].

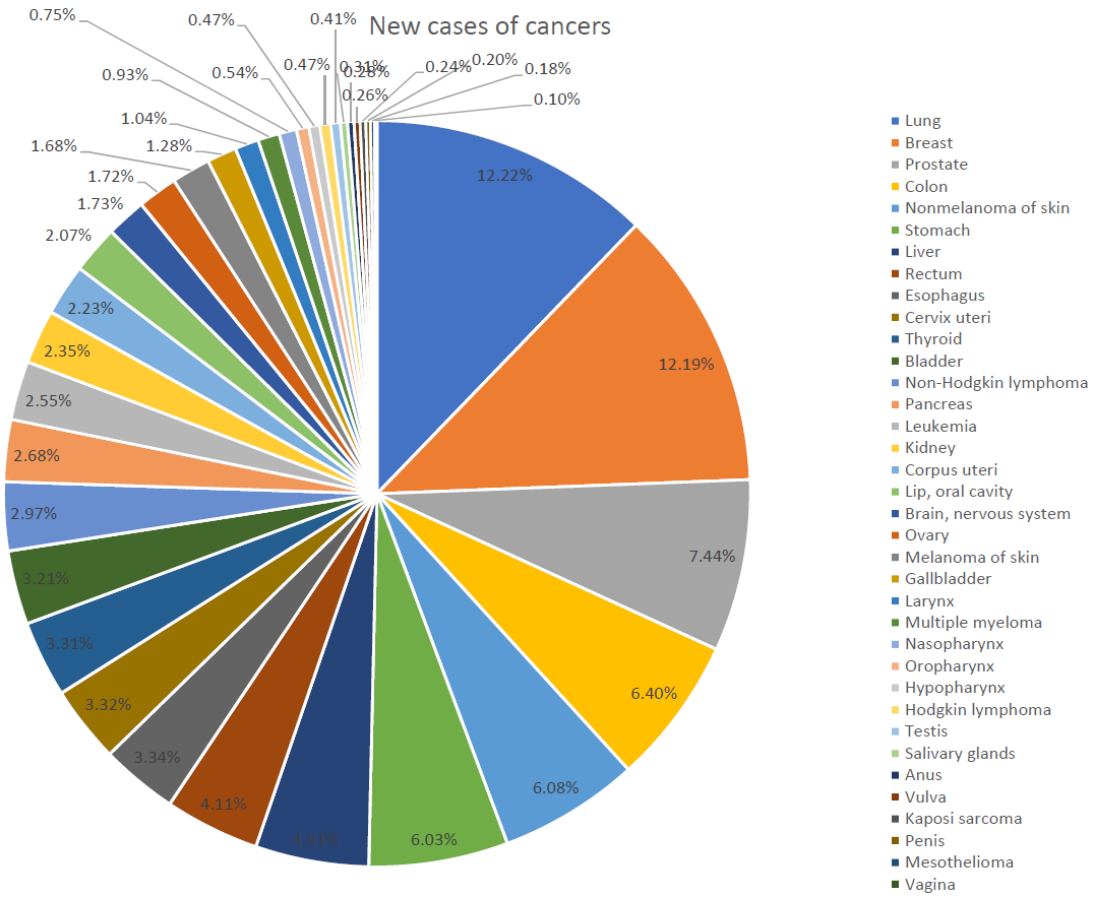

Figure 2-1 Estimated New Cases and Deaths for 36 Cancers and All Cancers Combined in 2018 [52]

With this growing global burden, prevention of cancer is one of the most significant public health challenges of the 21st century. As well as action by individuals, achieving healthy patterns of diet and sustained physical activity over the life course requires concerted and integrated action from all sectors of society, including private sector, health and other professions[10,71].

2.1.6 Cancer in Australia [7-9,11]

Cancer is a major cause of illness in Australia - there are over 1 million people alive in Australia who are either living with or have lived with cancer. Around 30 years ago, about 5 in 10 people survived for at least 5 years after their cancer diagnosis; more recent figures are closer to 7 in 10 people surviving at least 5 years. Understanding and avoiding the risk factors associated with cancer can help to reduce the chance of getting cancer, while cancer screening programs increase the likelihood of detecting cancer early, enabling better

outcomes from treatments. Improvements in treatments and care are also important contributors to improvements in survival. [7-9,11]

Even though cancer survival rates have increased, and cancer mortality rates continue to drop, cancer accounts for around 3 of every 10 deaths in Australia. Aboriginal and Torres Strait Islander people and people in lower socioeconomic groups both have lower cancer survival rates than other Australians. While cancer survival rates have improved overall, people diagnosed with cancers such as pancreatic cancer, lung cancer and mesothelioma have a less than 1 in 5 chance, on average, of surviving at least 5 years after being diagnosed. [7-9,11]

2.1.7 Primary prevention and early detection of cancers

Despite these confronting statistics, doctors have made great progress in understanding the biology of cancer cells, and they have been able to improve the diagnosis and treatment of cancer. People can do a lot to prevent the disease without hesitation, instead of waiting for new breakthroughs in treatment. Getting a regular check-up and screening tests that can detect cancer before the cancer symptoms develop are critical.

Screening tests can help detect malignant tumours early, but everyone should always be alert to the symptoms of the disease. [105]

- C: Change in bowel or bladder habits
- A: A sore that does not heal
- U: Unusual bleeding or discharge
- T: Thickening or lump in the breast or elsewhere
- I: Indigestion or difficulty in swallowing
- O: Obvious change in a wart or mole
- N: Nagging cough or hoarseness

This is at best a rough guide. Most of these symptoms are caused by non-malignant diseases, and many cancer symptoms that do not appear on the list, such as unexplainable weight loss or fatigue may be involved. This is a useful reminder to listen to the body and consult with your doctor.

Scientists at the Harvard School of Public Health estimate that up to 75% of cancer deaths in the United States are preventable. The American Cancer Society's optimism about

prevention is only slightly lower, and it is estimated that about 60% of cancer deaths in the United States can be avoided. A 2005 study found that more than 2.4 million of the 7 million cancer deaths worldwide each year can be attributed to nine potentially correctable risk factors [28,54].

For a long time, the cancer survival rate in the UK has lagged ~~behind~~ other countries with similar wealth and income levels. An international study published this week showed that despite rapid progress in the UK, there is still a large gap in the survival rate of cancer patients in the UK compared to countries such as Australia, Canada and Norway [33].

It was believed that this is because the number of scanners in the National Health Service (NHS) in UK is much lower than in Western Europe, English-speaking countries and similar countries in the G7 countries – about 7 MRI scanners per million people, with an average of nearly 20 in other countries [33].

According to Guardian News, a global study found that Australia leads in survival rates for bowel, oesophageal, pancreatic, stomach and rectal cancer, higher than other similar high-income countries [90].

Professor Sanchia Aranda, CEO of the Australian Cancer Society, indicated that:

• "Australia's higher survival rates can be attributed to earlier findings. Australia's public and private health care systems are separate, and doctors can refer public patients to private diagnostic services, part of which cost is covered by Medicare Service. but the survival rate between the rich and those with lower socioeconomic status still varies greatly." [90].

• "The population within the lowest socioeconomic community has a 37% higher cancer mortality rate than the one with the highest socio-economic status. The poorer are 40% more likely to be diagnosed with cervical cancer, and 2.5 times more likely to die from it. In indigenous communities, the mortality rate is 3.8 times higher. Only 40% of eligible Australians (aged between 50 and 74 years old) participated in the National Bowel Screening Program. Aranda said that by 2040, an early diagnosis, a 50% increase in participation rate will save an additional 84,000 lives." [90].

Thus, early detection of the cancer is critically important in cancer treatment.

According to a study by Queen Mary University in London, a new simple blood test method has been found to effectively and accurately detect the presence of invasive prostate cancer. Combined with current prostate specific antigen (PSA) testing, new tests can help men avoid an unnecessary invasive biopsy, overdiagnosis, and overtreatment. [79]

Prostate cancer is the most common cancer in men, with 1.3 million new cases diagnosed every year worldwide. It is currently detected by a blood test that measures PSA levels. Although it provides early diagnosis, the PSA blood test has low specificity (high false positive), and approximately 75% of PSA positive results end with negative biopsy and no cancer is found. [79]

When a higher level of PSA in the blood is detected, the patient will undergo a prostate biopsy, which is an invasive test with a high risk of bleeding and infection. In biopsies, most patients with elevated levels of PSA were found to have no cancer. In addition, most early diagnosed prostate cancers are not fatal if left untreated. The current combination of PSA testing and biopsy of prostate cancer has led to unnecessary biopsies and overdiagnosis and overtreatment in many men. The new non-invasive prostate cancer test will encourage the individuals to have a regular test that can improve early detection and save lives. [79]

According to the Australia ABC News reported, the breast implant has been attributed to causing lymphoma and breast cancer: [17]

- It is estimated 200,000 Australian women have breast implants now subject to possible suspension or cancellation by the TGA due to cancer risks
- One in five women with breast implant lymphoma also had breast cancer
- Experts also warn about the burgeoning industry promoting implant removal when patients have no symptoms
- New figures show that of the 107 cases in Australia, 21 women developed the lymphoma following mastectomies and reconstructions after breast cancer [17].

2.1.8 Cancer Risk Factors

Major risk factors for cancers are summarised in Table 2-1.

Table 2-1 Risk factors for cancers [22,54]

Risk factor	Percentage of cancer deaths
Smoking and tobacco use	30

Obesity and diet (red meat vs. fruits and vegetables)	30
Lack of exercise	5
Carcinogens in the workplace	5
Viruses (hepatitis, human papillomavirus)	5
Family history of cancer	5
Body size (taller, bigger people get more cancer)	5
Women's reproductive factors (late or no childbearing, late menopause, early periods)	3
Excessive alcohol consumption	3
Poverty (aside from bad diet)	3
Environmental pollution	2
Excessive exposure to sun	2
Medical procedures, drugs	1
Salt, food additives, contaminants	1

Preventative measures that reduce cancer risk factors, such as smoking, alcohol consumption, poor diet, physical inactivity, overweight and obesity, also help reduce the risk of other chronic diseases, including cardiovascular disease, type 2 diabetes and chronic respiratory disease.

Recommendations from the WCRF (World Cancer Research Fund International) and the AICR (Australia Institute for Cancer Research) on food, nutrition and physical activity to reduce cancer risk were recently assessed through an analysis of participants in the European Large Prospective Cancer Survey (EPIC).Consistency with WCRF and AICR recommendations was significantly associated with reduced risk of cancer, risk of death, and risk of death from cancer, circulatory and respiratory diseases[22,54].

WHO estimates that at least a third of cancer cases could be prevented, while other estimates suggest that more than half could be prevented through healthy lifestyles and regular screening.

Lifestyle changes could reduce the number of cancer cases. The WCRF and AICR estimate that 21-24% of cancers in high-income countries could be prevented by changing food, nutrition, physical activity and physical obesity. The WCRF and AICR estimated that by improving diet and physical activity and their impact on obesity could prevent an estimated 43,000 cancers in Australia by 2025.

Risk factors are any factors associated with an increased likelihood of developing a health disorder or illness, such as cancer. Having one or more risk factors does not mean a person will develop cancer. Many people have at least one cancer risk factor but will never get cancer, while others with cancer may not have known risk factors [22,54].

However, there are many modifiable lifestyle factors that can reduce the risk of cancer listed below: [22,54]

Tobacco and cancer

WHO identifies tobacco use as the single most avoidable risk factor for cancer mortality worldwide and estimates that smoking causes up to 1.5 million cancer deaths each year.

The IARC has identified tobacco consumption as the single biggest cause of lung cancer. About 90% of lung cancer in Australian men and 65% in Australian women is estimated to be the result of smoking. IARC identifies that smoking also causes cancer of the mouth, pharynx, nasal cavity and antrum, larynx, oesophagus, stomach, pancreas, colon, rectum, liver, kidney, ureter, bladder, cervix and ovary and myelogenous leukemia. IARC also reported a positive association between smoking and breast cancer in women, with a recent meta-analysis of nearly 32,000 breast cancer cases.

Alcohol consumption also has a synergistic effect with smoking to increase the incidence of cancer in the upper digestive tract (i.e., cancers of the mouth, pharynx, larynx and oesophagus) beyond the single additive effect of smoking or alcohol.

Second-hand smoke and cancer

The IARC paper classifies second-hand smoke as a group 1 carcinogen that causes lung cancer and is associated with pharyngeal and laryngeal cancers. Quitting smoking reduces the risk of lung cancer and other major cancers.

Five years after quitting, the risk of cancers of the mouth, throat, oesophagus, and bladder halved, and the risk of dying from lung cancer halved after 10 years.

Quitting smoking also promotes both short-term and long-term improvements in health, including, carbon monoxide levels in the blood drop dramatically, heart rate and blood pressure drop, circulation and lung function improve, cough and shortness of breath, coronary heart disease and stroke risk decrease.

In Australia, the proportion of daily smokers has been falling steadily, from 22.4 per cent in 2001 to 16.1 per cent in 2011.That's equivalent to 2.8 million adults smoking every day in 2011-12.

Overweight and obesity

Worldwide, an estimated 3.6% of all new cancers in adults can be attributed to being overweight, a total of 481,000 incidences.

In 2007, based on the systematic review the WCRF and AICR reported food, nutrition, physical activity and cancer prevention: a global perspective and the subsequent tumour specific updates, identifies the convincing evidence that obesity increases the risk of various cancers in the body, namely colorectal cancer, oesophageal adenocarcinoma, endometrial, pancreas, kidney, liver and postmenopausal breast cancers. More physical obesity has been identified as a possible cause of gallbladder, advanced prostate and ovarian cancers.

The 2007 WCRF and AICR report and subsequent updates confirm compelling evidence that abdominal obesity increases the risk of colorectal and endometrial cancers and may be a cause of pancreatic cancer and postmenopausal breast cancer.

Physical activity and sedentary behaviour

It is estimated that 5% of cancers in the United States are related to an inactivity or sedentary lifestyle. Worldwide an estimated 135,000 cancer deaths occur each year as a result of physical inactivity.

The 2007 WCRF and AICR report and tumour-specific update confirmed that physical activity prevents some cancers and limits weight gain, which is itself a cause of some cancers. There is compelling evidence for a protective effect of physical activity on colon cancer and possible evidence for postmenopausal breast cancer and endometrial cancer. Limited suggestive evidence supports a protective effect on premenopausal breast, lung, and liver cancers. To reduce the risk of cancer, the report recommends making physical activity a part of daily life, including at least 30 to 60 minutes a day, and limiting sedentary habits, such as watching TV.

Dietary fibre

It is estimated that diet-related cancer cases account for 5% of all cancer cases in the United States and 30% of European men. It is estimated that approximately 374,000 people worldwide die from cancer each year because of low intake of fruits and vegetables.

Foods containing dietary fibre, such as vegetables, fruits, beans and legumes, cereals were identified in the 2007 WCRF and AICR reports and updated with convincing evidence that they have protective effects on colorectal cancer while a limited evidence for oesophageal cancer. A recent meta-analysis of approximately 580,000 subjects identified a

protective relationship between dietary fibre and gastric cancer risk. The WCRF and AICR reports recommend eating at least 400gm of various starch-free vegetables plus fruits and relatively unrefined grains and/or beans with a meal daily to reduce the risk of cancer.

Overnutrition and weight gain

The WCRF and AICR reports that increased consumption of energy-dense foods and sugary drinks may lead to an increase in becoming overweight and obesity, which increases the risk of certain types of cancer. The report recommends limiting energy-dense foods and fast food and avoiding sugary drinks to prevent and control weight gain, overweight and obesity.

Red meat, processed meat and cancer

The WCRF and AICR reports and updates confirm compelling evidence that increased consumption of red and processed meat increases the risk of colorectal cancer, while limited evidence suggests an increased risk of oesophageal, lung, pancreatic and gastric cancers

Salt and cancer

The WCRF and AICR report identified evidence that salt (from salty foods, processed foods and added salt) may cause stomach cancer. As processed foods are a major source of salt, the WCRF and AICR reports recommend that individuals limit total salt intake (salt added to food and salt contained processed food) less than 6 gm (equivalent to about 2,300 milligrams of sodium) per day.

Alcohol

An estimated 5.6% of cancer cases in Australia each year can be attributed to long-term alcohol use. The latest data from eight European countries in the EPIC study show that 10% of cancers in men and 3% in women of cancers were attributed to current and previous alcohol consumption, much of which is linked to consumption above recommended limits. The increased alcohol consumption level equals to the degree of increased risk of cancer development.

The 2012 IARC dissertation on alcohol reviewed the evidence and concluded that alcohol is a group 1 carcinogen that causes oral, pharynx, larynx, oesophagus, colon, rectum, hepatocellular carcinoma and breast cancer in women. A positive association between alcohol and pancreatic cancer was also identified. A recent meta-analysis of 572 studies confirmed that alcohol increases the risk of these cancers.

The IARC monograph and the WCRF and AICR reports both report that total alcohol consumption affects cancer risk, regardless of the type of alcohol. The IARC monograph also classifies ethanol and acetaldehyde, which are related to alcohol consumption, as group 1 carcinogens. The WCRF and AICR 2007 report recommended limiting alcohol consumption based on evidence that even small amounts of alcohol increase cancer risk. The WCRF and AICR report recommends limiting alcohol consumption to two drinks a day for men and one drink a day for women.

Smoking and alcohol consumption together may increase the incidence of cancers in the upper aerodigestive tract beyond the single effects of smoking or alcohol.

UV radiation

Internationally, the percentage of cancer caused by ultraviolet (UV)/ionizing radiation ranges from 2% in the United States to 8-10% in European men. According to the WHO, 65,000 people worldwide died of melanoma in 2000.

International statistics may underestimate the impact of ultraviolet radiation on Australia, which is the country with the highest incidence of skin cancer in the world. The age-standardized incidence of Australian melanoma in 2008 was more than 12 times the global average. It is estimated that in Australia, approximately 95% of melanoma cases occur in highly exposed areas, and approximately 99% of non-melanoma skin cancers occur in Australia as well.

In Australia, non-melanoma skin cancer (including basal cell carcinoma and squamous cell carcinoma) is the biggest cause of cancer hospitalization, and about two-thirds of Australians have at least one non-melanoma skin cancer before the age of 70. Exposure to UV radiation, especially during childhood and adolescence, is believed to be the biggest risk factor for non-melanoma skin cancer.

The 2012 IARC Monograph on radiation classified UV radiation as a group 1 carcinogen, carcinogenic melanoma and other types of skin cancer, including basal cell carcinoma and squamous cell carcinoma. The IARC Monograph identified positive associations with lip and eye cancers (conjunctival squamous cell carcinoma and ocular melanoma). A 2001 systematic review reported that accumulative sun exposure may increase the risk of melanoma, especially repeated burns and blisters.

The IARC also classified UV-emitting tanning devices (solaria) as a group 1 carcinogen, with evidence that these devices cause melanoma of the skin and eyes and are

positively associated with squamous cell skin cancer. An increased risk of melanoma associated with use of solaria before age 30.

The Cancer Council of Australia recommends avoiding excessive sun exposure and wearing sunscreen and protective clothing to reduce the risk of skin cancer.

Infections

It is estimated that 3.3% of cancer cases in Australia and New Zealand are attributable to infection. Worldwide, it is estimated that 16.1% of cancer incidences are attributed to infections but estimates greatly vary among different regions.

The 2012 IARC Monograph on biological agents identified a number of different drugs that cause cancer. In the 2008 World Cancer Report, Human papillomavirus (HPV), Helicobacter pylori and hepatitis B and C viruses were identified as major infectious agents. It is accounted internationally for 6.1%, 5.4%, and 4.3% of all cancer cases, respectively, and 1.9 million cancer cases globally.

In the IARC Monograph identified that other infectious agents may cause cancer, including gastric cancer, lymphoma, nasopharyngeal cancer, cervical cancer, anal cancer, conjunctival cancer, Kaposi's sarcoma, adult t-cell leukemia/lymphoma, cholangiocarcinoma, and bladder cancer.

Cancer Australia recommends vaccination to protect against HPV and hepatitis B, as well as other protective practices, such as safe sex, safe injection, safe blood transfusion, to reduce the risk of hepatitis C [22,54].

Cancer prevention should be considered as a causal influence factor in the cancer treatment strategy, as cancer prevention has been associated with decreased rates of cancer incidence and increased survival.

Cancer prevention can be categorized into three categories: primary, secondary, and tertiary cancer prevention. Behavioural changes that reduce cancer risk are primary cancer prevention. The secondary prevention strategy focuses on early detection of existing cancers when it is more likely to achieve treatment and cure. In tertiary cancer prevention, the focus is on preventing and controlling the symptoms and morbidity caused by established cancer and cancer treatments and preventing the development of secondary cancers or other diseases. In addition to behavioural changes, there are other opportunities to reduce the risk

of cancer, such as secondary cancer prevention or early detection, which is associated with increased cancer survival [31].

For example, a study published in the Lancet Oncology Journal by the International Cancer Benchmarking Partnership that reviewed 3.9m cancer cases from Australia, New Zealand, the UK, Norway, Ireland, Canada and Denmark and compared the one-year and five-year survival rates for seven types of cancer: bowel, oesophageal, pancreatic, stomach, rectum, lung and ovarian. Australia had the highest five-year survival rate in all but lung and ovarian cancer [90].

The research found that "Australia's higher survival rates can be attributed to earlier findings. Australia's public and private health care systems are separate, and doctors can refer public patients to private diagnostic services, part of which cost is covered by Medicare Service. but the survival rate between the rich and those with lower socioeconomic status still varies greatly." [90].

The study's recommendation to further integrate cancer prevention into clinical practice are as follows:

1) More research funding to be allocated to cancer prevention research into clinical Practice.
2) To set up better tracking systems of cancer prevention research and its outcome.
3) Participation in cancer preventative services among the uninsured communities to provide wider access to cancer prevention services.
4) Funding and other assistance to schools for healthcare professionals.
5) Technology offers an opportunity to overcome some of the barriers to clinical cancer prevention to be made to maximize technology in implementing cancer prevention into practice.
6) Identification of barriers and opportunities for integrating multidisciplinary teams in cancer prevention care. [31]

Infection is one of the most common life-threatening complications of cancer and cancer treatment. This is because cancer and cancer treatment weaken the immune system. The immune system is the body's complex system for fighting off bacterial or viral infections [6].

Cancer prevention strategies have been associated with reduced cancer incidence and increased survival. It is worth noting the effect of cancer prevention on reducing cancer incidence, mortality and increasing survival. Therefore, prevention of cancer risk should be considered as a causal factor when assessing the effectiveness of cancer treatment.

2.2 THERAPIES FOR CANCER TREATMENT

Current commonly used cancer therapies can be summarized as below [28]:

- Biotherapy: These therapies are designed to help patients with natural defences against cancer.
- Bone marrow transplantation (BMT): The bone marrow transplantation is to treat cancer of blood cells.
- Chemotherapy: Chemotherapy is the term for many different drugs used to treat cancer.
- Cryotherapy (cryoablation): In cryotherapy, tumours are frozen to kill cancer cells.
- Hormone therapy: The growth of some cancers is caused by hormones, usually signals produced by the body. These treatments block/block signals.
- Immunotherapy: These treatments are designed to overcome the immune system block that cancer cells produce.
- Radiation therapy: Radiation therapy causes damage to cells and can kill cancer cells when it targets tumours.
- Radiofrequency ablation: The energy beams cause cancer cells to heat up and die. This beam is different from the beam used in radiotherapy.
- Surgery: Many tumours can be surgically removed.
- Targeted therapy: It is to attack cancer cells rather than defects found in abnormal cells.
- Vaccines to treat cancer: Vaccines are used to "show" the body's defence system, in which case what to attack -- cancer cells.

The treatment given for cancer is variable, depending on many factors, including the type, location and number of diseases and the health of the patient. Most treatments

kill/remove cancer cells directly or cause them to die by depriving them of the signals needed to survive. Other treatments work by stimulating the body's own defence against cancer cells.

There are three more commonly used cancer treatments:

- Surgery (performed by a surgical oncologist).
- Radiation therapy (provided by radiation oncologists).
- Systemic therapy (usually managed by a medical oncologist).

The goal of any treatment is to kill as many cancer cells as possible and minimize the death of normal cells. Each type of treatment has advantages and disadvantages. In most cancers, multiple treatments must be used together (simultaneously or one after another) to get the possible best results.

2.2.1 Surgery

For much of human history, surgery has been the first line of treatment for many solid tumours. After surgery, the patient is taken to the operating room and the tumour is removed under anaesthesia. For some cancers, the entire tumour cannot be removed, but a portion of it can be removed, a process known as tumour removal. Benign growth may also be eliminated [28].

The advantages of surgery include [28]:

- Removing the tumours can reduce the mass effect and immediately reduce symptoms.
- Remove cancer cells that produce blood factors that stimulate the growth of cancer cells elsewhere in the body.
- Removal of tumours in areas that cannot be treated with radiation (e.g., if the patient has received radiation) or in systems of treatment (e.g., in the brain where some chemotherapy cannot reach).
- Potential ability to remove all cancer cells in a small area (patients can be cured by surgery alone).
- The ability to see cancerous tissue.
- Tissue samples can be examined to determine the best treatment option for that particular patient.

- If the patient has been treated, these samples can be used to see how the cancer responds to previous treatments, to see if more treatment should be given or if the treatment needs to change.

The disadvantages of surgery include [28]:

- The inability to kill small lesions around the edges of the tumour may leave tumour cells behind after surgery.
- Patients must be able to tolerate surgery and anaesthesia (i.e., have minimal medical problems and good lung function without taking certain drugs).
- Damage to nearby normal tissue (e.g. removing ribs or normal lung tissue to reach the site of lung tumour).
- Surgical complications (such as infection, and other specific sites).
- Unable to remove cancer from other parts of the body (i.e. metastatic disease)
- In some parts of the body where radiation therapy may have fewer side effects (such as in some types of brain tumours), killing cells cannot be safely removed.
- Remove organs that may affect the patient's quality of life (e.g., breast, throat, intestine).
- Surgeons can't tell cancer cells from normal cells with the naked eye (especially after chemotherapy or radiation has been delivered to the site).
- Common side effects of cancer surgery: Pain; Fatigue; Appetite loss; Swelling around the site of surgery; Drainage from the site of surgery; Bruising around the site of surgery; Numbness, Bleeding.

2.2.2 Radiotherapy

The advantages of radiotherapy include [28]:

- Death of most cancer cells throughout the tumour (radiation alone can be used to treat small tumours)
- Microscopic death of disease, very small groups of cancer cells invisible to the naked eye (e.g. during surgery)

- The ability to shrink the tumour (which may help reduce its mass effect on nearby body parts), or to shrink the tumour before surgery to a size that can be treated surgically resectable.
- Relative safety of patients (radiation can be delivered from outside the body and focused on the tumour, is painless, and usually does not require anaesthesia)
- Focus on making systemic therapy more effective (i.e. the ability to treat more cells alone than any other therapy)
- Organ preservation (e.g., a portion of the breast, larynx, or gastrointestinal tract that is not removed and will have a significant negative impact on the patient's quality of life)
- Stimulating an immune response to the tumour

Disadvantages of radiotherapy include:

- Damage to surrounding tissues, such as the lungs and heart, depends on how close they are to the tumour
- Cancer cells that cannot be seen on imaging scans cannot be killed, so are not always included in the 3D models used to plan radiation. It may include cancer in nearby lymph nodes or cancer that has spread to distant areas (metastatic disease).
- It doesn't kill all the cancer cells in a tumour. It is more likely for large tumours.
- Unable to mitigate the mass effect in some parts of the body, such as the brain. It can lead to the need for surgery.
- In areas with insufficient oxygen supply (such as areas after surgery, areas with insufficient blood supply), cancer cell killing rates are low.
- Increased incidence of wound complications and poor healing (e.g., if surgery is performed after radiation, or in areas without good circulation)
- Inconvenience with radiotherapy (e.g. in some cases, must be 5 days a week, 1-2 weeks each month).
- Most common side effects of radiation therapy are: skin problems, especially at the radiation site, such as dryness, itchiness, peeling and blistering (similar to sunburn); fatigue (tiredness).

2.2.3 Systemic treatment

Systemic therapy includes drugs that affect the whole body (such as hormones, chemotherapy, targeted therapy, antibodies, vaccines, biological response modulators, tumour integrative therapy, immune modulators) [28].

Advantages of systemic therapy include [28]:

- The ability to kill many cancer cells throughout the body (including cancer cells in major tumours and other tumours in the body)
- Work with radiation therapy (that is, it can kill more cells than treatment alone)
- Can kill microscopic lesions that are invisible to the surgeon's eye at the edge of the primary tumour (thus reducing the chance of cancer cells being left behind during surgery)
- The customization of systemic therapy (such as specific hormone therapy for breast cancer, targeted therapy for lung cancer) for each patient is the body of personalized medicine
- Preserving organs (e.g., not removing breast, larynx, or gastrointestinal tract parts, which can have a significant negative impact on patients' quality of life)

Disadvantages of systemic therapy include:

- Tumours cannot be killed alone (in most cases, systemic therapy must be used with surgery or radiation)
- Systemic treatment is not possible if the patient is on certain medications (such as blood thinners), before and after surgery, or if the patient has certain medical conditions (such as kidney failure, liver failure, heart disease)
- Systemic toxicity (because treatment passes through the body and may affect all normal tissues). Side effects are related to differences in treatment and use of drugs
- Systemic treatment fails to reach tumours (e.g. through the blood-brain barrier, to poorly circulated limbs)
- Relatively uneven killing of cancer cells in tumours (similar to having hundreds of beach balls and randomly popping half of them, not knowing where the remaining beach balls [live cancer cells] are still located)

- The relative inconvenience of systemic treatment (for example, some forms of chemotherapy must be given daily, five days a week, several times a week, or orally for several years).

Side Effects of Systemic therapy

- Side effects of chemotherapy that can occur in the days or weeks after treatment include: fatigue, nausea; vomiting and loss of appetite; pain or soreness, such as headaches, muscle pain or nerve pain; sores in the throat or mouth; changes to the skin, such as itching, redness, dryness and acne; diarrhoea or constipation; weight gain or weight loss; hair loss (some drugs cause hair to thin or fall out but many others don't cause any hair loss); changes to your libido; changes to concentration and memory; emotional changes; blood cell disorders, which may result in anaemia, dizziness, shortness of breath and increased risk of infection; effects on the nervous system, such as tingling, burning or muscle weakness.
- Side effects of immunotherapy: fever; chills; weakness; dizziness; headache; nausea, vomiting and diarrhoea; muscle or joint aches; changes in weight; low blood pressure; fatigue; breathing difficulties; allergic reactions.
- Side Effects of Target therapy: changes to skin and pain, hair and nails; eye problems; high blood pressure; problems with bleeding or blood clotting; problems with wound healing; diarrhoea; heart damage; autoimmune reactions.
- Side Effects of Hormone Therapy: hot flushes; night sweats; headaches; nausea and vomiting; skin rashes; increased risk of blood clots and stroke; increased risk of some heart conditions; cataracts; changes in mood; loss of libido; joint pain; loss of bone density; loss of strength; vaginal dryness; disrupted menstrual cycles; onset of menopause; breast tenderness; increased risk of endometrial (uterine) cancers.

Life Quality Impact factors by Cancer and Cancer treatment

Emotional changes can occur any time after being diagnosed with a cancer. Some people feel depressed or anxious immediately after diagnosis. Others may have emotional changes during and after treatment. When cancer patients receive treatment, their bodies may react to it, including physical, physiological, and psychological reactions. Although mental changes may be difficult to detect, they are as important as any physical change.

There are two sectors of Quality of Life impact factors related to cancer. One is from the diagnosis of disease and the other one is from the treatments.

1) Emotional Responses to the diagnosis of cancer

Symptoms of mood changes responding to diagnosis of cancer include:

Feeling down or depressed, Difficulty concentrating and remembering, loss of sexual interest or problems with sexual performance, irritability, uncontrollable of sadness or anger, loss of interest in activities and socializing, insomnia or excessive sleeping, overeating or loss of appetite, loss of energy and motivation, fatigue, feelings hopelessness or worthlessness, anxiety, excessive alcohol consumption, fearfulness, panic attacks, upset stomach feeling, etc[1].

2) Quality of Life impact factors in cancer treatments

Most common life quality impact factors are side effects from chemotherapy which plays a significant role affecting daily activities.

Some demographic and clinical characteristics affect the quality of life of breast cancer survivors; age, menopausal status, and types of treatments and side effects that can influence quality of life. Affected areas include body functions, pain and vitality[2].

Most cancer patients may experience some of the above emotional changes. Nevertheless, the severity levels of the emotional changes are varied individually. Some of them may impact on their quality of life or life performance which can be contributed to by other causal relationship factors.

Therefore, the causal relationship factors that affect the patients' quality of life or life performance are very complicated because every individual is different. For the patients who have symptoms of original emotional changes from diagnosis of cancer plus the side effects from treatments can lead to a poorer quality of life. An assessment of the patient's life performance should be based on the patient's individual holistic conditions, not based on the type of therapy or name of disease.

[1] https://www.nccn.org/patients/resources/life_with_cancer/managing_symptoms/mood_changes.aspx
[2] https://www.ncbi.nlm.nih.gov/pubmed/30813488

Thus, the FCM weights of a patient's life performance should be considered comprehensively according to the objective and subjective figures when a medical doctor makes prediction and decision making on a cancer patient treatment.

2.3 TRADITIONAL CHINESE MEDICINE (TCM)

TCM is an ancient practice used by millions of people all over the world - even after the development of modern scientific medicine. TCM has been popularly used in the greater China area for thousands of years. One fundamental rationale behind TCM is the belief that a person is part of the universe that is a whole unit, that is, "one in whole of universe and human beings". The relationship between humans and the universe is a dynamic causal corresponding response [64,65].

In TCM, a person's general constitutional types are classified into Eight-One-Fundamental. Nevertheless, a person's constitution is also associated with genetic, ethnic, gender, age, physical, environment, family, social, diet, work, exercises, psychological attitude, emotional influences, chronic disease, and relationships, etc. It is hard for everybody to stay in an optimal health state all the time. The above-mentioned factors can affect a person's health constitution, leading to sustained, but reversible disharmony state [64,65].

However, individuals' adaptability and responses to the natural environment are distinct, and the causal relationships are different accordingly. It is believed in TCM that the relationships among human viscera are dynamically complicated in several distinct aspects, including independent, dependent, interdependent, co-dependent and counter-dependent [64,65].

TCM practitioners make use of a so-called holistic approach as dialectics of aetiology and pathogenesis of TCM diagnostics. In combination with the information of patient's medical history, living environment, type of work, and lifestyle, physical examinations are conducted via four major diagnostic methods, namely observation, auscultation and olfaction, interrogation, and pulse feeling and palpation, which can reflect messages for the pathological and physiological disharmony of a patient [64,65].

Nevertheless, the accuracy and efficiency in diagnosis and decision making significantly rely on the individual TCM practitioner's knowledge and experience. Medical decision making is a complex procedure, taking into account the evaluation a variety of causal factors and suggesting a diagnosis and decision. Computer-aided systems have been

used to aid doctors in making patients' diagnosis and medical decisions for decades. However, due to the complexity of TCM, the computer-aided decision making for TCM practitioners still requires lots of work [64,65].

The core of TCM is that the individual's microcosm is viewed as an integral part of nature's macrocosmos. Diagnosis in TCM may appear to be simply a grouping of symptoms and signs, indicating pattern(s) of disharmony. Thus, the treatment strategy is to match the conclusion of the diagnostic pattern [64,65].

For example, common cold has many patterns in TCM. The most common patterns fall under the categories of wind-cold and wind-heat. As exterior disorders of common cold involved by wind-cold may change very rapidly, therefore treatment strategies requires change over the course of the illness. Wind cold pattern commonly presents the following symptoms and signs: fever, shivering (these are more excessive than fever), inability to get warm by wearing more clothes, nasal or sinus congestion with clear colour mucus, cough with clear colour phlegm, stiff nape and shoulders / upper back, occipital headache. The slower than normal pace pulse can be sensitively felt by the TCM practitioner from the surface of the skin (floating pulse). Diaphoretic (sweating) herbal therapy is especially helpful in this condition, which can warm the body internally and expel the cold pathogen out by sweating. In the very early stages of this pattern, before getting an available appointment to see a TCM practitioner, it can be treated effectively with an alternative remedy of rice congee cooked with the white part of spring onion and fresh ginger. In case of advanced conditions, the TCM practitioner will use a full range of therapies, depending on the combination of symptoms [64,65].

When the pernicious influence of wind combines with heat, the fever is more excessive than the chills, and the pulse is faster than normal. The primary symptom is a sore throat with headache and irritability. If there is a cough, it is usually dry or non-productive, with occasional expectoration of yellow mucus, at the early stage. In this case, honey suckle flower, chrysanthemum and mulberry leaf tea can release the symptoms [64].

When treating cold or flu symptoms due to wind heat, the results are always more effective if the treatment begins at the earliest possible stage of the illness. It is important to get adequate rest, a vacation for stress release, and drink more soups and fresh juices. Sweets, tonics and spicy food may cause a rapid progression in the severity of the illness since they tend to "feed the pathogen" [64].

On the other hand, for the individual who has a weak general constitution and level of wellbeing often repeatedly catches a common cold, they can take ginseng remedy as a tonification to strengthen anti-pathogen vitality and resistance for prevention of catching cold. This distinction between building long-term immunity and fighting off an acute illness is an important contribution of TCM. While tonic herbs may need to be taken for the long-term, it is important to discontinue their use of it during an initial stage of cold or flu. Then, after the pathogen has been expelled from the body, the intake of tonic herbs can be resumed to build up strength and vitality over the long-term [64].

Nevertheless, if the person's ability of vitality and resistance to disease is too weak, in TCM named Qi deficiency, the person would not be able to recover from a cold easily, then a small dosage of ginseng or other Qi tonifying herbs combined with other herbs for expelling exogenous pathogens would be prescribed by a TCM practitioner [64].Qi is the essential substance which is as foundation of functional activities. It also refers to the physiological functions of viscera and meridians. It is a vital energy which can be interpreted as the "life energy; life force" [64,65].

2.3.1 TCM in cancer treatment

TCM treats diseases not only for the clinical manifestations of a disease, or an organ, or confined to the lesion itself, but from the holistic point of view to understand the characteristics of the contrast and unity between the focus and the body. Among the human organs, there is an internal and external causal relationship that may lead to self-regulation and adaptation of the organic whole.

The human body is analogous to a complex and precise mobile chemical and mechanical 'human ecosystem'. It is composed of a variety of organs and biophysical features. Those individual components are part of the whole, which have different structures and functions among each other. They are not isolated, separated, nor unrelated to each other, but interrelated, mutually restrained and mutually beneficial.

Therefore, cancer is a disease affecting patients' whole-body system. The treatment of the disease must be for the oppositional relationship between the tumour and the body, the occurrence and development of tumours, body resilience mutual restraint, mutual consumption and other status.

Local lesions of malignant tumours have a broad impact on the whole body. The treatment of tumours should not be confined to the local treatment of tumours, but to the

body as a whole ecosystem, according to the individual patient's body and mind balance (patients' mental status can have a big impact on their physical status).

Strengthening the Body Resistance to Eliminate Pathogenic Factors: All kinds of human diseases, including the formation and development of malignant tumours, are related to the causal relationship of pathogenic factors and the body immunity defending.

Therefore, the treatment of malignant tumours should differentiate the pathogenic factor and the body's normal physiological components in order to eliminate the pathogenic factors and to rectify the body to harmony.

Differentiation of Symptoms and Pattern of Diseases: Different diseases can have similar clinical manifestations; different patients with the same disease can have different clinical manifestations; the same patient with the same disease, the symptoms at different stages can be different. Therefore, it is a critically important step in TCM clinical practice to identify the symptom and the pattern associated with the disease and the patient.

Given that the same symptom can be caused by different factors interacting between the body ecosystem and the environment, identifying the causally related factors is critical in TCM practice. The corresponding combination of the driving factors is often referred to as a syndrome or disorder type. Not only might a same symptom can be caused by different syndromes, different patients with the same syndrome can also have different symptoms. In TCM practice, syndromes, as they are the key driving factors of the disease, are given higher priority in diagnosis and treatment. However, the treatment of symptoms and syndromes is more integrated than differentiated.

Priority in Treatment: Cancer treatment involves several mechanisms to rectify the symptoms, kill the cancer cells or promote their apoptosis. TCM's role often is to support this process by harmonising the whole-body conditions. For example, when the breast cancer mastitis has spread to liver which caused jaundice and ascites at the same time, the treatment is to rectify the ascites and control the liver tumour as priority. TCM can be helpful, as an adjunction therapy, to support the harmony of the whole body, suppress the pathogenic factors that cause the ascites and jaundice.

2.4 SPDT

SPDT is a combination therapy of photodynamic therapy (PDT) and sonodynamic therapy (SDT) which can be performed together as one unit of therapy or individually. SPDT

is a novel cancer treatment approach utilizing a photosensitizer to be activated by specific wavelength of light and low-intensity ultrasound exposure [62]. SPDT has previously demonstrated significant tumour cell inhibition in animal studies and several case reviews have reported clinical benefits in metastatic cancer patients [62]. Initial clinical observation suggests that SPDT is worthy of further investigation as an effective and well tolerated treatment for a wide variety of primary and metastatic tumours, including those that have a refractory response to chemotherapy [61]

Even though there are large numbers of clinical research reports showing that SPDT is a safe and significant effective therapy for cancer treatment, other than the percentage of response to the treatment and efficacy, there is lack of detailed systematic clinical analysis. It is worthy of further investigation for systematic understanding about SPDT in cancer treatment which is not available in Australia yet. In addition, there is no comprehensive clinical study report available which was published by Australian scholars.

2.4.1 Photodynamic Therapy (PDT)

All plants, animals, human beings and most microbes cannot live without light and photosynthesis.

PDT was developed from the foundation knowledge of using sunlight to treat disease by ancient Egyptians, Indians and Greeks as far back as 3000 BC [36] Ancient Egyptian first utilized light-absorbing herbal photosensitizing compounds, applied through vegetable substances to produce photoreactions in skin tissues, for treating skin diseases such as de-pigmented skin lesions (vitillio) [36]. In 1550 BC, photo-medical procedures were also described in Ebers papyrus and the holy Indian Book Atharva Veda [36]. In 1903 the Danish doctor, Niels Reyberg Fishen, the pioneer of Phototherapy in Dermatology, received the "The Nobel Prize in Physiology or Medicine" in recognition of his innovation in using concentrated light radiation on the treatment of diseases, in particular of lupus vulgaris [nobelprize.org]. Following Dr. Fishen's steps, PDT was first used medically in 1904 to cure skin cancer. This innovation led the photo-medical therapy to become today's reasonably common treatment for skin cancer [109]. However, the modern PDT only began to form in the 1960s after Lipson et al reported hematoporphyrin derivative (HpD) by treating hematoporphrin chloride with hydrochloric acid and sulfuric acid [36,56,60]. The development of HpD established the basis of today's PDT [32,60].

In1978, Dougherty first reported the treatment of skin tumours by PDT with an argon dye. In 1980, bronchofiberscopic PDT for early stage central type squamous cell carcinoma was first performed and a complete cure was obtained for the first time in the world [60]. These studies confirmed the effectiveness and non-invasive safety of PDT since then.

Since 1993, regulatory approval for photodynamic therapy involving use of a partially purified, commercially available hematoporphyrin derivative（HpD) compound (Photofrin®) in patients with early and advanced stage cancer of the lung, digestive tract, and genitourinary tract has been obtained in Canada; approvals from Netherlands and France for treatment of advanced esophageal and lung cancers; Germany for treatment of early stage lung; Japan for early stage lung cancer, esophageal, gastric and cervical cancers as well as cervical dysplasia [44,51,60]. The photofrin, first PDT reagent, was approved in 1993 for the bladder cancer treatment. Currently, photofrin has been approved for various type of cancer by Food and Drug Administration (FDA). In 1998, PDT received U.S. Food and Drug Administration (FDA) approval for use of Photofrin for early stage lung cancer [12,84].

PDT, a useful therapy for the treatment of cancer, is a form of photodynamic therapy utilizing a specific wavelength of nontoxic light to the absorption of the photosensitizer which can selectively incorporate into cancer cells [16,37,53,83]. In the presence of oxygen, this light-activated photosensitizer can generate reactive oxygen species into singlet oxygen free radicals that cause the apoptosis and/or necrosis of tumour cells [35,37,83].

2.4.2 Sonodynamic Therapy (SDT)

Sonodynamic therapy (SDT) has been developed as a complementary or alternative therapy to PDT [94]. Similar to PDT, SDT uses ultrasound instead of light to activate the sensitizer. PDT and SDT can be used individually or in combination for synergistic effect. Ultrasound can penetrate deeply into malignant tissues and can be focused into a small region of a tumour [82]. Mechanisms of SDT include generation of reactive oxygen species especially single oxygen, which initiate chain peroxidation of membrane lipids [82]. Ultrasound can penetrate into tissue better than light, and generally its bioeffects are intensity and frequency dependent. A higher intensity results in efficient heat production, and a lower frequency facilitates acoustic cavitation [82].

Ultrasound has been demonstrated to activate a number of sono-sensitive agents allowing the possibility of non-invasive targeted treatment of deeper tumour sites than PDT [29,34,61,94]. SDT is based on preferential uptake of a sonosensitizer in tumour tissues and

the ultrasound dependent enhancement of cytotoxic activities of the drug [29,34]. Animal studies demonstrate that SDT with a sonosensitizer named Sonoflora 1 (SF1) inhibits the growth of mouse S-180 sarcoma, even when the tumour is covered by a bone [94], which is not achievable by PDT. SF1 is a chlorophyll derivative with very high sonodynamic as well as photodynamic activity [94]. Embryonic zebra fish assay data provided by Advanced Technologies, the original SF1 developer, show no evidence of toxicity in the experiment [94]. SDT is a potential cancer treatment modality that has been gaining support due to its effectiveness in both in vitro and in vivo studies. The therapeutic method combines ultrasonic irradiation with drugs known as sonosensitizers that amplify its ability to inflict preferential damage on malignant cells [92].

SPDT has previously demonstrated significant tumour cell inhibition in animal studies [43,61]. Since most photosensitizers are susceptible to ultrasound, and it has been found that photochemically active porphyrins also show significant anti-tumour effects when activated with ultrasound [34]. It is expected that SPDT might be able to give more synergistic effects than just using PDT or SDT alone [56]. SPDT has been clinically proved as a safe and non-toxic effective cancer therapy with very minimum tolerable side effects [61,94].

2.5 TREATMENT FOR SIDE EFFECTS OF THERAPIES

All treatments for cancer have risks of different types and levels of side effects. This will depend on the individual's type of cancer, the stage of the cancer, types of treatment and a range of personal factors. Some side effects can be very distressing, but most will lessen, then disappear in the weeks and months after treatment stops.

Complementary therapies may be used together with conventional medical treatments to support and enhance patient's quality of life and well-being. They do not aim to cure the person's cancer. Instead they are used to help control symptoms such as pain and fatigue. Complementary, therapies include relaxation, talking therapies, meditation, visualisation, herbal medicine, acupuncture, aromatherapy, reflexology, music therapy, art therapy and massage.

For example, acupuncture is a part of Chinese medicine which also practised by some Western medicine doctors. It can work in sickness caused by chemotherapy and some other symptoms. Side effects from acupuncture are rare.

Traditional Chinese medicine suggests that energy (called Qi in TCM) flows through the body. It moves along channels called meridians. Acupuncture alters this flow to restore or optimise good health.

Acupuncture is used to treat a wide range of pain conditions and some other symptoms. Many doctors train in Western medical acupuncture alongside anti-cancer treatments. People with cancer might have acupuncture to relieve pain and a range of sicknesses. This can be because of chemotherapy or other cancer drugs resulting in tiredness and fatigue, a dry mouth, breathlessness, hot flushes, nausea, vomiting, anxiety, nervous stress, depression, diarrhea, constipation or headache, as examples.

Western medical research shows that acupuncture works by stimulating nerves. It releases the natural morphine-like substances (endorphins) in the spinal cord and brain. This relieves pain. Acupuncture also releases serotonin. Serotonin is a pain reliever which can promote a feeling of wellbeing. The release of these substances can reduce cancer symptoms [26,27].

Side effect of chemotherapy:

Myelosuppression is the most common side effect in cancer chemotherapy. This side effect is the quantitative limiting toxicity of many chemotherapy drugs, which is also an important reason for stopping the chemotherapy in many patients. Myelosuppression is primarily the effect of chemotherapeutic drugs on specific stem cell motility, which damages specific stem cells in the bone marrow, resulting in a decrease in the number of mature, functional blood cells in the surrounding blood. The degree of reduction is related to the survival of cellular components in the peripheral blood. RBC has a half-life of 120 days, Platelet of 5 – 7 days, and a granulocyte of 6 – 8 hours. Therefore, side effects of chemotherapy usually begin with a decrease in WBC, followed by a decrease in Platelet, and finally a decrease in RBC. Leukopenia and neutropenia are most common in chemotherapy [93].

Leukopenia and Agranulocytosis:

Granulocytopenia is caused by some factors other than radiation and chemotherapy that inhibit the growth of bone marrow hematopoietic stem cells or progenitor cells. If tumour is transferred inside marrow, squeeze bone marrow hemopoietic organization or granulocyte mature obstacle or invalid hyperplasia. Some serious infection may cause granulocyte destruction to increase, or granulocyte consumption increases, causing a large number of granulocytes to leave the bone marrow storage pool to enter the lesion or the infected site.

Tumour disease, chronic liver disease and other factors lead to hypersplenism and the increase of antibodies in the blood, thereby shortening the survival of granulocytes.

Clinical risk of Myelosuppression:

- The decrease in WBC, especially granulocytopenia, is primarily associated with an increased risk of severe infection.
- The low thrombocytopenia is associated with a risk of bleeding, and when it is severe, it may cause central nervous system bleeding, gastrointestinal and respiratory bleeding.
- Anaemia

TCM's Diagnosis in Myelosuppression:

Myelosuppression is clinically characterized by leukopenia, thrombocytopenia, and anaemia. Chinese medicine classifies them as Qi and blood deficiency, Yin and Blood Deficiency, Kidney and Blood Deficiency.

TCM treating principle:
Qi and blood deficiency: to tonify Qi and Blood using Gui Pi Tang formula.
Qi and blood deficiency: tonify Yin and Blood using Zuo Gui Wan and Si Wu Tang formula.
Kidney and Blood Deficiency: Tonify Kidney and blood using You Gui Wan formula. [93]

2.6 FUZZY COGNITIVE MAPS

Fuzzy Cognitive Maps (FCMs) is a soft computing technique that follows a reasoning approach similar to the human reasoning and human decision-making process [76]. Uncertain causal knowledge is stored in FCM which is a fuzzy signed diagraph with feedback [63]. FCMs [68,69] is a form of visualized knowledge that has features making it suitable for domain experts to use directly [69]. FCMs unlike data driven models, can be built on modelling human expertise [75]. It represents and models how the human knowledge and expertise are applied in decision making process [75]. It allows loops that can model widely existing feedback; it is not a "rigid" model, consequently allowing multiple experts to contribute their knowledge without needing to compromise in order to maintain a certain structure (e.g., the tree structure in classic logic) [68.69]. The FCMs has been widely applied by domain experts because of its easy to use feature as compared with many formal knowledge modelling tools [67].

Medical decision systems are complex systems that can be deconstructed to non-related and related subsystems and elements, where many factors have to be taken into consideration. These factors may be complementary, contradictory, and competitive. The factors influence each other and determine the overall clinical decision to a different degree. [75]

Thus, FCM is suitable for medical Decision Support Systems by helping analyse the views and events that are carried on a medical subject with qualitative and quantitative methods [75]. FCM has two major functions: one is to reason about the causal factors between the causal relationships for prediction; another function is to analyse the results from the causation. FCM has been used for Medical Decision Support Systems; Medical Diagnosis; Long-term Prediction of Diseases; Disease Risk Assessment and Management; Disease prognosis, etc.

Treating a cancer patient, it should be considered that everyone is very different even for the same type of cancer patients. The treatment of each patient should vary accordingly. Some patients could have one or more than one course of cancer therapy only; some might have chemotherapy and/or radiotherapy plus, other therapies in the same treating period. This study is not a Case Study Report, and it is difficult to do a systemic research study and report to present the results from influential relationship factors of each patient with traditional tools of data analysis and assessment. Therefore, FCM is the most suitable tool to be used in this study which is to do the data analysis and assessment on the effects of cancer treatment using FCM. The key causal relationship factors of data analysis and therapy effectiveness assessment will be based on the cancer stage, side effects, response to therapy (cancer status change), and Life Performance Status Level to evaluate holistically.

In the last thirty years various studies have demonstrated the prognostic value of the Karnofsky Performance Status (KPS), primary for various cancers, but also for other disease entities [78]. The assessment of overall physical functionality as a predictor of overall survival is quite understandable pathophysiologically because poorer prognoses are generally associated with increasingly severe symptoms and a greater burden of disease [78]. However, the patients' vitality depends on many factors other than merely the KPS, including but not limited to Cancer TNM Staging, age, gender, molecular genetic markers [78], response to therapy, etc. It is easy for researchers to draw causal relationships of key factors into a causal link map (causal structure) as shown in Fig. 2-2. A tool for researchers to record the map electronically.

- Quantitative modelling of the causal relationships is needed after finishing the causal structure. This will include 'fuzzification' of membership functions, modelling the fuzzy weights of causal relationships, modelling the decision functions of nodes and performing normalizations. In the previous study [68], it was discovered that a particular state mapping is equivalent to a fuzzy cognitive map obtained from the formal modelling process. As Fig 1 shows, factor V2 (cancer therapy #1) has a causal impact on V1 (cancer stage) and V3 (side effects from therapy), and V4 (KPS). The treatment response is combined within V4 (KPS) though. The researchers would know in what case V2 and V5 lead to the corresponding V1, V3 and V4, and the connect weight matrix (Fig. 2-2), thus is able to fill those entries in the table.
- An auto-fitting tool (agent program) is to monitor the mapping tables, automatically filling the left-out entries from adjacent values, and then automatically generating the corresponding fuzzy cognitive map model.

The Causal Structure of Factors in Fig. 2-2 is a conceptualized FCM model. The actual Causal Structure of Factors in the FCM model will be added with more causal nodes and more loops according to the real cases in the analysis, such as when there is a combination of different therapy courses which will need to add more causal structure factors into the FCM map accordingly. However, the example of FCM model of Causal Structure of Factor in Fig. 2-2 is specified for a hypothesis treatment analysis and assessment purposes.

FCM incorporates the available knowledge and experts and the interactions between concepts. FCM can be represented as a signed fuzzy weighted graph with closed loops. It consisted of nodes and directed arcs connecting between them [34]. FCM nodes represent variable phenomena or fuzzy sets. An FCM node nonlinearly transforms weighted summed inputs into numerical output, again in analogy to a dynamical system model neuron. FCM resonant states are limit cycles, or time-varying patterns [63]. Each node in the map below represents the concept (V) in the problem demand. The inter relation between the concept (V1, V2) is given by the strength values (weight W12) which reflects the degree of causal influence between them. The weights strongly incorporate the available knowledge and expertise in the field [88]. The inference proceeds by nonlinear spreading activation [63].

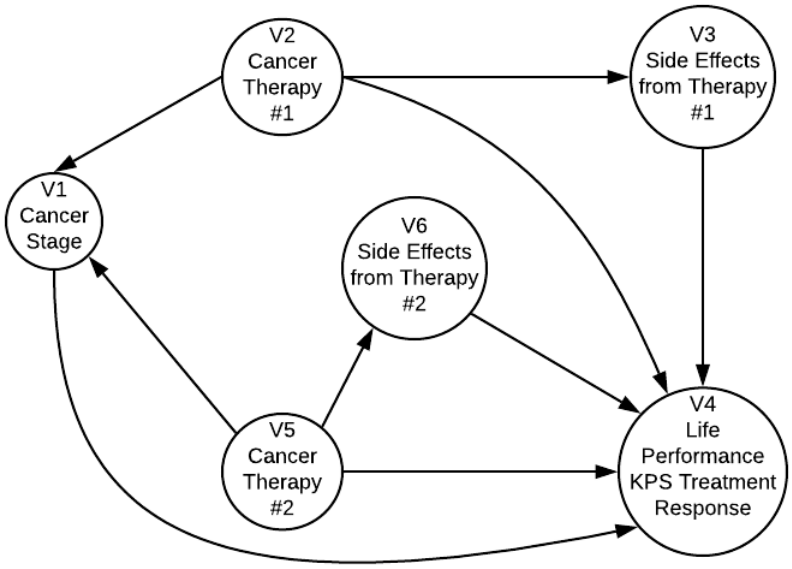

Figure 2-2 An example of FCM

Definition and Fuzzification Confirm the States [74]

V1 - Cancer Stage (TNM):

IA (T1 / N0 / M0); IB (T2 / N0 / M0); IIA (T1 / N1 / M0); IIB (T2-3 / N1 / M0);

IIIA (T1-3 / N1-2 / M0); IIIB (T1-4 / N0-3 / M0); IV (T1-4 / N0-3 / M1).

Tis in situ cancer or pre-cancer are not included in this study.

V2 – Cancer Therapy, Type 1

V3 – Side Effects from therapy # 1

V4 - Life Performance KPS %:

10% (Completely bedridden and comatose or barely arousable);

20% (Completely bedridden and dependent upon extensive nursing care by professionals and or family);

30% (Almost Completely Bedridden);

40% (Bedridden > 50% of time);

50% (Considerable Assistance);

60% (Occasional Assist);

70% (No Assistance);

80% (Moderate Symptoms);

90% (Mild Symptoms);

100% (No Symptoms)

V5 – Cancer Therapy type 2:

V6 – Side Effects from therapy # 2

Illustration of KPS [78,80]

*** Progressive Disease** (PD): At least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LDrecorded since the treatment started or the appearance of one or more new lesions

*** No Change** (Stable Disease): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

*** Partial Response** (PR):At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD

*** Complete Response** (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to<10 mm.

This matrix isomorphism with an FCM allows experts to graphically represent their knowledge by drawing causal pictures and allows that knowledge to be processed in feedback associative memory fashion by operating on the underlying connection matrices. Simple signed FCMs, rather than real-valued FCMs, are easier to get from experts. Simple FCMs are also usually more reliable, because experts are more likely to agree on causal signs than on magnitudes [63-65]. Obviously, the weights strongly incorporate the available knowledge and expertise in the field. Normally, FCM weights can be determined by the following two methods: [63-65].

- From experts. This is a typical approach. It appears to be a rough estimation at the start point but can be rather effective and accurate through continuous adjustments. For example, in the context of medicine, as doctors can view the whole process of the inference, they can thus easily see the inappropriate value of weights and make adjustment. Thus, the weights can be quite accurate after a few rounds of adjustments.
- From data. This is similar to any data approach for coefficient modelling. This will need sufficient data and multivariable analysis. In our study, we mainly focus on the method from experts, while the data-based weight modelling after initial knowledge structure of FCM is the next step of the study.

$$W = \begin{array}{c} \\ v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{array} \begin{array}{c} \begin{array}{cccccc} v_1 & v_2 & v_3 & v_4 & v_5 & v_6 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & w_{14} & 0 & 0 \\ w_{21} & 0 & w_{23} & w_{24} & 0 & 0 \\ 0 & 0 & 0 & w_{34} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ w_{51} & 0 & 0 & w_{54} & 0 & w_{56} \\ 0 & 0 & 0 & w_{64} & 0 & 0 \end{bmatrix} \end{array}$$

Figure 2-3 Connect Weight Matrix

Figure 2-3 gives the connect weight matrix that represents the graphical FCM. The FCM consists of five conceptual nodes (V1 to V5) and eight weights (W12, W15, W23, W24, W34, W41, W53, W54, W56, W64), w_{ij} represents the weight of arc from concept node v_i to v_j. The weights are the fuzzification values which are calculated from the function related nodes; and values of causal factor of each node is determined by medical experts with their experience knowledge.All the figures used in the example tables are under hypothesis from my clinical experience.

The FCM causal structure link map can let researchers represent (or see the representation of other researchers) the relationship between the causal factors and the inference of individual treatment which conventional research tools cannot do.

2.7 FCM FOR MEDICAL SCIENCE

Some work has been done to investigate the efficiency of FCM to model the established knowledge from standard medical literature and accumulated expertise of clinical oncologists for the specific application of breast cancer risk assessment. It was concluded that the proposed decision support approach has the capacity to accurately evaluate the breast cancer risk factors and to assess the overall risk grade, by providing clinical oncologists with information for adjusting the patients' intervention procedure [88].

Another study was focused on analysing the symptoms of breast cancer with 100 women in age group of 26 to 65 in Adyar Cancer Institute with the experts' opinions by using FCM models. It was concluded that use of FCM model analysis can accurately evaluate the risk of breast cancer from the causal relationships of breast pain with other critical symptoms of nipple turning inward, redness, scarring, or thickness of nipple/breast skin and abnormal discharge which are all in high risk of breast cancer [14].

An enhanced version of the evolutionary learning approach of FCMs, considering a parameter that defines a long prediction horizon, was investigated for its application to the prediction of prostate cancer. It was concluded that the fitness function of the enhanced learning algorithm enabled a better optimization of FCM for the task of long-term prediction of multivariate time series. The calculated prediction errors were small for the FCM-II due to the improved optimization of FCM that was accomplished using the approach. The proposed solution was validated in a pilot study using real medical data [47].

Another study on brain tumour concluded that the results of the proposed grading model present reasonably high accuracy, and are comparable with existing algorithms, such as decision trees and fuzzy decision trees which were tested at the same type of initial data. The main advantage of the proposed FCM grading model is the sufficient interpretability and transparency in the decision process, which make it a convenient consulting tool in characterizing tumour aggressiveness for every day clinical practice [76]. Furthermore, the ability of the FCMs to model and structure accumulated knowledge and expertise might be an important contributor in enhancing the pathologists' consensus at the diagnostic level.

Medical Decision Making is a complex procedure, taking into evaluation a variety of causal factors and it concludes a diagnosis and decision. Computer systems have been used in aiding doctors to make patients' diagnoses and medical decisions for many decades. In order to reduce doctors' workload in making accurate medical decisions, it is important to have a consistent system as a support. It has to include process and evaluation of high amounts of data information from multi-disciplinary sources, such as patient's background information and records, doctors' physical examination, laboratory tests, medical devices examinations, treatment records and results, and to clarify unclear and/or missing information [15].

A study on Fuzzy Cognitive Map structures for Medical Decision Support Systems (MDSS) has concluded that soft computing techniques such as FCMs can be used as a consistent MDSS, achieving better solutions in diagnosis, treatment, prediction and so on. FCMs can be a powerful tool as the experience of many experts and knowledge from historical data can be combined and contribute to form the FCMs [15].

A study has been done by the modelling of medical knowledge/ guidelines and the behaviour of the system for decision support in urinary tract infection (UTI) diagnosis based on the use of a new soft computing technology consisting of FCMs implemented in a Semantic Web approach. This work establishes a decision support tool based on FCM

formalism for UTI diagnosis, by proposing the appropriate diagnosis for each individual case [40]. In a word, FCM is suitable for Medical Decision Support Systems by helping analyse the views and events that are carried on a medical subject with qualitative and quantitative methods [75].

The basis of this study is the combination of SPDT and TCM with modern Western medicine therapies, which is different from the evaluation of the effectiveness of single cancer treatment regimen in medical field. Using FCM in the diagnosis and treatment analysis of TCM is also a unique study, while TCM considers human body in whole where various organs can causally affect each other in cancer treatments.

2.8 TCM

Western medical laboratory tests or Western modern medical device examination reports may or may not assist the TCM practitioner in doing diagnostic decision-making. Nevertheless, within a limited 10 to 20 minutes involved in initial consultation, the TCM practitioner makes a diagnostic conclusion and decides on a treatment approach with a prescription.

It is a very complicated task for a TCM practitioner to have in-depth knowledge of hundreds of Chinese herbs for diagnostic decision-making of a prescription for any specific patient within few minutes, along with the practice guidelines of safety and patient's best interest as a health care provider. There has been a lack of modern facility support in TCM practice.

In TCM, in the last decade, there has been a tongue detecting device used to do the tongue diagnosis, assisting or replacing the TCM practitioner's observation by taking photos of the patient's tongue for analysis by the computer. It was based on the Fuzzy C–Means Clustering algorithm for decision making in the diagnosis. Thus, it has been proven that FCM can be used as a clinical decision-making support system for TCM [58]. However, the device of tongue diagnosis is not commonly used by TCM practitioners yet.

Over recent decades, Chinese medicine has been widely accepted by the world as an alternative medicine and many Western Integrative medicine practitioners have included Chinese medicine as part of their treatment approach. It is believed that to improve the diagnostic accuracy of traditional Chinese medicine, improve the curative effect and ensure the patient's medication safety, the modernization of TCM with innovation technologies has become an important object in our societies.

Chapter 3: Research Methodology

In this research, FCM is used to provide cognitive modelling of practitioners of their analysis and assessment on effects of different therapies in cancer treatment so that the factors, their causal relationship, the inference and decision making can be analysed and communicated later. In this chapter, the intuition behind the methodology is discussed. The methodology is illustrated by a case study of TCM treatment on different types of cold, which could support cancer patients in their treatment.

Cases analysed with FCM were collected from Ren kang Hospital. Ethics approvals granted by institutions involved, Victoria University Human Research Ethics Committee project number HRE15-077.

3.1 RATIONALE

Fuzzy Cognitive Mapping (FCM) is a knowledge-based technology that combines elements of fuzzy logic and neural networks and acts as an artificial cognitive network [46]. FCM is a cognitive process that applies the main features of fuzzy logic and neural processes to situations involving imprecise and uncertain descriptions, like intuitional human reasoning [40]. FCM uses nodes to describe domains, also known as concepts (variables, states, inputs: facts, outputs: decisions) and the fuzzy relationships between them (the influence of concepts). The fuzzy approach provides the degree of causality, expressed as the relationship between concepts (variables, states, inputs, and outputs). This structure establishes forward and reverse propagation of causality, allowing the knowledge base to evolve by adding, modifying or deleting of concepts and the connections between them [40]. FCM represents knowledge and encodes relationships between mental landscape elements in order to assess their impact. FCM applies fuzzy logic to cognitive maps to predict the changes of concepts represented in cognitive maps. The graphical description of FCM is a signed and directed graph with feedback, consisting of nodes and weighted interconnections [40]. Nodes represent the concept of system description behaviour, and links represent causal relationships between concepts. In FCM theory, the fuzzy value of a concept represents the degree to which a concept is active in a general system, usually bounded by the normalized range of [0, 1]. In addition, the weight of

interaction relationship among the systems reflects the degree of influence of the causal relationship between the two concepts, which is determined by the experts in a linguistic manner. They function by capturing and representing causal relationships [45,87].

Nodes correspond to concepts: variables and states used to describe the behaviour of the system [40]. Nodes are connected by weighted arrows that represent cognitive relationships between nodes. Each concept is characterized by a series of values, usually in the interval of [0,1] or [-1,1]. Through the cognitive strength of their relationships, conceptual interactions suggest the dynamics of the system. Cognitive relations are represented in linguistic terms by fuzzy sets of correlations. It allows for a degree of causation. This structure establishes forward and backward propagation of causality, allowing the knowledge base to increase as concepts and the connections between them increase [39,41].

FCM represents a form of system that has a close similarity to human perception. Experts in various fields of science express their knowledge by drawing weighted causal relationship digraphs with simple representation. The represented model is easy to understand, even for non-technical people, and each parameter has a perceptible distinguishable meaning. In the graphical model, FCM is a specialized cognitive fuzzy-weighted graph containing feedback, including the nodes that connect them and directed links.

FCM can be used for a variety of purposes, including [44,45,67-69,88]:

- to redevelop the premise behind specific agent actions, to understand the reasoning for their actions and decisions, to highlight any functions of distortions and limitations represented in the situation.
- to predict future decisions and actions, or the reasoning of the given agent's justification on new occurrences as prediction functions;
- to help decision-makers think through their representations of given specific situations to determine their adequacy and possibly prompt introducing any necessary changes as reflective functions;
- to provide more accurate descriptions of difficult situations as strategic functions.

FCMs are developed by integrating the existing systematic experience and knowledge. This can be done by using a group of human experts to describe the structure and behaviour of the system under different conditions. With FCM, it's often easy to figure out which factors to modify and how, in that sense, FCM is a dynamic modelling tool that can increase the resolution of the system representation by applying further mappings. As a simple mathematical model, FCM represents the structural causal knowledge of qualitative and quantitative inference. The fuzzy model can be used to analyse, simulate and test the influence of parameters and predict the behaviour of the system.

The significant advantages of using FCM are:

- ease of use;
- easy to construct and parameterize;
- flexibility in representation;
- short implementation timeframe;
- easily understandable/transparent to non-experts and lay people;
- handle complex issues related to knowledge elicitation and management;
- handle dynamic effects due to the feedback structure of the modelled system.

In addition, individual FCMs pertaining factors to a domain can be combined mathematically. This means that FCM allows for the inclusion of different expert and/or stakeholder perspectives and can provide a useful mechanism for combining information from many sources to create a rich body of knowledge. Vector-matrix operations allow an FCM to model dynamic systems and thus capture dynamic aspects of system behaviour.

FCM develops actuated models for systems that leverage experience and expertise. FCM’s applicability in complex system has been successfully applied in many different industrial fields. The advantage of FCM model is that it can be given a solution based on historical data rather than human factors, and it is transparent, that is, every node and edge in the FCM diagram can be artificially interpreted. The model can be predicted by learning FCM and has long-term predictive power. It uses a learning method based on evolutionary algorithm, namely real-coded genetic algorithm. The RCGA algorithm (Real-Coded Genetic Algorithm) has been used for

the prediction of medical cases, such as long-term prediction of prostate cancer. The algorithm used is genetic based on real coding. The first long-term prediction of prostate cancer demonstrated the superiority of the method. The resulting evolution based FCM can predict the state of the patient after treatment for a period following the recommended treatment regimen [44,45,67-69,88].

Treatment decision making in medicine and support for handling uncertainty requires consideration of the patient's clinical parameters, the context of disease, the physician's medical knowledge, and guidelines for recommending treatment options. FCM techniques can use processes like human reasoning to handle situations including uncertain descriptions [2]. FCM's technology combines the robustness of fuzzy logic and neural networks and is an attractive knowledge-based approach [85]. Abdollah Amirkhani et al. used FCMs as a modelling and classification tool to diagnose breast lesions [2]. P. Spyridonos et al. used FCM causal knowledge as signed and directed digraphs with feedback and provided an intuitive framework to incorporate the knowledge and experience of experts to investigate the accuracy of brain tumour grading [85].

FCM has two major functions: one is to reason about the causal factors between the causal relationships for prediction; the other function is to analyse the results from the causation. In this research, FCM is mainly used for cognitive modelling of various medical treatments. A simple example is given in the next section to illustrate the basic procedure. After the illustration, Chapter 4 will present the larger-scale case analyses to demonstrate the application of FCM into the modelling of different therapies in cancer treatment.

3.2 ILLUSTRATION – FCM FOR TCM

In this study, we evaluate the applicability of FCM in TCM based on the common cold syndromes. Since TCM is heavily involved in our case study (Chapter 4), it is appropriate and valuable to use TCM treatment in the illustration of the proposed approach.

In TCM, the common cold can be classified into different types such as Wind Cold, Wind Heat, and Summer Heat with Dampness. The deficiency types related to the cold are subdivided as Qi Deficiency (low energy); Blood Deficiency (poor blood

level / circulation type); Yang Deficiency (cold or hypo-activity type); Yin Deficiency (false heat type).

Generally, a healthy person will have stronger individual type of cold symptoms and can recover quickly if he or she catches a common cold from Wind Cold; Wind Heat; or Summer Heat with Dampness pathogen. Nevertheless, when a person who is under deficiency condition is invaded by Wind Cold Pathogen, it will take much longer to recover.

During the treatment, it is very likely that the patient's disease will develop into a different syndrome as well. For example, when a Qi-deficient person catches a wind cold, it can transfer from cold syndrome to heat that changes the symptoms accordingly as well. For such a case, the treatment principle is to improve the Qi deficiency and to relieve superficies syndrome of the cold.

If the cold symptoms of a Wind Cold pathogenic caused common cold did not get treated and recovered in time, the cold patterned symptoms could then generate deficient heat and to be transformed to heat patterns, such as thirsty and dry mouth desiring to drink cold water; yellow thick phlegm; pharyngeal pain and other symptoms, etc. This is more likely to happen in Qi deficiency condition people. The recurrence of cold can worsen the patient's Qi strength, and so on. The prolonged Common Cold disease can lead to recurrence of the Cold as well. Common cold can also transmit other diseases in other organs, such as palpitation, oedema, etc.

More specifically, the syndrome Wind Cold mainly happens to the individual when invaded by exogenous pathogenic factors of Wind and Cold. It may be more prevalent in winter, or cold windy days, or in a cold environment such those with air-conditioning rooms. The clinical manifestations are sneeze, headache, chills, runny nose or nasal congestion, cough, thin and clear colour sputum, muscles ache, absence of fever or low fever, thin white tongue coating, floating or floating tight pulse.

Based on the above knowledge from experts, an FCM can be constructed, as shown in Figure 3-1. In the map, the concept "Wind Cold" represents the fundamental syndromes of wind cold, including blocked nose, sneezing, temperature, headache, and so on.

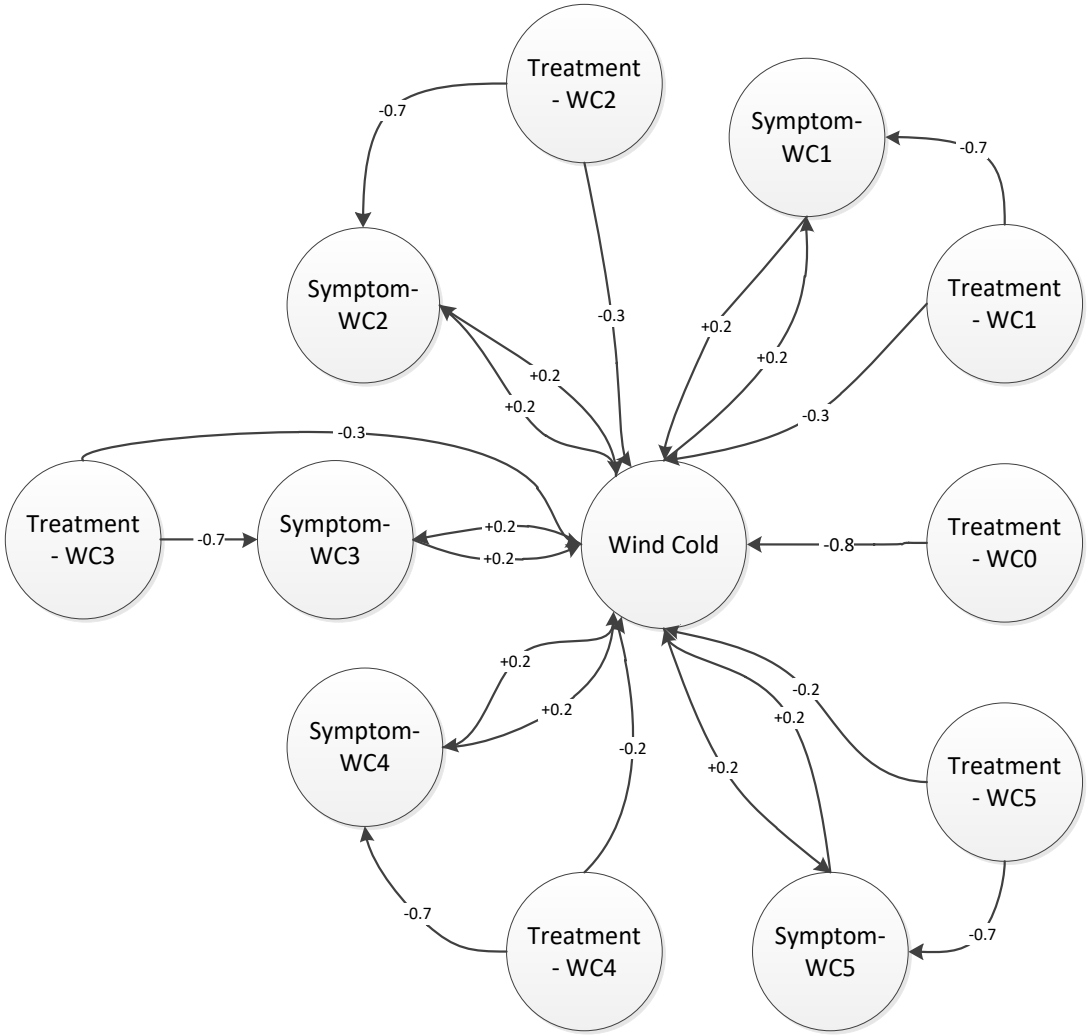

Figure 3-1 FCM map for wind cold[64]

The treatment principle is to expel exogenous pathogens with characteristic warm herbs to dispel internal cold for promoting lung functions, represented by "Treatment-WC0" can be applied to address the fundamental syndromes. "Jing Fang Bai Du San formula" can be used as a basic prescription.

However, a patient may develop extra syndromes, such as fever with shivering and lack of sweating represented by "Syndrome-WC1"; excessive cough with abundant clear colour phlegm represented by "Syndrome-WC2"; severe headache represented by "Syndrome-WC3"; rigid stiffness of nape and upper back represented by "Syndrome-WC4"; and nausea represented by "Syndrome-WC5".

For these extra syndromes, different additional treatments can be applied, by adding Ma Huang (Herba Ephedrae)、Gui Zhi (Ramulus Cinnamomi) to expel

internal cold represented by “Treatment-WC1”; adding Xing Ren (Semen Armeniacae)、Zhe Bei Mu (Bulbus Fritillariae Thunbergii) to expel phlegm represented by “Treatment-WC2”; adding Bai Zhi (Radix Angelicae Dahuricae) to dispel wind pathogen and relieve headache represented by “Treatment-WC3”; adding Ge Gen (Radix Puerariae) to relieve tightness of muscles and relieve pain represented by “Treatment-WC4”; and adding “Xiang Shu San formula” represented by “Treatment-WC5”. The weights among these concepts are provided by the expert.

Also drawn are the FCM maps for Wind-heat cold, Summer-dampness cold, and Qi-deficiency cold. The maps are shown in Figures 3-2 to 3-4, respectively. Let us use the wind-heat cold case to show how these maps help doctors make a decision on treatment. The primary symptoms of wind-heat cold included fever and aversion to wind, or may feel slightly chilled, headache, congestion of nose with thick yellow discharge, cough with yellow phlegm, thirsty and dry mouth, pharynx swollen and sore, redness on edge of tongue, thin yellow tongue coating, rapid floating pulse. The fundamental treating principle (represented by “Treatment–WH0” in Figure 3) is to use cold characteristic herbs to cool down the body to expel the exogenous pathogens, which can be treated with a basic prescription of “Yin Qiao San formula”. The individual’s symptoms can be variously distinct according the progress of the disease. In Figure 3, “Symptom–WH1” represents the severe sinus blockage, which can be treated by adding Shi Chang Pu (Rhizoma Acori Tatarinowii), Cang Er Zi (Fructus Xanthii), Xin Yi (Flos Magnoliae Lilliflorae), Bai Zhi (Angelica Dahurica), to clear sinus passage and relieve headache by dispelling pathogenic wind factors (“Treatment–WH1”). “Symptom–WH2” denotes the severe headache, treated by adding Sang Ye (Folium Mori), Ju Hua (Flos Chrysanthemi), Man Jing Zi (Fructus Viticis) to expel the heat for enforcing the meridians circulation around the head for headache relief (“Treatment–WH2”). “Symptom–WH3” represents the severe swollen and sore throat, by treated by adding Xuan Shen (Radix Scrophulariae), Ma Bo (Lasiosphera/Calvatia), Ban Lan Gen (Radix Isatidis) as antipyretic and detoxifying to relieve sore throat (“Treatment–WH3”). “Symptom–WH4” represents the excessive thirsty and dry mouth, treated by adding Tian Hua Fen (Trichosanthes kirilowii), Lu Gen (Rhizoma Phragmitis), Zhi Mu (Rhizoma Anemarrhenae) to clear heat for improving saliva production to relieve thirsty (“Treatment–WH4”). “Symptom–WH5” denotes the high fever, treated by adding Huang Qin (Radix Scutellariae), Shi Gao

(Gypsum Fibrosum), Da Qing Ye (Folium Isatidis) to clear internal heat for getting rid of fever ("Treatment–WH5"). "Symptom–WH6" represents the cough with thick yellow phlegm, which can be treated by adding Huang Qin (Radix Scutellariae), Zhi Mu (Rhizoma Anemarrhenae), Zhe Bei Mu (Bulbus Fritillariae Thunbergii), Xing Ren (Semen Armeniacae) Gua Lou Ren (Trichosanthis Semen) to expel the phlegm for clearing lung turbidity ("Treatment–WH6") [64].

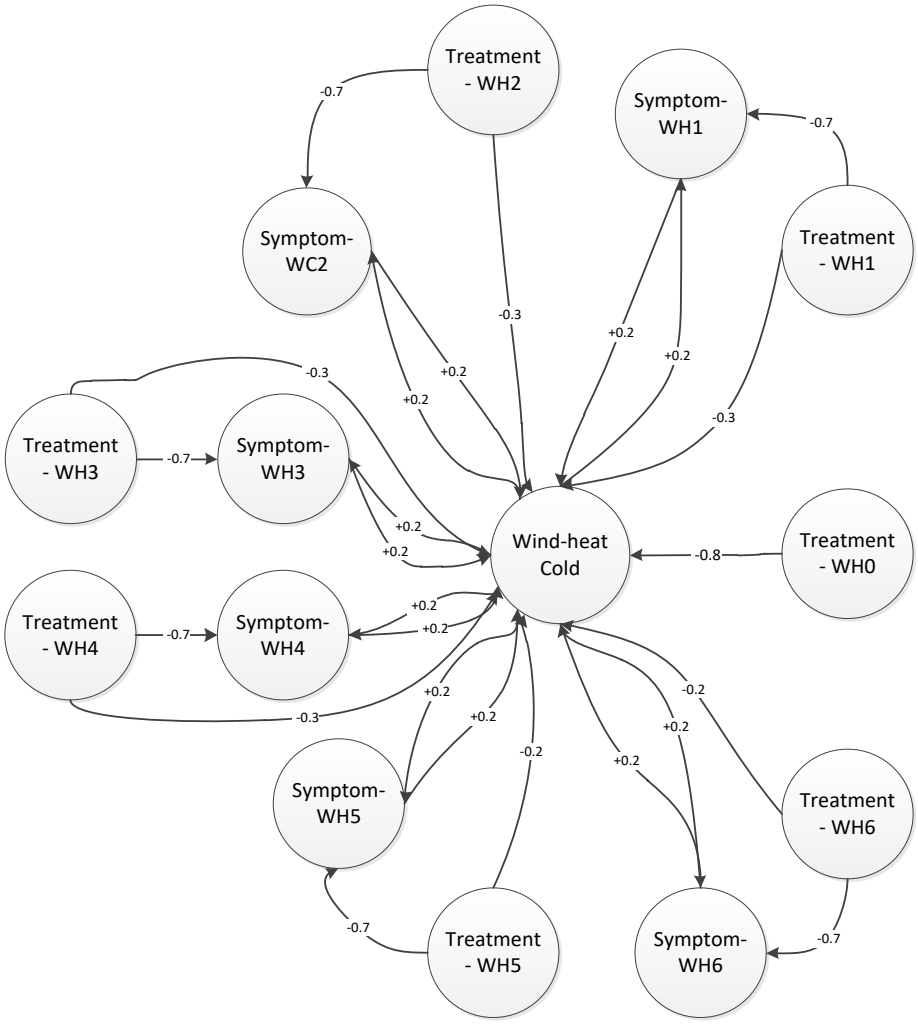

Figure 3-2 FCM map for wind-heat cold [64]

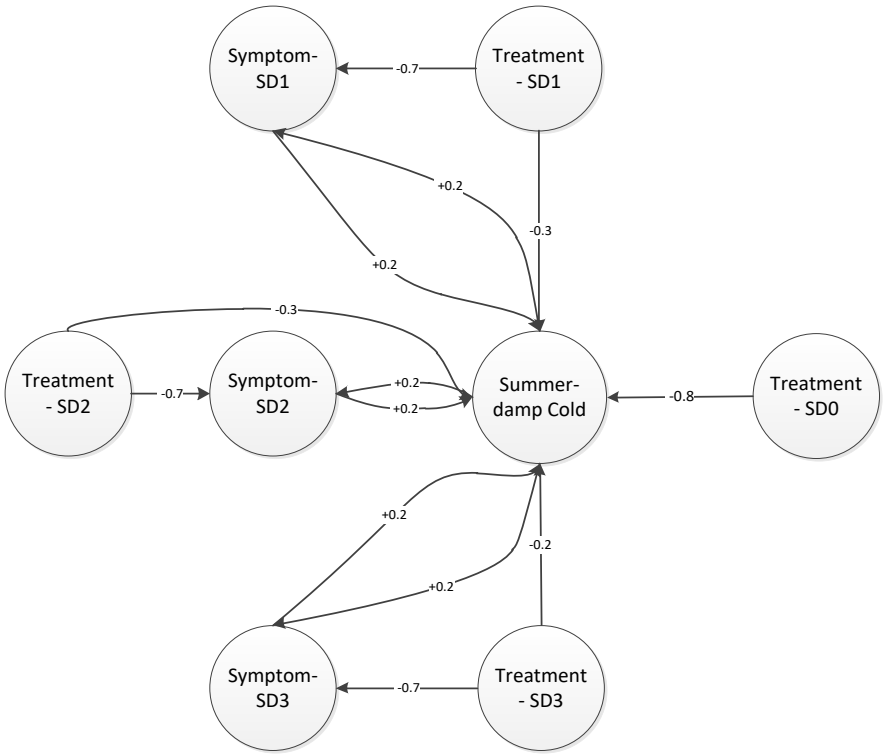

Figure 3-3 FCM map for summer-dampness cold [64]

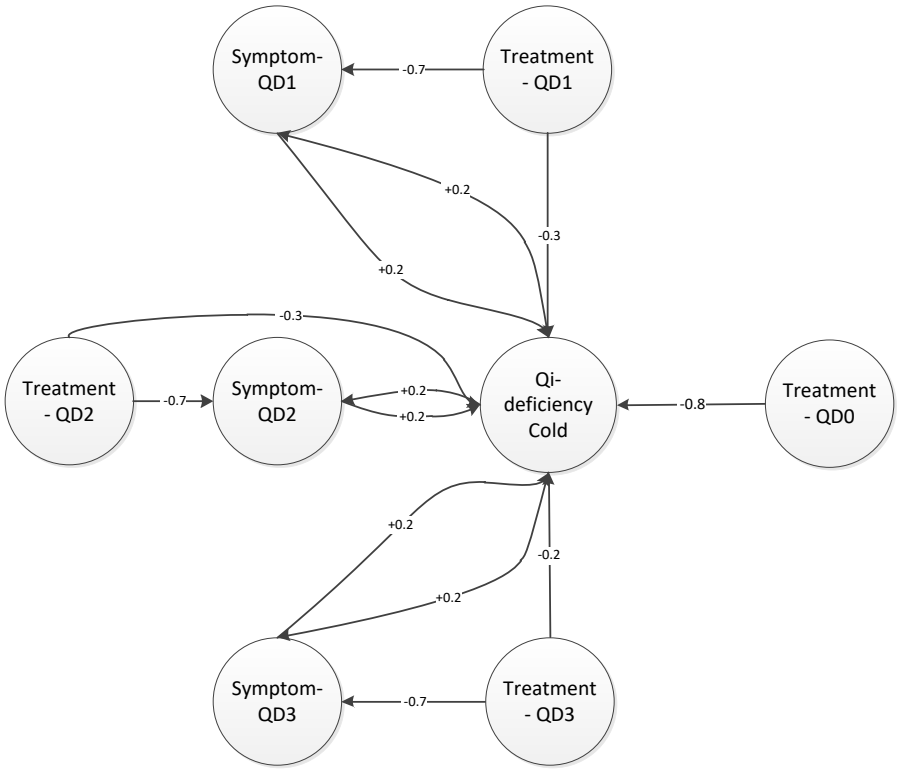

Figure 3-4 FCM map for Qi-deficiency cold [64]

TCM theory model is a large combination of interrelated theories which is more like a theoretical system. The theoretical system of TCM is based on ancient Chinese philosophical speculation. The constitution of TCM model has more associated with philosophy of intuitive thinking, more than a mathematical model.

The tools that TCM is used for reasoning are basically intuitive thinking models that are transformed from real things. The model system of TCM may seem a little messy at first, but after careful analysis, it can be found that the model of TCM can be classified according to different levels of consciousness. Some models belong to direct perceptual forms, such as exterior, interior, cold and heat models. Some tend to be reasonable, for example, dynamic Qi circulation and meridian transmission model; Some are philosophical, such as the Yin and Yang model and the five elements model. There is also a mixture of intuition, sub-consciousness and philosophy, such as the unity of man and nature. These different types of intuitive models are stored at the corresponding levels of consciousness. The interaction of consciousness hierarchy requires that they tend to be consistent, so that they each have a reasonable basis [108].

The common Cold case study [64] illustrated the application of FCM in supporting the decision making in TCM. Particularly, we have conducted a case study based on the treatments for common cold to demonstrate the applicability and effectiveness of the FCM-based decision making for TCM. The result FCM models the practitioner's cognition on the causally related factors of the patient, which supports the diagnosis and the decision making of the treatment. Additionally, the FCM improves the record of the cases, which has only the symptom description and prescriptions. The FCM can help in the further analysis and communication of related cases, which can improve the diagnostic accuracy of TCM, improve the curative effect, help to ensure the patient's medication safety, and support TCM practitioners' medical activities [64].

Chapter 4: Results

4.1 OBJECTS FOR STUDY

Cancer therapies vary according to the types and the stages of diseases. Most types of cancer therapy may cause side effects, some of which can impact the quality of life, or even cause other illnesses. In general, the traditional methods of cancer treatment assessments adopt linear treatment outcomes data, which lack the multiple causal factors interactions in relationships analysis.

This project aims to analyse and assess the data collected from our research study Hospital in China, using SPDT and other therapies to discover patterns, the effectiveness, the affecting factors, and the cross impact of the factors. The analysis of the effectiveness on curative cancer therapies and cancer prevention has become critically important while the cancer burdens keep increasing. The application of FCM in the medical auxiliary system is an important scheme. This project aims to model the causal relationship among the affecting factors of patients' diseases and their treatments, and the interaction with the outcome of the therapies in cancer treatment by using FCM, to support further analysis and decision making.

In this research study we selected different types of cancer cases for analysing the effectiveness of treatment based on FCM. They are breast cancer, pancreas cancer, colonic cancer, oesophageal cancer, and lung cancer. The breast cancer and pancreatic cancer cases are the patients who received a combination of conventional Western therapies and Chinese herbal medicine and dietary managements. The other three cases of colonic cancer, oesophageal and lung cancers are those who received conventional Western therapies and an alternative SPDT therapy without Chinese medicine treatment. We examined every patient's illness background, medical histories, types of therapies, side effects, and results. The causal influence factors are our major focus assessment and analysis based on FCM. Note that the modelling is based on the data collected from the hospital, the PhD researcher's knowledge, and consultation with clinical expert, Jaung-Geng Lin, Chair Professor of China Medical University.

1. Breast Cancer

Breast cancer is the most common cancer in Australian women. In 2019, it is estimated that 19,371 women and 164 men will be diagnosed with breast cancer, and it will account for around 29% of all new Australian cancers in 2019; an average of 53 people will be diagnosed with breast cancer each day. There are about 5% to 10% of breast cancers which are related to family history or genetic mutations, such as BRCA1 or BRCA2. The risk of being diagnosed with breast cancer increases with age. There are about 79% of new breast cancer cases which occur in women over the age of 50. The average age at which women are first diagnosed with breast cancer is 61 years of age. Considering the ageing of the population, the number of women diagnosed with breast cancer each year is expected to continue to increase. In 2020, it is estimated that 20,168 Australians will be diagnosed with breast cancer, and 20,825 in 2021. The number of Australian diagnosed with breast cancer is increasing, while the number of deaths due to breast cancer is decreasing. The risk of being diagnosed with breast cancer by age 85 is 1 in 7 for women and 1 in 675 for men. [20]

Fortunately, Australia is one of the countries with the highest breast cancer survival rate in the world. The 5-year relative survival rate has risen from 74.0% in 1986-1990 to 90.8% in 2011-2015. The percentage of relatively survival to 10 years is 83%. Early diagnosis by screening and improving treatment contributes to improved survival. Premenopausal women generally have worse survival outcomes than older women. Other subpopulations with lower survival rates include women living in rural and remote areas, Aboriginal and Torres Strait Islander men and women. The major factors causing the risk of breast cancer include gene mutation, overweight or obesity, drinking alcohol, smoking, personal history of early breast cancer, benign breast conditions, dense breasts, radiation to chest or face before age 30, and using HRT (Hormone Replacement Therapy).

Breast cancer can affect the life performance both emotionally and physically. Emotional effects include depression and anxiety. On the other hand, breast cancer may also result in insomnia and fatigue. [59]

With early detected breast cancer, women have a much greater chance of successful treatment, and for most women, breast cancer does not recur after successful treatment. The following therapies can be used in the breast cancer treatment:

- Chemotherapy;
- Radiotherapy;
- Target Therapy;
- Hormonal Therapy;
- Surgery;
- SPDT.

However, all these therapies have side effects, as listed in the following:

- Chemotherapy: Anaemia, Fatigue, Infection, Mouth sore, Neuropathy problems, Digestion problems, Skin changes and pain, Lymphedema, Lung problems, Painful breathing, Short of breath, Heart problems, Nail changes, etc.
- Radiotherapy: Pain and skin changes, Fatigue, Lymphedema, Digestion problems, Rib fracture, Heart problems, Lung problems, Mouth Sore, Infection, etc.
- Target Therapy: Fatigue, Anaemia, Digestion problems, Mouth Sore, Taste & Smell Change, Infection, Heart Problems, etc.
- Hormonal Therapy: Fatigue, Digestion problems, Risk of infection, Loss of Appetite, Heart Problems, etc.
- Surgery: Fatigue, Chest Numbness and tingling, Lymphoedema, etc.
- SPDT therapy: Skin changes and pain, Painful breathing, Lung problems, Short of breath, etc.

2. Colorectal Cancer

Colorectal Cancer in Australia [73]

Colorectal cancer (CRC) is the second most common cancer, next to breast cancer in Australia. Following lung cancer, it is the second most common cancer death. Statistics from the Australian Institute of Health and Welfare (AIHW) estimated that 17,004 new incidences of CRC will be diagnosed in 2018.

The incidence of colorectal cancer in Australia ranks second in the world.

• About 17,000 Australians are diagnosed with colorectal cancer each year, 93% of whom are over 50 years old.

• Colorectal cancer is one of the most common cancers in Australia. About 1 / 19 of men and 1 / 28 of women will develop colorectal cancer before the age of 75.

• About 80 patients die each week from colorectal cancer in Australia. Colorectal cancer is the second leading cause of cancer-related death after lung cancer.

Colorectal cancer is a common malignant tumour, including colon and rectal cancer. In general, the incidence of colorectal cancer descends from the rectum, sigmoid colon, cecum, ascending colon, descending colon, and transverse colon from high to low. Its pathogenesis is closely related to lifestyle, heredity and colon adenoma.

Colorectal cancer and colon cancer are often considered to be the same thing or a subset of another. In fact, even for health professionals, these terms are often used interchangeably. However, although there are similarities, the difference between colon cancer and colorectal cancer may be very significant.

For some people, the term "colon cancer" can include both colon and rectal cancer. For others, "colorectal cancer" may be used to describe a malignant tumour of the colon, even if the rectum itself is not involved. Both are good, but are they correct? A vaguer term describing colorectal cancer is bowel cancer, which describes cancer that begins in the colon or rectum.

There are quite a few clinical manifestations of significant similarities and differences between colon cancer and rectal cancer.

Similarities between colon and rectal cancer include:

- Incidence: Colorectal cancer is the third leading cause of cancer-related deaths in the United States. About 25% of colorectal cancers are rectal cancers.
- Risk factors: Colon cancer and rectal cancer have more similarities in terms of aetiology and risk factors than differences. They both link to diets of red meat while it is more pronounced in rectal cancer; and in contrast, colon cancer is more strongly related to alcohol consumption.
- Symptoms: Both colon and rectal cancer symptoms are very similar, although some may vary. For example, upper colon bleeding is more likely

to have brown or black blood, while distal cancer usually results in brighter red blood.

- Genetics: From a molecular point of view, colon cancer and rectal cancer are very similar and can even be attributed to the type of genetic mutation that causes them to grow. There are some variations, but in general, these two cancers are clearly related.

Differences between colon and rectal cancer are:

- Anatomy: The blood supply, lymphatic drainage, and nerve supply of the colon and rectum are very different. This is important because cancer is transferred to other parts of the body through the blood and lymphatics.
- Gender preference: Colon cancer is roughly the same distribution between the sexes, and rectal cancer is more common in men than in women.
- Disease recurrence: This is probably the biggest difference. In general, rectal cancer is more difficult to cure, and the relapse rates are 15% to 45%.
- Invasion of nearby tissues: Colon cancer is in the abdomen, with more "space" around it, and rectal cancer occurs in a tighter spot. Therefore, rectal cancer has a greater possibility of spreading to nearby tissues.
- Surgery: Surgery for colon cancer may be recommended at any stage of the disease, and surgery alone without chemotherapy or radiotherapy is usually recommended only in stages 1 and 2. In contrast, surgery for rectal cancer can be performed from stage 1 to 3, that usually requires chemotherapy and radiation therapy to be administered.
- Surgical difficulty: Colon cancer surgery is much simpler than rectal cancer. Rectal surgery is more difficult to access tumours, and it is more difficult to avoid invading many structures around the tumour during the procedures of operation.
- Colostomy: Patients who have undergone surgery for rectal cancer are more likely to have a permanent colostomy, because it is often required to remove the anal sphincter, which cannot be replaced or reconstructed.

- Radiation therapy: Radiation therapy is generally not recommended for colon cancer, while the rectal cancer is strongly recommended for stage 2 and 3.
- Chemotherapy: Chemotherapy for colon cancer is usually an adjunct to surgery at the stage 3 and 4, and sometimes at stage 2 as well.
- Postoperative complications: Patients with rectal cancer are more prone to postoperative complications than colon cancer patients, and colon cancer patients are more prone to short-term clinical complications.

Traditional therapies for the treatment of colorectal cancer include surgery, chemotherapy, radiation therapy, targeted drug therapy, immunotherapy, and proton beam therapy. As usual, all these therapies have side effects, as listed in the following:

- Surgery: fatigue, infection, bleeding, blood clots, damage to nearby organs, or leaking from the joins between the removed parts of the bowel, temporary or permanent stoma.
- Chemotherapy: hair loss, mouth sores, loss of appetite, nausea and vomiting, diarrhea, risk of infections, easy bruising or bleeding, fatigue, hand-foot syndrome (redness in the hands and feet, and then progress to pain and sensitivity in the palms and soles), neuropathy, intense sensitivity oesophagus and the palms of hands, skin rash, chest tightness and trouble breathing.
- Radiation therapy: skin irritation, redness progressing to blistering and peeling, nausea, rectal irritation, diarrhoea, painful bowel movements, blood in the stool bowel incontinence, bladder irritation, burning/pain while urinating, blood in the urine, fatigue, sexual problems.
- Target drug therapy: fatigue, skin problems, headache, fever, bleeding, blood clots, mouth sores, loss of appetite, diarrhoea, low white blood cell counts.
- Immunotherapies: fatigue, rash, diarrhoea, nausea, fever, muscle pain, bone pain, joint pain, abdominal pain, itching, vomiting, cough, decreased appetite, and shortness of breath.

3. Oesophageal Cancer

Oesophageal cancer in Australia

In Australia, it is most common in the lower oesophagus, adjacent to the stomach. The main types of oesophageal cancer are:

- Squamous cell carcinoma, a cell that originates in the oesophagus which is more common in Asia.
- Adenocarcinoma, the glandular tissue that originates in the oesophageal epithelial cells.
- In 2015, 1469 new incidences of oesophageal cancer in Australia.
- In 2016, 1338 Australians died of oesophageal cancer.
- The five-year survival rate for oesophageal cancer is 21%.

In general, oesophageal cancer develops slowly and it is usually not detected until found in the advanced stages because there may be no symptoms at an early stage.

Symptoms of oesophageal cancer may include:

- pain or dysphagia;
- heartburn;
- vomiting blood;
- black or bloody stools;
- unexplained fatigue;
- discomfort in the upper abdomen particularly when eating;
- weight loss;
- cough;
- hoarseness;
- bleeding.

Risk factors for oesophageal cancer include:

- high alcohol consumption
- smoking tobacco
- diet low in fresh fruit and vegetables
- eating smoked, salted or pickled food
- obesity

- drinking very hot liquids (above 65°C) frequently
- exposure to certain chemical fumes
- family history of gastrointestinal disorders
- certain medical conditions such as Barrett's oesophagus or gastro-intestinal reflux disease.

In Australia, it is most common in the lower oesophagus, adjacent to the stomach. The main types of oesophageal cancer are:

- Squamous cell carcinoma, a cell that originates in the oesophagus which is more common in Asia.
- Adenocarcinoma, the glandular tissue that originates in the oesophageal epithelial cells.

Possible therapies for treating oesophageal cancer include surgery, chemotherapy, radiation, targeted therapy, and SPDT.

4. Lung Cancer

Lung cancer is the leading cause of cancer death in Australia and the fifth most common cancer, and it is responsible for almost one in five of cancer deaths. In 2015, there were 11,788 new incidences of lung cancer in Australia, including small cell lung cancer and non-small cell lung cancer. This accounts for nearly 9% of all cancer diagnoses. In Australia, the risk of lung cancer diagnosed by men by age 85 is 1 in 13 and 1 in 21 for women. In 2016, there were 8,410 deaths due to lung cancer in Australia. The five-year survival rate for lung cancer is 17%.

There are two main types of lung cancer:

- Non-small cell lung cancer: It is the most common type of lung cancer, accounting for about 80% of lung cancer cases. There are three most common subtypes of non-small cell lung cancer:
    - Adenocarcinoma – begins with cells that produce mucus, accounting for about 40% of lung cancer. Although it is the most common diagnosis in current or former smokers; but it is also the most common form of lung cancer in non-smokers.

    - Squamous cell carcinoma (epidermal) - usually occurs in the large airways of the lungs.
    - Large cell undifferentiated carcinoma - can occur anywhere in the lung, not obviously squamous cells or adenocarcinoma.

- Small cell lung cancer: It usually begins in the middle of the lung and spreads faster than non-small-cell lung cancer, counting for about 15% of lung cancer.

The majority (85%) of lung cancer patients smoke for a long time, but about 10-15% of patients never smoke, which is often caused by genetic factors and inhalation of asbestos, second-hand smoke or other air pollutants. Lung cancer can be diagnosed by chest X-ray or CT scan, or by bronchoscopy or CT-guided biopsy. The most common clinical manifestations of lung cancer include:

- shortness of breath and wheezing
- hoarseness
- chest pain
- coughing or spitting up blood
- a new cough that does not go away
- recurring bronchitis or pneumonia
- loss of appetite
- unexplained weight loss
- fatigue.

Aetiology

- Cell carcinogenesis is associated with information of genetic mutations such as DNA and epigenetics which affect normal function of cells, including cell proliferation, programmed apoptosis and DNA repair.
- Smoking is by far the leading cause of lung cancer. Year 2000, in developing countries, counting for 90% of men who died of lung cancer were smokers, and 70% of women. 85% of lung cancer patients are smokers.
- Passive smoking can also cause lung cancer to non-smokers.
- Studies showed that in the United States, Europe, and the United Kingdom

there is a significant increase in the risk of lung cancer in passive smokers.

- People living with smokers have a 20-30% increased risk of illness, while those who have second-hand smoke in the work environment have an increased risk of 16-19%.
- Studies have also shown that side-stream smoking is more dangerous than direct smoking. In the United States, approximately 3,400 people die each year from lung cancer caused by passive smoking [24].

Based on understanding of the above different types of cancers, the case assessment and analysis are illustrated in the following.

4.2 FCM FOR TCM'S EFFECTS ON CANCER TREATMENT

Through application of the computational intelligence training technology activating Hebbian algorithm, the classification ability of FCM models can be improved [86]. The main advantage of the FCM grading model is that it has good interpretability and transparency in the decision-making process, which makes it a convenient consulting tool for charactering the tumour invasiveness in daily clinical practice.

For decades, computer systems have been used to help doctors diagnose and make medical decisions. In order to reduce the workload of doctors in making accurate medical decisions, it is important to have a supporting system which includes the functions of processing and evaluation of large amounts of data from multidisciplinary sources, such as patient background information and medical records, medical examinations, laboratory tests, medical device examinations, treatment records, and results; clarify unclear information and promptly supplement missing information. [15]

In TCM diagnosis, practitioners need to establish the causal relationships among various factors related to the disorder of patients to find out the cause of the disorder and decide possible intervention to help the patient. Thus, it is natural to use FCM technology to model the TCM diagnosis process and improve the accuracy and efficiency. In the following, FCM is applied into TCM decision making. A case analysis has been conducted on the treatment of breast cancer, which demonstrates the applicability and effectiveness of the FCM-based decision-making for TCM. The experiment results clearly indicate that FCMs can support practitioners make the

correct decision in their diagnosis and the corresponding treatment selection for breast cancer treatment. [65]

4.2.1 Pathogenic Patterns of Cancer in TCM

According to TCM, there are different types of pathogenic patterns. They are functional disorders of the viscera and general meridians circulation disharmony. I used a symbol system to represent different types of disorders so that they can be further categorised, compared and analysed. The disorder type or syndrome can be represented as a triple T(L, S, S-N), where T is the type of the disorder, L is the location, S is the substance of the disorder, S-N is the symptom of the disorder and its corresponding strength or severity. TCM has a list of typical elements for L, S and S-N. N is the value to represent the degree of severity of the disorder. It is important in dosage selection or in the balance of conflicting factors. In conceptual modelling, N is often omitted (noted in form of S-). When the disorder is applicable to any part of the location, the L can be noted with '-'. In this article we will use the following identifiers for the typical elements [65]:

L = {1-Whole body, 2-Heart, 3-Liver, 4-Kindey, 5- Lung, 6-Spleen, 7-Meridians, 8-Reproduction System}

S = {1-Qi, 2-Yin, 3-Yang, 4-Phlegm, 5-Fire, 6- Dampness, 7- General function, 8-Chong Ren, 9-Blood}

S-N = {1-Deficiency, 2-Stagnation, 3-Blockage, 4-Stasis, 5-Excess, 6-Disharmony/disorder}

As an example, T(1,1,1-) notes that the whole body (L = 1) has Qi (S = 1) Deficiency (S-N = 1-, the severity was not presented); T(3,1,2-0.3) notes that the Liver (L=3) has Qi (S=1) Stagnation with severity 0.3 (S-N =2-0.3). Each type of the disorder is derived from long-term practice observations. The followings are five example types of disorders. They are often related to breast cancer.

- T1 = T(1,1,1-) + T(1,2,1-) – T1 type of disorder is noted in TCM as Qi and Yin Deficiency. Patients with T1 disorder normally have low energy level and lack of nourishment by useful body fluid.

- T2 = T(6,7,1-)+T(4,7,1-) – T2 type of disorder is noted in TCM as Spleen and Kidney Deficiency. Patients with T2 disorder normally have weak digestive function, hormone imbalance and weak reproductive function.
- T3 = T(3,1,2-) + T(3,4,4-) – T3 type of disorder is noted in TCM as Liver Qi Stagnation with Phlegm Stasis. Patients with T3 disorder often have stress, unhappiness, abdominal bloating and accumulation of phlegm or water retention.
- T4 = T(3,5,5-) – T4 type of disorder is noted in TCM as Liver-fire Excessive. Patients normally run into anger or annoyed state easily.
- T5 = T(7,4,3-) – T5 type of disorder is noted in TCM as Phlegm Blockage in Meridians. Patients often have nodules or tumour in meridians.

4.2.2 Major Approaches to TCM in Cancer Treatment

The principle of TCM support in cancer treatment is to strengthen patients' energy, their 'defensive' ability and blood supplement. Therefore, the body ecosystem is stronger and able to resist or eliminate pathogenic factors.

It often takes a long time for cancers to develop before a diagnosable symptom emerges. Many cancers are due to the constitutional physiology disorders in the viscera. Cancer therefore can be considered as a chronic disease. Tumour cells damage the physiological balance and consume huge energy, leaving people in a weak state. To reconcile the balance of the body, strengthening the body's immune system against pathogenic factors (supporting the growth of tumour) is one of the prime approaches in cancer treatment.

Detoxification:

The aggressive growing cancer cells can affect the body in a typical status. It is called toxic heat condition in TCM (noted as THC in this paper). The condition is represented with typical tumour symptoms such as burning pain, thirst, constipation, dark yellow urine, infections and weak rapid pulse. THC is common in the late staged cancer patients.

The treatment method is to apply different mechanisms to eliminate the toxic substance accumulated in the abnormality. Besides THC, there are other conditions

TCM identified through the long-term practice, such as accumulated phlegm and dampness [48].

Harmonise the Liver Qi Stagnation:

TCM thinks a low-level function status of organs is an important factor associated with many diseases. It is termed as Qi stagnation in TCM, noted as a disorder of type T(-,1,2-) in this paper. T(-,1,2-) can present in many organs or body systems. In the liver, as T(3,1,2-), it is considered as one of the common pathological factors contributing to liver tumour development. For example, fatty liver causes the liver to function at a low level. People with fatty liver have a higher chance to develop a liver tumour. It also contributes to malfunction of other organs and body systems, increasing their chance of developing cancer. Thus, it is very important to harmonise the body ecosystem and improve the disorder type T(3,1,2-).

Other than medical treatments, diet therapy is an important supportive treatment in cancer. TCM classify status of human viscera, internal systems and environment factors as different factors. For example, HOT food represents food that contains spicy or a substance that promotes circulation. Hot food includes ginger, onion, pepper. TCM practitioners will consider the causal relationships of the factors to develop dietary therapy to help patients restore balance. A patient who often feels cold, pale, lack of energy could be classified as having a COLD body type. The patient should take more HOT food to balance. [107]

4.2.3 Breast Cancer Related Disorder Types (Patterns of Disharmony)

Through clinical observations, TCM researchers and practitioners form a cognition of the disorders and their causal relationship. The most common disorders are

- T(1,1,1-) + T(1,2,1-): Patients often have low energy level and lack nourishment of usage body fluid.
- T(1,1,1-) + T(1,9,1-): Patients often have low energy and blood supplement deficiency.
- T(8,8,6-): Patients often have functional disorder relevant to the reproductive system.

– T(3,1,2-): Patients often have weak liver function, are emotional, upset or in stress.

– T(4,2,1-): Patients often have reduced estrogen level, dryness, hot flushes, or scanty menstrual bleeding.

– T(1,9,2-) + T(1,4,2-): Patients often have weak circulation functions or blood fluid flow disorder.

TCM researchers and practitioners identify the disorder type of patients through observation of their symptoms, and then intervene with Chinese medicine or dietary therapy. The treatment impact on the disorders (and the elements) is part of the cognitive modelling and decision-making process. However, due to the complexity of the modelling process and the lack of computing models, it is difficult for large scale communication of the cognitive modelling and decision making among different practitioners or cases. Most of the cases are presented in natural language or meta-data format. The causal relationship among factors is either missing or not modelled in a way that computer aided analysis can be performed. In order to model the causal relationships for further communication and analysis, this paper applies FCM method to systematically model the classification of the disorders and the causal relationships involved, particularly for breast cancer TCM supportive treatment. [64,65]

A series of studies investigated the disorder types (or pattern of disharmony in TCM) among middle-aged women's groups, explored the relationship between the disorder types and specific biomarkers associated with breast cancer [108]. The study of Fu and Xu in TCM assessment [49] indicated that disorder type T(3,1,1) and disorder type T(3,2,1-) + T(4,2,1-) are the main disorder types in middle-aged women hormone fluctuation or pre-clinical breast diseases. The corresponding treatment widely adopted in TCM is therefore the treatments that can help with the disorder T(-,1,1-) and T(-,2,1-) [121]. The studies show that there was no significant change in the control group. As a comparison, the severity of the disorder (disharmony pattern score) in the treatment group was significantly lower at post-trial, indicating an improvement in overall health [49].

Result of this case observation

Studies on clinical observations in breast cancer related disorder types are summarised in Table 4-1.

A case study [71] has applied FCM to model the practitioner's cognition on the causal relationship between disordered types and the symptoms, and the changes at pre- and post-herbal treatment. The model is presented in Figure 4-1. The patient is a 35-year-old woman, diagnosed with stage III breast cancer. She received chemotherapy and radiotherapy before taking Chinese herbs. The TCM diagnosis shows T(-,1,1-) + T(-,2,1-) disorder type. Chinese herbs which can improve the disorder type were prescribed.

Table 4-1 Summary of clinical observations in breast cancer common disorder type studies

	Liu [105]: 407 cases	Xu [79]: 241 cases	Wu [22,106]: 108 cases	Liu [66]: 302 cases
T(-,1,1-) + T(-,2,1-) (Qi and Yin deficiency)	94.35%	50.62%	55.56%	19.54% (Qi)/ 110.93% (Yin)
T(-1,1,1-) + T(-,9,1-) (Qi and blood deficiency)	51.41%	34.02%	75.00% (Qi)/ 23.05% (blood)	
T(8,8,6-) (Chong Ren disharmony)*	81.57%	57.26%	52.78%	29.14%

*The Chong Ren disharmony is closely associated with Liver and Kidneys function disorder and especially Liver and Kidney Qi and Yin disharmony in Chinese Medicine theory and practice.

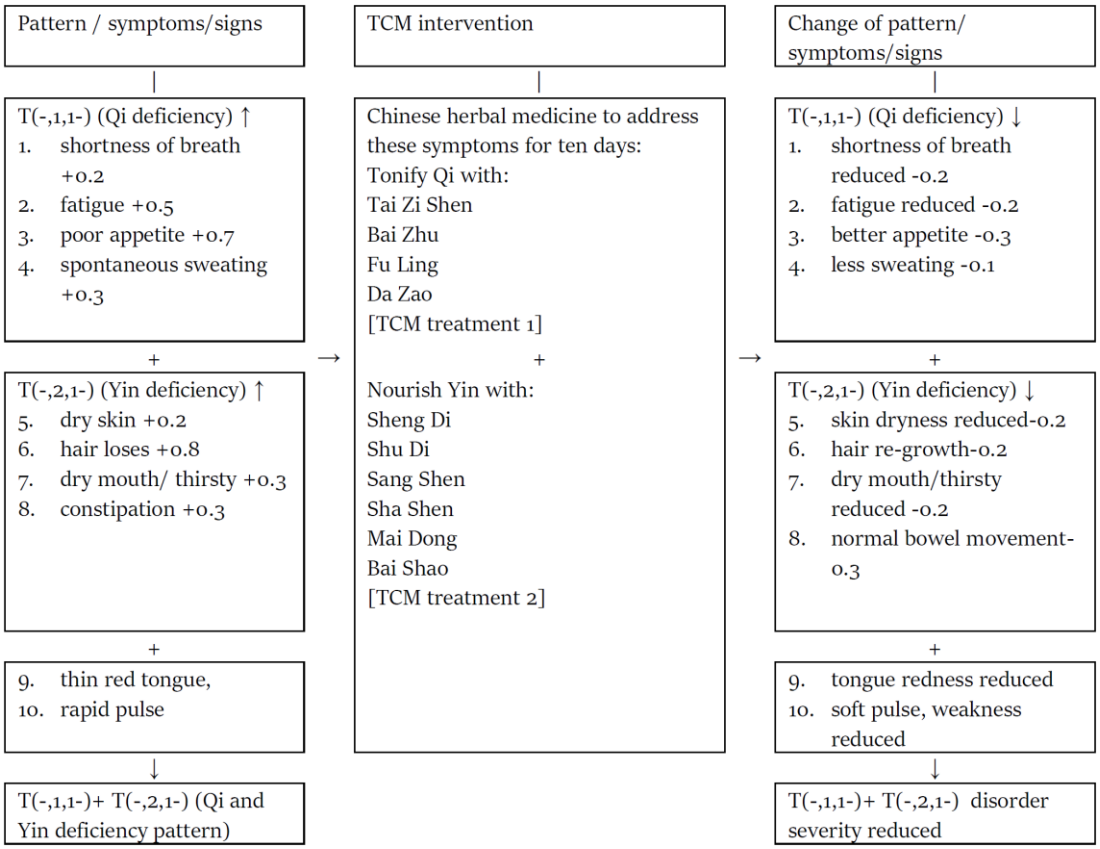

Figure 4-1 Symptoms and signs change at pre and post herbal treatment

Based on Figure 4-1 and scores provided by practitioners, an FCM was constructed. The FCM shows the causal effects of TCM on breast cancer treatment, as given in Figure 4-2. The weights in the figure are based on the senior TCM practitioners' experience in treating cancer patients. In this pilot study, the weights assignments of causal influence are exercised as a cognitive hypothesis. The actual weights assignments are determined in the actual medical practice by practitioners, but have never been formally modelled and recorded, for communication, verification and analysis. [65,71]

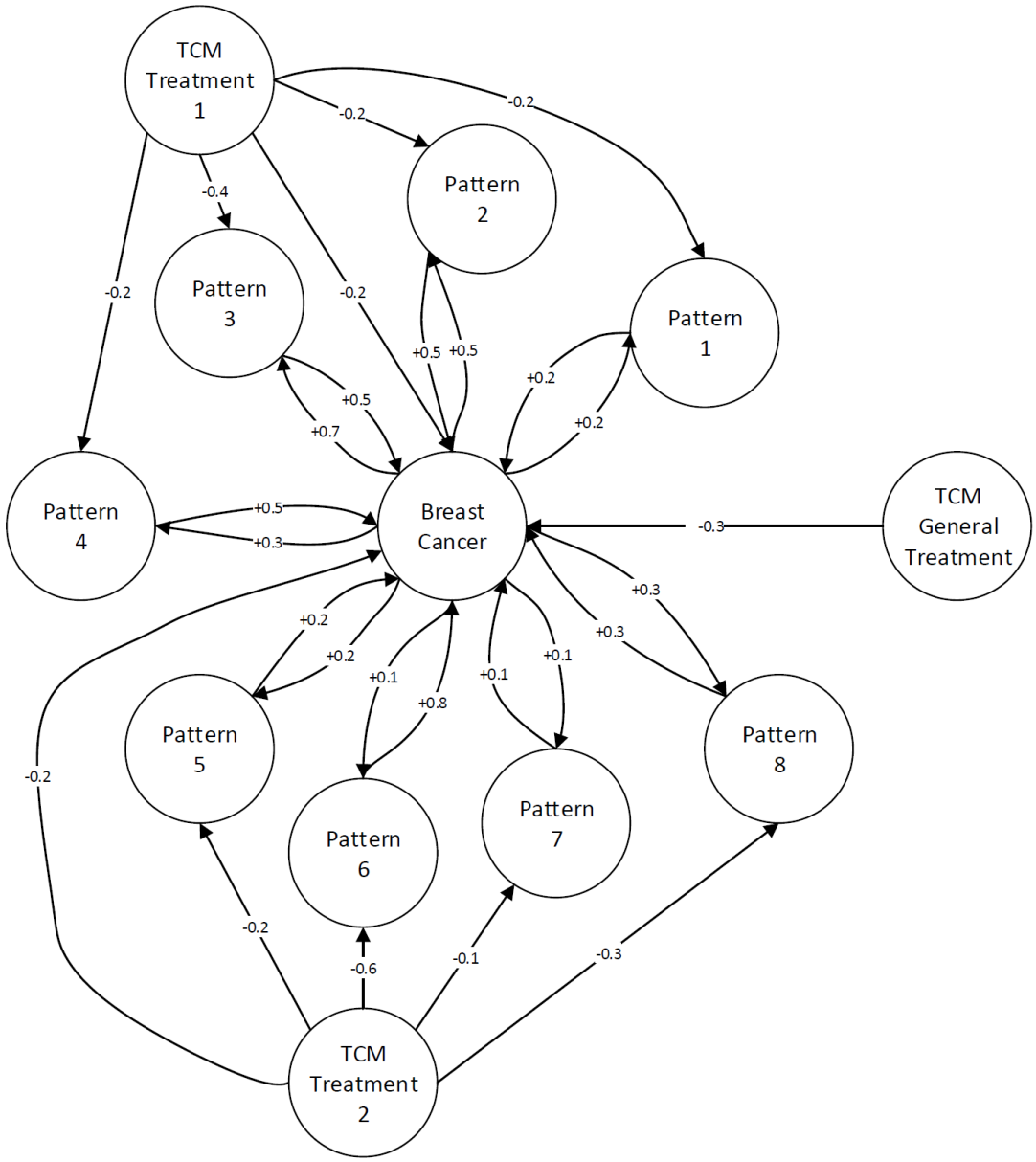

Figure 4-2 FCM map for TCM treatment on breast cancer [65]

Figure 4-1 shows that how individual symptoms and signs led (causal relationship in decision making process) to the identification of the disorder type T(-,1,1-) + T(-,2,1-); the TCM treatment 1, which can help with the disorder type T(-,1,1-), and TCM treatment 2, which can help with the disorder type T(-,2,1-) have been applied. The effects of the treatment were the improvement to the symptoms (the severity of the disorder has been significantly reduced). Figure 4-2 presents the causal knowledge of these factors and their interactions. To support the cognitive modelling, common disorder types and the corresponding TCM treatment have been developed in this research, referring TCM theory and practice [65]:

1) Disorder type T(-,1,1-) (Qi Deficiency Pattern in TCM)

- Symptoms of disorder type T(-,1,1-) include: Fatigue, shortness of breath, lack desire to talk, spontaneous sweating, listlessness, mental depression, prolapse of organs (stomach, uterus, intestines, anus, vagina or bladder), empty pulse, a swollen tongue with teeth marks on the side.
- Treatment Principle in TCM: To tonify and replenish Qi and upright Qi level.
- Common Chinese herbs used for treatment of T(-,1,1-) disorder are (denoted by Treatment 1 in Figure 4-2):
    - Single herbs: e.g. Ren Shen (Panax ginseng C.A. Mey), American Ren Shen (Panax quinquefolium L), Tai Zi Shen (Radix Pesudostellariae), Dang Shen (Radix Codonopsis), Huang Qi (Radix Astragali), Bai Zhu (Atractylodis Rhizome), Shan Yao (Rhizoma Dioscoreae), Bai Bian Dou (Semen Dolichorus Lablab), Gan Cao (Glycyrrhiza Uralensis).
    - Chinese herbs in classic formulae: e.g. Si Jun Zi Tang, Bu Zhong Yi Qi Tang, Shen Ling Bai Zhu San, Sheng Mai San.

2) Disorder Type T(-,2,1-) (Yin Deficiency Pattern in TCM)

- Symptoms of disorder type T(-,2,1-) include: Afternoon fever, malar flush, heat sensation in the palms and soles, night sweating during sleep, dryness of the throat and mouth, yellow urine, dry stool, red tongue with little coating, thready and rapid pulse.
- Treatment Principle in TCM: To tonify Yin and eliminate deficient heat.
- Common Chinese herbs used for T(-,2,1-) disorder are (denoted by Treatment 2 in Figure 4-2):
    - Single herbs: e.g. Bei Sha Shen (Radix Glehniae), Bai He (Bulbus Lilii), Nan Sha Shen (Radix Adenophorae), Mai Men Dong (Tuber Ophiopogonis Japonici), Tian Men Dong (Radix Asparagi), Shi Hu (Herba Dendrobii), Yu Zhu (Rhizoma Polygonati Odorati), Huang Jing (Rhizoma Polygonati), Go Qi Zi (Fructus Lycii), Mo Han Lian (Herba Ecliptae), Nv Zhen Zi (Fructus Ligustri Lucidi), Sang Shen (Fructus Mori), HeiZhi Ma (Semen Sesame Nigrum), Sheng Di

Huang (Radix Rehmanniae), Xuan Shen (Radix Scrophulariae), Mu Dan Pi (Cortex Moutan).

- Chinese herbs in classic formulae: e.g. Liu Wei Di Huang Wan, Zuo Gui Wan, Da Bu Yin Wan, Yi Guan Jian.

3) Disorder Type T(-,9,1-) (Blood Deficiency Pattern in TCM)

- Symptoms of disorder type T(-,9,1-) include: Fatigue, pale complexion, shortness of breath, dizziness, palpitations, insomnia, dreams, whiteness, fatigue, fatigue, cold limbs, red tongue, weak pulse, pale tongue colour, brittle nails, headache.
- Treatment Principle: To replenish Qi and nourish blood.
- Common Chinese herbs which can help with T(-,9,1-) are:
  - Single herbs: e.g. Dang Gui (Radix Angelicae Sinensis), Shu Di Huang (Processed Radix Rehmanniae), Bai Shao (Radix Paeoniae Alba), He Shou Wu (Polygonum multiflorum), E Jiao (Gelatinum CoriiAsini), Long Yuan Rou (Arillus Euphoriae Longanae), Da Zhao (Fructus Jujube).
  - Chinese herbs in formula: e.g. Si Wu Tang, Dang Gui Bu Xue Tang, Gui Pi Tang.

4) Disorder Type T(8,8,6-) (Chong Ren Disharmony Pattern)

- Symptoms of disorder type T(8,8,6-) has combination of disorder type T(-,2,1-) +T(-,3,1-) +T(-,1,2-). Its symptoms often have: dizziness, tinnitus, menstrual cycle disorder, irregularly alert cold and hot feeling, irritability, hypertension, breast hyperplasia, urticaria, premenstrual tension, tenderness in lateral side rib cage, headache, dizziness, dry mouth and throat, irregular menstruation, breast pain during menstruation, breast hyperplasia, string pulse, thin yellow tongue coating.
- Treatment Principle: To rebalance Yin and Yang and smooth Qi stagnation.
- Common Chinese herbs used for T(8,8,6-) are:
  - Single herbs: e.g. Xian Mao (Rhizoma Curculiginis), Yin Yang Huo (Herba Epimedii), Ba Ji Tian (Radix Morindae Officinalis), Dang

Gui (Radix Angelicae Sinensis), Huang Bai (Cortex Phellodendri), Zhi Mu (Rhizoma Anemarrhenae), Nu Zhen Zi (Fructus Ligustri Lucidi), Mo Han Lian (Herba Ecliptae), Bai Shao (Radix Paeoniae Alba), Bai Zhu (Atractylodis Rhizome), Fu Ling (Sclerotium Poriae Cocos), Chai Hu (Radix Bupleuri), Gan Cao (Glycyrrhiza Uralensis).

- Chinese herbs in classic formulae: e.g. Er Xian Tang, Er Zhi Wan, Jia Wei Xiao Yao San, Si Ni San.

5) Disorder Type T(3,1,2-) (Liver Qi Stagnation Pattern)

- Symptoms of disorder type T(3,1,2-) include: Pain lateral side rib cage, chest tightness, gastrectasia, burping or belching, anorexia, constipation, irregular menstruation.
- Treatment Principle: To disperse liver Qi stasis and rectify Qi stagnation.
- Common Chinese herbs used for disorder type T(3,1,2-):
  - Single herbs: e.g. Chai Hu (Radix Bupleuri), Xiang Fu (Rhizoma Cyperi), Qing Pi (Pericarpium Citri Reticulate Viride), Yuan Hu Suo (Rhizoma Corydalis), Chuan Lian Zi (Fructus Toosendan), Yu Jin (Radix Curcumae), Wu Yao (Radix Linderae), FoShou (Fructus Citri Sarcodactylis), Da Fu Pi (Pericarpium Arecae), Hou Po (Cortex MagnoliaeOfficinalis), Zhi Shi (Fructus AurantiiImmaturus), Mu Xiang (Radix Aucklandiae), Shan Zha (Fructus Crataegi).
  - Chinese Herbs in formula: e.g. Chai Hu Shu Gan Tang, Ban Xia Ho Po Tang, Zhi Shi Xiao Pi Wan.

6) Disorder Type T(4, 2, 1-) (Kidney Yin Deficiency Pattern)

- Symptoms of disorder type T(4,2,1-) include: Dizziness, tinnitus, lower back sore/stiffness, Knees weakness, insomnia, lots of dreams, hot flashes, night sweats at sleep, hot feeling in palms and , pharyngeal sore, dry mouth, hair loss, body weight loss, scanty urine or dry stool, red tongue, rapid and thin pulse, male nocturnal emission/premature ejaculation, female amenorrhea, uterine excessive bleeding menstruation.
- Treatment Principle: To tonify Yin and nourish Kidney.

– Common herbs used for disorder type T(4,2,1-) are:

  - Single herbs: e.g. Huang Jing (Rhizoma Polygonati), Bai He, (Bulbus Lilii), Wu Wei Zi (Fructus Schisandrae), Nu Zhen Zi (Fructus Ligustri Lucidi), Sang Shen (Fructus Mori), Mo Han Lian (Herba Ecliptae).
  - Herbs in formula: e.g. Liu Wei Di Huang Wan, Zhou Gui Wan.

7) Disorder type T(-, 9, 2-) as a consequence of disorder type T(-, 1, 2-) (Blood Stagnation due to Qi Stagnation Pattern)

– Symptoms of disorder type T(-,9,2-) caused by T(-, 1, 2-) include: Chest tight and pain in lateral rib cage, Irritability, depression, stress, slightly purple colour nails or in finger tips, sluggish bowel movement, dysmenorrhea, amenorrhea, dark blood with clots in menstruation, bloody purple dark lips, dark purple tongue, dark purple tongue or ecchymosis in tongue, thin and tight or wiry pulse.

– Treatment Principle: To rectify Qi stagnation and promote blood circulation.

– Common Chinese herbs used for disorder type T(-,9,2-) caused by T(-, 1, 2-) are:

  - Single herbs: e.g. Chuan Xiong (Rhizoma Chuanxiong), Yuan Hu Suo (Rhizoma Corydalis), Yu Jin (Radix Curcumae), Jiang Huang (Rhizoma Curcumae Longae), Ru Xiang (Gummi Olibani), Mo Yao (Resina Commiphorae), Qing Pi (PericarpiumCitri Reticulate Viride), Zhi Shi (Fructus Aurantii Immaturus), Mu Xiang (Radix Aucklandiae), Chuan Lian Zi ((Fructus Toosendan), Xiang Fu (Rhizoma Cyperi), Wu Yao (Radix Linderae), Da Fu Pi (Pericarpium Arecae).
  - Herbs in formula: e.g. Xue Fu Zhu Yu Tang, Fu Yuan Huo Xue Tang, Shao Fu Zhu Yu Tang, Tong Qiao Huo Xue Tang, Ge Xia Zhu Yu Tang.

8) Disorder Type T(-, 8, 2-) (Phlegm Stagnation Pattern)

– Symptoms of disorder type T(-,8,2-) are: chest tightness/heaviness, gastrectasia, anorexia, nausea, vomiting, dizziness, heavy body feeling,

confuse heavy feeling head, thick greasy tongue coating, slippery or wiry pulse.

- Treatment Principle: To expel phlegm and rectify stagnation.
- Common herbs used for improving disorder type T(-, 8, 2-) are:
    - Single herbs: e.g. Ban Xia (Pinellia Rhizome), Tian Nan Xing (Pulpit Rhizome), Bai Jie Zi (Semen Sinapis), Xuan Fu Hua (FlosInulae), Qian Hu (Radix Peucedani), Jie Geng (Radix Platycodi), Kun Bu (Thallus Eckloniae), Zhe Bei Mu (Bulbus Fritillariae Thunbergii), Gua Lou Shi (Fructus Trichosanthis), Hai Zao (Herba Sargassii), Zhi Shi (Fructus Aurantii Immaturus), Hou Po (Cortex Magnoliae Officinalis), Shi Cang Pu (Rhizoma Acori Tatarinowii).
    - Herbs in classic formulae: e.g. Er Chen Tang, Fu Ling Wan, Wen Dan Tang, Qing Qi Hua Tan Wan, Xiao Xian Xiong Tang.

In this case analysis, FCM is applied to model the causal relationship among factors in cancer treatment, as a computing model to represent the cognition of practitioners in their decision-making process [65].

It has been shown that the effects of Chinese herbal medicine in supporting breast cancer disorder management are positive. The FCM drawn is a visualised representation of the relevant knowledge. This pilot study shows that FCM is a simple yet effective way to model the cognition of TCM practitioners in their cancer treatment. Although FCM has been effective in modelling the structural causal relationship, there is a need for weights learning. Currently the severity of each disorder type is roughly estimated or generally noted. The model presented in this research enables the data collection of patients' symptoms and disorder severity, which enable data estimation of models to learn from the history data and automatically assign the severity in the future [65].

4.3 FCM FOR DIFFERENT THERAPIES ON CANCER TREATMENTS

Following the methodology shown in Sections 3.2 and 4.2, a variety of cases were further analysed to assess the effects of different therapies on the treatment of various cancers. These case analyses are expected to achieve the following three goals:

- To reveal the relationship between interactions of the multiple factors and the effectiveness of various types of therapy in cancer treatments so as to provide valuable information for Australian communities.
- To provide a form of visualized knowledge that has features that are suitable for domain experts to use directly.
- To provide a knowledge model that is easy to use for communication among data analysts, patients and oncologists for treatment indication and even for prediction of prognosis.

The data collected from Ren Kang Hospital in Guang Zhou (where ethics approved data collection venue) were from a wide range of cancer types. The results of these analyses and assessments are visualised by FCM maps. Note that these maps are associated with different sets of therapies.

4.3.1 Colonic cancer treatment with SPDT

In this study, a colonic cancer case is particularly selected and analysed, where the patient received SPDT in conjunction with a combination of chemotherapy. The detailed clinical records are as below:

Patient: Female, 32 years old, diagnosis: Colonic Adenocarcinoma

January 2007

The patient had abdominal pain, constipation and even hematochezia under no predisposing causes. As her colonoscopy indicated space-occupying tumour lesions, she undertook a total colostomy (the polyposis and the primary tumour in descending colon resected). The histopathology indicated colonic adenocarcinoma. No mutation was found in the KRAS. Her chest CT scan indicated there are three lesions in the left inferior lung, of which the pathology is unclear.

April-December 2007 (3 months later)

- undertook 8 cycles of chemotherapy (chemo regimen: Xeloda + Oxaliplatin + Bevacizumab).

Side effects: nausea, vomiting, abdominal pain, diarrhea, and numbness or tingling of the fingers.

- The rechecked CT scan after the chemotherapy showed no big changes in the lesions of left inferior lung.

October 2008 (10 months later)

- rechecked CT scan showed slight increase was found in the lesions of the left inferior lung, a resection was therefore done. The pathology indicated again colonic adenocarcinoma.

November 2008 (11 months after last chemotherapy)

- received 4 cycles of chemotherapy (chemo regimen: Irinotecan+ 5FU+ Folic acid).
- Side effects: nausea and had vomiting, diarrhoea and constipation.

2009- May 2010 (18 months later)

- pregnant and got one lovely girl.
- rechecked CT in May 2010 (after the girl's birth) showed new lesions found in the left inferior lung.
- received one more resection on the lung and again the biopsy indicated adenocarcinoma.

April 2012 (23 months later)

- rechecked CT scan found recurrent lesions in the left inferior lung again and even one new space-occupying lesion in the right adrenal gland.

- undertook one more surgery resection the lesions on left inferior lung and the right adrenal gland (4/12).
- the biopsy indicated adenocarcinoma.
- After the surgery, she began treatment with naturopathy.
- No side effects from naturopathy presented.

August 2012 (4 months later)

- Both lungs got recurrent lesions but chose no other treatment except natural therapy.
- No side effects presented from naturopathy reported.

February 2014 (18 months later)

- A mass found in the right fronto-parietal skull.

May 2014 (3 months later)

- Jaundice occurred.
- Her CT scan on 14th indicated bilateral pulmonary lesions include right apex 20mm and left lower lobe 40mm.
- Obstruction lesion associated with the common bile duct.
- Her MRI scan on 15th indicated metastatic obstruction of extrahepatic bile duct, 3 pulmonary lesions in right middle and lower lobes.
- Therefore, on 16th, she undertook a metal stent implantation under the ERCP (Endoscopic retrograde cholangio-pancreatography).
- Her rechecked jaundice was gone right after the operation.

June 2014 (1 month later)

- a head CT scan indicated a permeated destruction on right fronto-parietal bony metastases with associated intra- and extradural masses

9thJuly 2014

For further treatment, she came to the research study hospital.

MAIN EXAMINATIONS:

10th July 2014 Chest CT scan (assessment **before treatment**)

Diagnosis Suggestion:

1. Multiple metastases in both lungs with changes after treatment for the left inferior lung are found.
2. Multiple low-density shadows found in the liver, considered to be metastases.
3. Small amount of effusion is found in the pericardial cavity.
4. Bilateral pleura thickened.

Treatment history at the research study hospital

11th – 21stJuly 2014:

- **1st cycle of SPDT + chemotherapy** (chemo regimen: calcium folinate 200mg/m^2, 290mg, D2, 9, + 5-FU 3400mg/m^2 , 2500mg, D2,9 + Irinotecan 100mg/m^2 , 145mg, D3,10) from July11, 2014.
- Side effects from chemotherapy: slight diarrhoea, but no nausea or vomiting, and no bone marrow suppression.
- Her tumour markers indicated: CA125 57.24U/ml; CA15-3 62.81U/ml; CA19-9 533.0U/ml, CEA 148.3ng/ml.

1st – 15thAugust 2014 (10 days interval after last chemotherapy)**:**

- **the 2nd cycle of SPDT+ chemotherapy** (chemo regimen: calcium folinate 200mg/m^2, 290mg, D2, 9, + 5-FU 3400mg/m^2, 2500mg, D2,9 + Irinotecan 100mg/m^2, 145mg, D3,10)
- followed by targeted treatment (regimen: endostatin, 15mg, D1-14) from August 1, 2014. During the treatment.
- No side effects indicated.
- Her tumour markers indicated: CA125 47.06U/ml; CA15-3 65.70U/ml; CA19-9 146.9U/ml; CEA 30.07 ng/ml.

20 August 2014 Chest CT scan (assessment after the second cycle of treatment)

Diagnosis Suggestion:

- Multiple metastases found in both lungs after surgery on left lung.
- High possibility for multiple metastases in the liver.
- Fibrosis foci and calcification seen in bilateral lungs. Sacciform bright shadows found in the lower lobe of left lung.
- Pericardial effusion is suspected.

22ndAugust– 5th September2014 (6 days interval after last chemotherapy)**:**

- **the 3rd cycle and 4th of SPDT+ chemotherapy + targeted therapy** (chemo regimen: calcium folinate 200mg/m^2, 290mg, D2, 9, + 5-FU 3400mg/m^2, 2500mg, D2,9 + Irinotecan 100mg/m^2 , 145mg, D3,10) plus targeted treatment(regimen: endostatin, 15mg, D1-14).
- She can tolerate well during the treatment.
- Her tumour markers indicated: CA15-3 59.47U/ml, CA19-9 71.59U/ml, CEA

15.70 ng/ml.

3rd Oct 2014 Chest CT scan(assessment after the fourth cycle of treatment)

Diagnosis Suggestion:

- Postoperative change is indicated in the left lung, considered tobe multiple metastatic tumours in both lungs.
- Fibrosis and calcification are found in bilateral lungs andemphysema found.
- Sacciform bright shadows are detected in the lower lobe of left Lung.
- Pericardial effusion suspected.

3rd Oct 2014 Abdomen CT scan (liver, gall bladder, pancreas and spleen)

Assessment after the fourth cycle of treatment

Diagnosis Suggestion:

1. Multiple metastatic tumours are suggested in the liver.
2. Postoperative changes found after bile duct stent implantation.
3. Higher density shadow found in the stent cavity.
4. Pneumatosis detected in the intrahepatic bile duct.
5. Partial wall of gall bladder seems thicker.
6. Local changes found in the lumbar vertebrate, and metastases cannot be excluded.
7. The spleen enlarged.

7th October– 21stOctober 2014 (30 days interval after last chemotherapy):

- the 5th cycle of SPDT+ Interventional Therapy (TACI + TACE) + venous

chemotherapy + targeted therapy (TACI regimen: Irinotecan 145mg, D3 + 5-FU 2500mg, D3 for hepatic arteries and bronchial arteries, TACE regimen: iodinated oil 10ml + mitomycin 10mg for the right hepatic arteries) plus venous chemotherapy (chemo regimen: Irinotecan 145mg, D10 +calcium folinate 200mg/m^2, 290mg, D 9, + 5-FU 3400mg/m^2, 2500mg, D10) plus targeted treatment (regimen: endostatin, 15mg, D1-14).

- Side effects from chemotherapy: grade three bone marrow suppression, hair loss, chill, nausea, vomiting, fatigue, anaemia, skin dry and pain.
- Her tumour markers indicated: CA15-3 51.14U/ml, CA19-9 31.44U/ml, CEA 9.80 ng/ml.
- Her tumour markers dropped further.

29thOctober – 12 November 2014 (7 days interval after last chemotherapy, even the patient had grade three bone marrow suppression that needs at least 21 – 28 days to recover[23]):

- **the 6th cycle of SPDT+ Interventional Therapy (TACE) + targeted therapy** (TACI regimen: Irinotecan 145mg, D10 + 5-FU 2500mg,D10 for hepatic arteries and bronchial arteries, TACE regimen: iodinated oil 10ml + mitomycin 10mg for the right hepatic arteries) plus targeted treatment(regimen: endostatin, 15mg, D1-14).
- The patient had dull pain in the liver area during the treatment; correspondingly, Silymarin (140mg) was administered for treatment of liver disease,
- Naltrexone (4mg) was given as anti-inflammatory for liver pain.
- Selenious Yeast Tablets (50mcg) was given as food supplement for improving thyroid function.

Clinical Report on 25th November 2014 prior to discharge from the hospital

- Her tumour maker indicated CA15-3 30.43U/ml, CEA 20.77 ng/ml.
- The patient's blood test indicated WBC 2.1 109/L, NEUT# 1.2 109 /L, RBC 3.07 1012/L, HGB 86 g/L, PLT 102 109/L. It was believed as side effect of chemotherapy. Recombinant Human Granulocyte Colony Stimulating Factor was administered.
- Compared to before, CA15-3 has dropped, but CEA goes up slightly, which is difficult to conclude the assessment.
- The patient started having high fever repeatedly from 17th November 2014, with the highest temperature reaching 40.5 ℃ suspected as infection due to low level of WBC.
- As her rechecked blood routine on 19th November 2014 indicated WBC 1.5 109/L, NEUT# 0.6 109 /L, RBC 2.99 1012/L, HGB 82 g/L, PLT 33 109/L, she was offered Recombinant Human Granulocyte Colony Stimulating Factor for treatment and also antibiotics to prevent infection in outpatient clinic.
- Another follow-up blood checked on 20th November still indicated WBC 2.0 109/L, NEUT# 0.6 109 /L, RBC 2.80 1012/L, HGB 77 g/L, PLT 24 109/L, she was admitted into the hospital again for symptomatic treatment.
- After several days' symptomatic treatment (Recombinant Human Granulocyte Colony Stimulating Factor, antibiotic treatment and Chinese herbal drink). Then, the patient's temperature and blood function have already become normal and she was permitted to discharge and go home.

The patient discharged from the hospital on 25th November 2014 and no follow up records available.

Treatment summary prior to attend the research study hospital for treatment

- **January 2007:** Colonic cancer diagnosed.

  Total colostomy.

  (3 months later)

- **April-December 2007:** 8 cycles of chemotherapy

  (10 months later)

- **October 2008:** tumour resection on lung lesions.

  (no other therapy since last chemotherapy)

  (11 months after last chemotherapy)

- **November 2008**: 4 cycles of chemotherapy.

  (18 months later)

- **2009- May 2010**: Pregnancy giving birth to a child.

  (no treatment for cancer for 17 months of period)

(23 months later)

- **April 2012:** Surgery on lung lesions.

  Commenced natural therapy.

(4 months later)

- **August 2012:** Natural therapy

  (18 months later)

- **February 2014:** Natural therapy

  (3 months later)

- **May 2014:** Natural therapy

  (1 month later)

- **June 2014:** Natural therapy

Combination of SPDT and chemotherapy at the research study hospital

- 11th July 2014 – 21st July 2014:
- 22nd August – 5th September 2014
- 7th October – **21st October 2014**
- **29th October** – 12 November 2014

During the period of 91 months from diagnosed cancer in January 2007 till June 2014, the types of therapy and the interval can be summarized as below:

- Four sessions of surgery, separated in 2007, 2008, 2009 and 2012.
- Two cycles of chemotherapy, separated in 2007 (8 courses) and 2008 (4 courses)
- Other than the 4 sessions of surgery and/or natural therapy, there was not any conventional Western systemic therapies for a long period of 68 months interval since the last chemotherapy in November 2008.

Assessment of this case

- It presented that the long period of interval without effective treatments could be a causal factor to her cancer progression with more extensive metastasis distantly.
- The two cycles of chemotherapy in January 2007 and November 2008 plus three sessions of tumour resection in lungs seemed to have some degree of effectiveness.
    - The patient used natural therapy for more than 2 years, however her cancer gradually progressed. It is hard to measure the effect of the natural

therapy without scientific evidence, even though it did not record/present side effects as well.

Side effects from chemotherapy

- Side effects: nausea, vomiting, abdominal pain, diarrhoea, and numbness or tingling of the fingers.

Other side effects from the treatment include: slight diarrhoea, nausea or vomiting, bone marrow suppression and dull pain in the liver area during the treatment.

Analysis of this case

- This case presented that the interval between the treatments can become an influence causal factor affecting the outcomes of the treatment. In addition, the surgery often cannot thoroughly get rid of the cancerous cells which may recur anytime as a mine.
- The alternative therapy such as Chinese medicine, natural therapy and SPDT used in conjunction with Western conventional therapies maybe beneficial.
- The blood test of cancer markers indicated significant drop during the four months combination treatments with SPDT and conventional therapies which is positive, however there are different interruption of cancer marker change [70] which needs to be studied further.

The patient's condition report on 25th November 2014:

The side effects from the chemotherapy as the diagnosis reports after treatments:

- Intermittent complaint of dull pain in the liver area.
- The physical examinations indicated that the patient is conscious.

- A lump in the right skull bone.
- Breath sounds are clear in bilateral lungs without rale heard inside.
- The abdomen is normal without obvious lumps.
- Her rechecked blood routine indicated that WBC 2.1 109/L, NEUT# 1.2 109 /L, RBC 3.07 1012/L, HGB 86 g/L,PLT 102 109/L.
- Her blood biochemistry indicated that TP 64.4 g/L, ALB 36.2 g/L, BUN 2.41 mmol/L, UA 113.9 umol/L, Na+ 136.9 mmol/L.
- Her tumour maker indicated that CA15-3 30.43U/ml, CEA 20.77 ng/ml.
- The patient's dropping WBC is caused by the chemotherapy and has already been dealt with Recombinant Human Granulocyte Colony Stimulating Factor.
- Compared to before, CA15-3 has dropped, but CEA goes up slightly, which is difficult to conclude the assessment.
- Five days after the last chemotherapy, the patient started having high fever repeatedly from 17th November with the highest temperature up to 40.5 ℃ suspected as infection due to low level of WBC.
- Follow up blood check on 19th November 2014 indicated WBC 1.5 109/L, NEUT# 0.6 1^{09} /L, RBC 2.9^{9} 10^{12}/L, HGB 82 $^{g/}$L,PLT 33 $^{10}9/^{L,}$
- The patientwas offered Recombinant Human Granulocyte Colony Stimulating Factor for treatment of critical low level of WBC, and antibiotics to prevent infection.
- Follow up blood test on 20th November, the results still indicated in critical status. WBC 2.0 109/L, NEUT# 0.6 ^{10}9 /L, RBC 2.^{80} 1^{01}2/L, HGB 77 ^{g}/L,
  PLT 24 $109^{/L}$,
- The patient was given further symptomatic treatment in the hospital.
- Several days' after the symptomatic treatment (Recombinant Human Granulocyte Colony Stimulating Factor, antibiotic treatment and Chinese herbal drink), then the patient's temperature and blood function improved and she is permitted to discharge from the research study hospital on 24th November 2014.
- According to the other reports comparing with the CT scan reports from admitted to the hospital in July 2014, August 2014 and September 2014, the results were not all paralleled.

The causal relationship and weighting of several factors are illustrated as the FCM map below by the researcher (based on the researcher's view of case record):

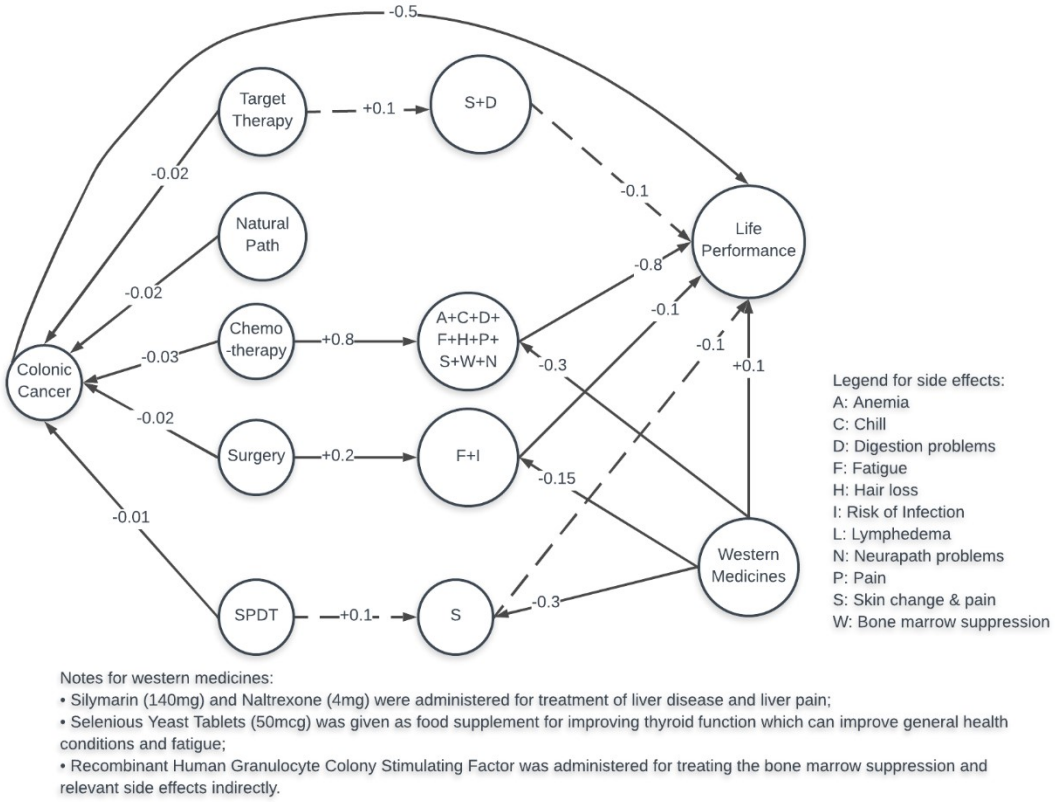

Figure 4-3 FCM map for colonic cancer treatment with SPDT combined with other therapies of treatment

The treatment of side effects from cancer treatments with Western medicine are summarised below:

- Silymarin (140mg) and Naltrexone (4mg) were administered for treatment of liver disease and liver pain.
- Selenious Yeast Tablets (50mcg) was given as food supplement for improving thyroid function which can improve general health conditions and fatigue.
- Recombinant Human Granulocyte Colony Stimulating Factor was administered for treating the bone marrow suppression and the relevant symptoms indirectly.

Note:

1. Surgery was done before the patient came to the research study hospital for SPDT and other treatments. There were no clinical records about the side effects and affecting impact on Life Performance related surgery provided to the hospital.
2. The weights on the FCM related to surgery were obtained from an experienced oncologist surgeon.

The FCM weights can be illustrated with a formula of T(R,E,E-P) as:

- T stands for therapy. In this case, T1 = targeted therapy, T2 = chemotherapy, T3 = surgery, T4 = SPDT.
- R stands for type of side effects from therapy.
- E stands for the severity of side effects occurred.
- E-P stands for the influence of Life Performance.

The weights presentation on this study can be presented as below:

T = T1(S/D,+0.6,-0.3) + T2(A/C/D/F/H/P/S/W/N,+0.8,-0.8) + T3(F/I,+0.2,-0.1) + T4(S,+0.3,-0.2)

The key consideration in the decision of the weight are based on the following causal relationship factors.

- For some causal relationships, such as side effects that affect life performance, the weight in the FCM is primarily determined by reviewing the patient's medical records. It is worth noting that the impact on Life Performance is a constant changing process.
- For other causal relationships, such as treatments that cause side effects, the weights are determined both objectively and subjectively by the researcher. On the one hand, objective observation of different treatments and different intervals can lead to various levels of side effects. In addition, specific weight values can be determined by consulting medical experts using their expertise and experience. For example, side effects caused by chemotherapy lead to grade III myelosuppression (a severe drop in white blood cell and platelet counts to dangerous levels), which can seriously affect her life performance. In this case, after the patient received a series of four constant chemotherapy

sessions within three months, this resulted in III Grade bone marrow suppression. Thus, it was estimated that the side effect from chemotherapy was given +0.8 and -0.8 of weight affecting life performance in the FCM modelling which are an average approximation from previous clinical experience and consultation with other experts.

- There are also some causal relationships related to weights, which are primarily subjectively determined. Generally, different drugs and different individuals' response to the drugs with side effects are varied. However, communication with medical experts shows that this relationship varies from patient to patient due to similar illnesses and treatments. In this case, extensive consultations and investigations have been conducted to give a fair assessment of these relationships. For example, the patient has side effects of pain in the liver during treatment combined with targeted therapy and SPDT plus different type of Transarterial chemoembolization (TACE) regimen for liver cancer metastasis. This liver pain side effect is an additional one to other anticipated side-effects from regular chemotherapy. There was no record showing side effect from targeted therapy.
- The patient used natural therapy for more than 2 years, however her cancer gradually progressed. It hard to measure the effect of the natural therapy even though it did not present side effects to her.
- The blood test reports showed that the cancer markers continuously declined without evidence of tumour reduction. As such, estimation was given based on previous clinical experience and consultation with other specialists, i.e., the figures of -0.01 to -0.03 separately as improvement from multi therapies.
- In this case study, the cancer had progressed. It was estimated that the worsen cancer status could impact the life performance with a weight of -0.5.

The considerations for determining weighting values represents the practitioner's/researcher's cognition on the causal relationship of the factors. Different researchers and practitioners may have different interpretations and thus might lead to distinct FCMs. It provide a mechanism for such causal relationship to be modelled to support their decision making, facilitate communication on the diagnosis and intervention, and make it possible for further analysis of the decisions and cases.

4.3.2 Oesophageal cancer treatment with SPDT

In this study, an oesophagus cancer case is examined, where the patient received combination of conventional therapies and SPDT. The detailed clinical records are as below:

Patient: Female, 55 Years Old

May 2013

- Started to feel discomfort in the upper abdomen under no obvious predisposition causes.
- No improvement after general symptomatic treatment.

(three months later)

August 2013

- undertook a gastroendoscopy, from which the biopsy indicated adenocarcinoma in the lower oesophagus.
- A further PET/CT scan indicated there was a lump found in the lower oesophagus, metastases were found.
- received 3 rounds of chemotherapy (regimen: ECF) before surgery.
- After the chemotherapy, a rechecked CT scan indicated the tumour was reduced.

(five months later)

January 2014

- undertook inferior oesophageal resection plus partial gastrectomy together with lymph nodes dissection.
- The postoperative pathology indicated inferior oesophagus moderately differentiated adenocarcinoma.
- The tumour measures about 30 X 25 x20mm, Lymph nodes 9/32 (+).
- After the surgery, she was offered another 3 cycles of chemotherapy (regimen: ECF).

May 2014

- Follow up CT scan found no obvious tumour.

August 2014

- Follow up blood tests, tumour marker CEA is 27.3ng/ml.

November 2014

- Follow up CT scan showed a lump measuring about 32 x 27 x 22mm in the left anterior side of the oesophageal hiatus -- tumour recurrence.

January 2015

- started 2 rounds of chemotherapy (regimen: FOLFOX6), finished the last chemotherapy on January 21, 2015.
- During the last chemotherapy, she had difficulty in breathing (about 10 minutes) but turned to normal after treatment.

31st January 2015 **came to the research study Hospital for further treatment**

February 2015

PET/CT scan reports:

- A hypermetabolic mass noted in the retroperitoneal region, considered as metastasis.
- Hypermetabolism in oesophagus-stomach stomas, considered as anastomotic inflammation.
- Thickening mucous membrane of the maxillary sinus.
- A small benign nodule is noted in the right lobe of the thyroid.
- Multiple obsolete lesions are noted in the superior and middle lobes of the right lung.
- Hepatic fatty infiltration.
- A small benign nodule is noted in the subcutis of the left back.

5th February 2015 – 14th February Treatment

- started the first cycle of SPDT plus chemotherapy (regimen: paclitaxol liposome, 120mg, d2, d9 + cisplatin 30mg, d2,d3,d8,d9 + 5-Fu 1.5g,CIV48h, d2-3,d8-9).
- no bone marrow suppression

26th February – 7th March 2015

- continued the second cycle of SPDT plus chemotherapy (regimen: paclitaxol liposome, 120mg, d2, d9 + cisplatin 30mg, d2,d3,d8,d9 + 5-Fu 1.5g,CIV48h, d2-3,d8-9)

Side effects:

- Had fatigue, diarrhea, anaemia, grade II of bone marrow suppression. White Bl Skin rash and pain from SPDT therapy.
- Blood Cell and Platelet declined (side effects from chemotherapy treatment).

Treatment for side effects:

- Epogen was given intravenously 3 times a week for bone marrow suppression.
- The digestive symptoms were treated by diet management.
- Phosphatidylcholine Capsules (tabs, tid) for inhibiting inflammatory response and Vitamin B6 (20mg, tid) were given at the same time with Xeloda to reduce side effects of skin rash with pain.

28thMarch 2015

- received radio seeds implantation (80 radio seeds) for the retroperitoneal tumour.
- Side effects: chills, feeling sick, diarrhoea, stomach-ache.

2nd April 2015 – 11th April 2015

- Continued the third cycle of SPDT plus chemotherapy (regimen: paclitaxol liposome, 120mg, d2, d9 + cisplatin 30mg, d2,d3,d8,d9 + 5-Fu 1.5g,CIV48h, d2-3,d8-9).

- Fatigue, diarrhoea, hair loss, anaemia and Grade II of bone marrow suppression side effects from chemotherapy and skin rash with pain from SPDT therapy.
- The rechecked PET/CT scan indicated the tumour metabolism in the retroperitoneum was reduced and the size was smaller, however, she still had multiple new metastases found in the liver.

25 April 2015

- He had another radio seeds implantation (30 radio seeds) for three liver tumour lesions

Side effects:

Chills, feeling sick, diarrhoea, stomach-ache, vomiting, palpitation, dizziness (similar to dumping syndrome).

Treatment for side effects:

- Epogen was given intravenously 3 times a week for bone marrow suppression.
- The digestive symptoms were treated by diet management.

Treatment Response:

The rechecked PET/CT scan indicated the tumour metabolism in the retroperitoneum was reduced and the size was smaller, however, she had multiple new metastases found in the liver.

30th June 2015

- Follow up PET/CT scan on June 30, 2015 in Australia and found multiple new growths of metastatic lesions in the liver.

2nd July 2015

- Started Xeloda (regimen: 1.5g,Bid,D1-14,Q3w) from July 2, 2015.
- Skin rash and pain on palms and soles, sore mouth side effects from secondary chemotherapy drug Xeloda.

- Phosphatidylcholine Capsules (tabs, tid) for inhibiting inflammatory response and Vitamin B6 (20mg, tid) to reduce the skin rash with pain from the Xeloda, SPDT and Hyperthermia therapy.

1st August 2015 returned to the research study hospital

2nd August 2015 Abdominal CT scan:

Impression:

- After the surgery of oesophagogastrostomy, and after radio seeds implantation for partial intrathoracic stomach, the lower segment of the right liver and the pancreas body, multiple round low densities are seen bilateral lobes of the liver. After contrast, the lesion gradually intensified unevenly. The structure of the portal vein and the pancreas is blurry, but the size is slightly enlarged. No obvious abnormal intensified lesion is detected.
- Quasi-circular mass is seen in the upper back of pancreatic body with shrinkage in range.
- The front fascia of the left kidney is thickened. Others are normal.
- Diagnostic opinion: After surgery for oesophageal tumour, partial intrathoracic stomach is seen. Multiple metastatic lesions are found in the liver. Radio seeds are detected in the metastatic lesions of the right back liver lobe and the upper back of pancreatic body of the retroperitoneum.

Main Treatment：

5th August 2015 – 19th August 2015(SPDT + Chemotherapy +Hyperthermia therapy)

- Continued the 4th round of SPDT (Sono-Photo Dynamic Therapy) plus chemotherapy (regimen: Irinotecon, 120mg, D3, D10 + Xeloda, 1.5g, Bid, D1-14), treatment combined with 4 applications of hyperthermia therapy.
- The tumour marker after this round dropped and her liver ultrasound indicated the metastatic lesion in the liver had shrunk slightly, thus her treatment was considered as a partial response.

- Received the 5th round of SPDT (Sono-Photo Dynamic Therapy) plus chemotherapy (regimen: Irinotecon, 120mg, D3, D10 + Xeloda, 1.5g, Bid, D1-14)
- Treatment combined with 4 applications of hyperthermia therapy.
- Had the first round of bone marrow suppression during the chemotherapy.
- Side effects from chemotherapy: Grade I of bone marrow suppression.
- Skin rash with pain from SPDT therapy.
- Skin burns and pain on the site from hyperthermia therapy.
- Skin rash with pain on palms and soles, sore mouth side effects from Xeloda chemotherapy.

(Six days interval after last round of SPDT + Chemotherapy + Hyperthermia therapy)

26th August 2015 – 8th September 2015

- She kept going with the 5th round of SPDT (Sono-Photo Dynamic Therapy) plus chemotherapy (regimen: Irinotecon, 120mg, D3, D10 + Xeloda, 1.5g, Bid, D1-14) together with 4 times of hyperthermia therapy.

Side effect:

- had the Grade I of bone marrow suppression during the chemotherapy.

The patient discharged from the hospital on 8th September 2015. No follow up records available

In summary, in the last six months treatment, the patient received:

- 6 rounds of Chemotherapy
- 5 rounds of SPDT therapy
- 2 sessions of Radio seeds implantation (80seeds and 30 seeds)
- 8 sessions of hyperthermia therapy

Major side effects include:

- 1st and 2nd degree of bone marrow suppression
- Hyperthermia therapy: Skin burns and pain on the site from.

- SPDT therapy: skin rash with pain.
- Chemotherapy: skin rash with pain on palms and soles; fatigue, diarrhoea, anaemia, hair loss and a second degree of bone marrow suppression side effects from chemotherapy
- Radio Seed cancer implantation treatment side effects: chills, feeling sick, diarrhoea, stomach-ache, fingers pins and needle sensation.

The FCM map resulted from the above analysis is given in Figure 4-4based on the researcher's review.

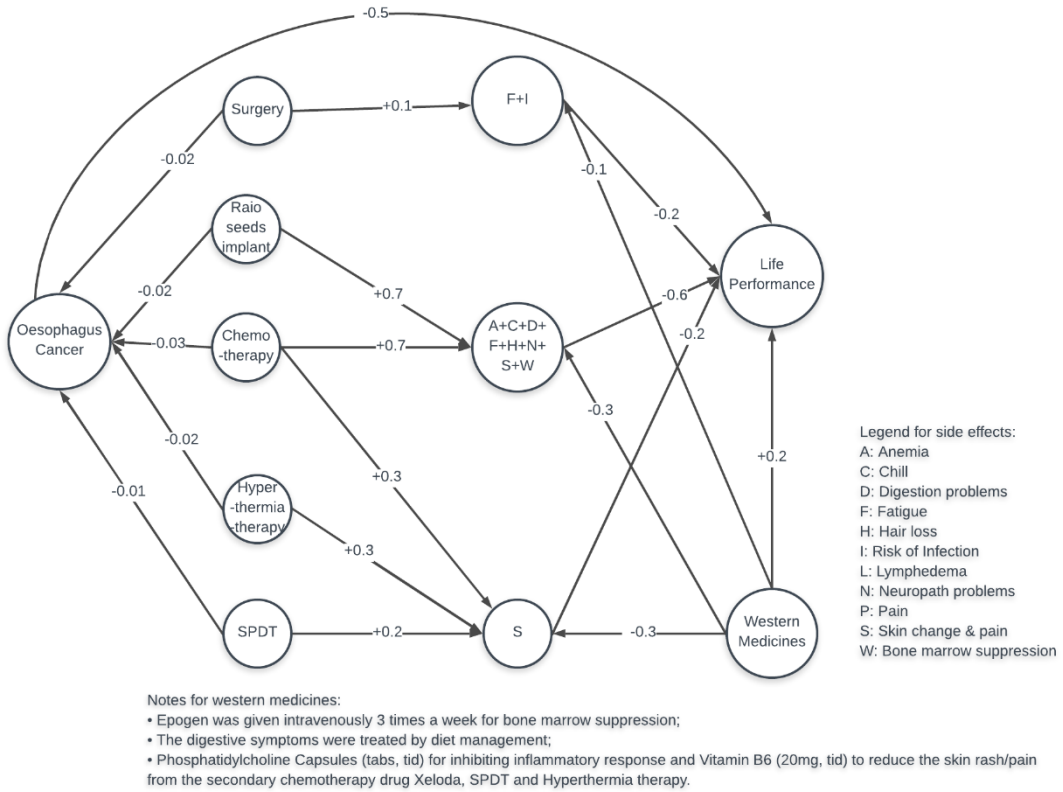

Figure 4-4 FCM map for oesophagus cancer treatment with combinations of surgery, chemotherapy, radio seeds implant, SPDT and hyperthermia therapy

The treatment of side effects from cancer treatments with Western medicine are summarised below:

- Epogen was given intravenously 3 times a week for bone marrow suppression.
- The digestive symptoms were treated by diet management.

- Phosphatidylcholine Capsules (tabs, tid) for inhibiting inflammatory response and Vitamin B6 (20mg, tid) were given at the same time with Xeloda to reduce side effects of skin rash with pain.

Note:

1. Surgery was done before the patient came to the research study hospital for SPDT and other treatments. There were no clinical records about the side effects and affecting impact on Life Performance related surgery provided to the hospital.
2. The weights related to surgery on the FCM was obtained from an experienced oncologist surgeon.

The FCM weights can be illustrated with a formula of T(R,E,E-P) as:

- T stands for therapy. In this case, T1 = surgery, T2 = radio seeds implant, T3 = chemotherapy, T4 = Hyperthermia therapy, T5 = SPDT.
- R stands for type of side effects from therapy.
- E stands for the severity of side effects occurred.
- E-P stands for the influence of Life Performance.

The weights presentation on this study can be presented as below:

T = T1(F/I,+0.1,-0.2) + T2(A/C/D/F/H/N/S/W,+0.7,-0.6) + T3(A/C/D/F/H/N/S/W,+0.7,-0.6) + T4(S,+0.3,-0.2) + T5(S,+0.2,-0.2)

The key consideration in the decision of the weight are based on the following causal relationship factors.

The weightings in the FCM map (Figure 4-6) were decided via the following steps:

- The FCM weighting between the treatment and the Life Performance assessed both an objective and subjective assessment as well. Based on literature review and researcher's clinical experience, it is understood that most common life quality impact factors are side effects from chemotherapy which plays a significant role affecting daily activities. The weights can be figured out according to the patient's medical records. In this case study, there was one occasion of treatment as a result of SPDT with a combination of chemotherapy that the rechecked PET/CT scan indicated the tumour metabolism in the retroperitoneum was reduced and the size was smaller, however, she still had multiple new metastases found in the liver. But there

was not a specific tumour size reduction figure in the report. Another occasion showed that the tumour marker after this round dropped and her liver ultrasound indicated the metastatic lesion in the liver had shrunk slightly, thus her treatment was considered as a partial response. It was estimated the effect weights as -0.01 to -0.03 separately based on the researcher's clinical experience and consultation with other specialists.

- Note that the influence on life performance is a continuously varying process, especially by different combination therapies and different treatment intervals that varied the degrees of side effects of bone marrow suppression, I Grade, and then to II Grade in a different session of chemotherapy and/or other therapies. So, this weighting is an average approximation. In addition, the concrete weighting value was determined by consulting medical experts, leveraging their expertise and experience. For example, radio seeds implantation on 28th March 2015 caused side effects including chills, feeling sick, diarrhoea and stomach-ache, but within a few days the SPDT and chemotherapy followed and caused multiple side effects which may impact the life quality further. As the treatment interval between radio seeds implantation and chemotherapy is very short and there were some similar side effects, the side effects are combined from radio seeds implantation into the group with chemotherapy with same weights of +0.7 side effects and impact to life performance with weight of -0.6 accordingly. The side effect of skin change with pain generally is not very severe such that it was estimated with a weight of +0.3 separately.
- Still other causal relationships are associated with the weightings that were decided predominantly in a subjective way. However, the communications with medical experts revealed that such relationships did exist in many patients with similar disease. In such a situation, extensive consultations and investigations were conducted to give a fair value for these relationships. The patient had so many different types of therapy at different intervals causing similar side effects which caused multi impacts on life performance in weighting. For instance, the patient had treatments between 5th August 2015 until 8th September 2015 (with 6 days interval in between). The treatments included two rounds of intravenous chemotherapies and oral chemo drugs

combined with SPDT and eight sessions of Hyperthermia therapy. Both chemotherapies in August and September caused Grade 1 Bone Marrow Suppression plus both SPDT and Hyperthermia therapy caused similar skin burns with pain while the oral drug chemotherapy Xeloda's side effects also caused mouth sores, skin rash, skin peeling off and burning pain. All the three different therapies of oral chemotherapy, Hyperthermia and SPDT caused the same type of side effect in skin change with pain. Estimation was done based on previous clinical experience, giving them the weights of +0.2 and +0.3 separately.

- The causal factors of "multi plus" side effects from intensive therapies to a Stage 4 cancer patient strongly impacted her life quality weighting. The final result showed that the multi metastatic tumours were worsened such that the impact weight on life performance was estimated as -0.5.

Similar to the earlier cases, the determination of weights involved some interpretation from the researcher's medical knowledge and clinical experience. A different practitioner may build up a different FCM map according to different interpretations. The model developed in this research provided a new approach for these cognitions to be communicated, compared and further analysed.

Case summary

The patients started feeling discomfort in the upper abdomen under no obvious predisposition causes. There was no improvement after general symptomatic treatment. It seemed a bit too late for the patient to have a thorough screen to check her discomfort in the upper abdomen. The late diagnosis delayed her treatment that caused a negative impact on her later treatment effectiveness. The patient had two courses of surgery plus chemotherapy in August 2013 and January 2014.

Her follow up blood tests in August 2014 showed the tumour marker increased up to CEA 27.3ng/ml. Further, November 2014 CT scan showed a lump measuring about 32 x 27 x 22mm in the left anterior side of the oesophageal hiatus indicated the recurrence of the tumour. However, the patient had no further treatment until January 2015.The interval period of treatment was too long, that might have allowed the cancer continued rapid progression.

When the patient attended the research study hospital for treatment, her cancer had already progressed to Stage 4.

The patient received a series of combination treatments of chemotherapy, radio-seed implantation, SPDT therapy and hyperthermia therapy within six months, of which side effects impacted her immunity capacity and life performance. This causal relationship interacted across the whole series of treatment administration.

This case indicates that the early diagnosis of cancer and persistent treatment before the metastasis occurs is vitally important. The assessment of this patient's treatment can be concluded as a partial response. If the patient had earlier diagnosis and treatment, her outcome of treatments would be much more effective. The early detection of cancer is considered as a causal relationship factor in the cancer fight.

4.3.3 Lung cancer treatment with SPDT

In this study, a representative case was selected to show the lung cancer treatment with SPDT combined with other therapies. The detailed records for the case are as follows:

Patient: Male, 52 Years Old

April 2012

- Started coughing under no obvious predisposing causes and he went to a local hospital for a check-up.
- PET/CT scan indicated right lung cancer with one suspicious nodule in left upper lung and one in left lower lung.
- He was diagnosed in the right lung with a moderately differentiated adenocarcinoma.
- He then received a minimally invasive resection of tumour on the upper lobe of right lung, yet no radiotherapy or chemotherapy.

(seven months later)

November 2012

- His rechecked CT indicated the previous small nodule in left upper lung enlarged slightly, measuring about 6-7mm, which was suggested to be monitored.

(two months later)

January 2013

- repeated CT and it indicated the previous small nodule in left upper lung kept enlarging, measuring about 10 mm.

February 2013

- He received a minimally invasive resection of tumour on the left upper lung.
- The gene test of EGFR indicated no mutation.
- No treatment undertaken.

May 2013

- rechecked CT indicated no abnormality.

(nine months after surgery)

November 2013

- rechecked CT indicated the previous suspicious small nodule in left lower lung enlarged slightly, measuring about 7mm, and a new nodule measuring about 7mm was found in right inferior lung.

19th December 2013

- he received a minimally invasive resection of tumour for both lower lungs, yet still no chemotherapy or radiotherapy.

(two months later)

9th February 2014

He came to the research study Hospital for treatment.

- The PET/CT scan indication:

1) After surgery for the lung cancer of right upper lobe and multiple pulmonary metastases, hypermetabolic node in the inferior lobe of left lung is considered as metastasis.
2) Pneumonia in the inferior lobe of left lung.
3) Thickening of mucous membrane of left maxillary sinus. Left and right coronary artery calcifications.

4) Degenerative changes in thoracic and lumbar vertebra.

5) No other abnormal hypermetabolic lesion is detected in other parts of the whole body

14th February 2014

- He undertook the radio seeds implantation for the left lower lung. 40 I-125 radio seeds were implanted into the left lower lung.
- Side effects: Slight chills, feeling sick (stomach upset), diarrhoea.

16th February – 21 March 2014

- He undertook 2 cycles of SPDT therapy.
- He had 2 cycles of chemotherapy (chemo regime: Pemetrexed 800mg + carboplatin 350mg).

Side Effects:

- Slight fatigue, anaemia, bone marrow suppression (white blood cell and blood platelet declined)from chemotherapy.
- Skin rash with pain from SPDT.
- He was discharged from hospital in March.

(two months later)

8th April 2014

- The patient returned to the research study hospital.
- He received three rounds of NK immunotherapy(the first infusion of NK),

15th April 2014

- He undertook the infusion of NK immunotherapy.

22nd April 2014

- He undertook the infusion of NK immunotherapy.
- Side effects: Fatigue, short of breath.
- He discharged from hospital in April

(four months later)

6th August 2014

- He returned to the Hospital to receive further three rounds of NK immunotherapy:
- He undertook the infusion of NK immunotherapy.

13th August

- Undertook the infusion of NK immunotherapy.

20th August

- Undertook the infusion of NK immunotherapy.
- Side effects: Slight fatigue, short of breath.

(two months later)

10th October 2014

- He had a CT scan in Australia:
  1) A new subpleural nodule medial left upper zone(max diameter 6.9mm, vol 0.129ml) found.
  2) A new left lung upper zone nodule detected, considered as tumour recurrence.

3 November 2014

- The patient returned to the Hospital again on 3rd to receive further three rounds of NK immunotherapy.
- Side effects: Slight fatigue, short of breath.
- No follow up records available

Based on the above analysis, the FCM map can be drawn based on the researcher's review as Figure 4-5.

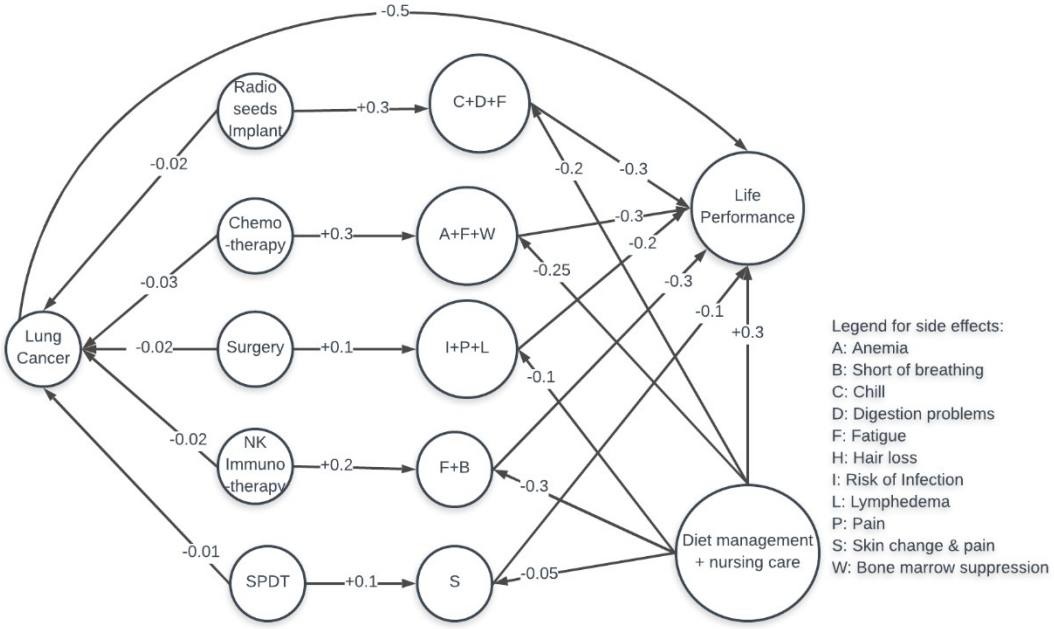

Figure 4-5 FCM map for lung cancer treatment with combinations of surgery, chemotherapy, radio seed implant, SPDT and immunotherapy

The levels of side effects from cancer treatments were not serious and not treated by specific medication other than nursing management in hospital and diet management by the patient. Thus, there was no medication prescription record provided in our data collections.

Note:

1. Surgery was done before the patient came to the research study hospital for SPDT and other treatments. There were no clinical records about the side effects and affecting impact on Life Performance related surgery provided to the hospital.
2. The weights on the FCM related to surgery was obtained from an experienced oncologist surgeon.

The FCM weights can be illustrated with a formula of T(R,E,E-P) as:

- T stands for therapy. In this case, T1 = radio seeds implant, T2 = chemotherapy, T3 = surgery, T4 = NK immunotherapy, T5 = SPDT.
- R stands for type of side effects from therapy.
- E stands for the severity of side effects occurred.
- E-P stands for the influence of Life Performance.

The weights presentation on this study can be presented as below:

T = T1(C/D/F,+0.5,-0.4) + T2(A/F/W,+0.6,-0.5) + T3(I/P/L,+0.1,-0.2) + T4(F/B,+0.2,-0.3) + T5(S,+0.1,-0.1)

The key consideration in the decision of the weight are based on the following causal relationship factors.

The weightings in the FCM map (Figure 4-7) were decided via the following steps:

- The FCM causal relationships, such as some side effects affecting Life Performance, the weighting can be decided by examining the patient's medical history primarily in objective and subjective ways. Based on previous clinical experience and literature review that nearly every conventional cancer therapy may cause side effects. It is well known that chemotherapy is the worst in impacting life performance. The influences on life performance are normally recorded in a patient's file. On the other hand, if the patient's medical files did not record the level of side effects, the concrete weighting value would be determined by consulting medical experts, leveraging their expertise and experience. Therefore, the weights of every individual therapy and influence on the life performance in this case study were estimated in a subjective way based on the researcher's experience and consultation with other experts.
- Note that the influence on life performance by treatment is a continuously varying process, especially by different therapies that varied the degrees of side effects. Generally, different drugs and different individuals' responses to the drugs with side effects are varied. For other causal relationships, such as treatments side effects, the weighting will be determined both objectively and subjectively. On the one hand, objective observation of different treatments and different intervals can lead to various side effects. Such as, the patient undertook the radio seeds implantation for the left lower lung. 40 I-125 radio seeds were implanted into the left lower lung on 14th February 2014. It gave him side effects with chills, feeling sick of stomach upset, diarrhoea. However, nearly immediately after, from 16th February 2014 – 21st March 2014, he received two cycles of SPDT in combination with chemotherapy which gave him side effects of fatigue, anaemia, bone marrow suppression from chemotherapy and skin rash with pain from SPDT. These constant treatments

without a considerably long enough interval between therapies can heavily impact life performance. The weights on radio seeds implantation and chemotherapy were estimated with +0.6 and +0.5 of side effects and life performance -0.4 and -0.5 respectively in a subjective way. The SPDT side effect of skin change with pain was given +0.1 and on life performance for -0.1 as a subjectively estimated weight.

- In this case study, very minimum figures of -0.01, -0.02 and -0.03 were given respectively as weights of effect from every individual therapy in subjective way from communication with medical experts' experience in many patients with similar treatments and diseases.

In addition to the analysis on the data provided in medical history, the above weight decision process also involves the researcher's personal interpretations that are from the researcher's clinical experience and expertise, and data collected from the hospital and consultation with clinical experts. If widely applied, this method will enable more data accumulated with the corresponding FCM modelling the practitioners' cognition, which will significantly change the landscape of the decision-making process in the treatment.

The treatment history is summarised as follows:

From diagnosed lung cancer in April 2012 till December 2013, other than three courses of surgery, the patient did not undertake any therapy. The patient was admitted into the research study hospital in February 2014. Since then, the patient had the following therapies:

- Three courses of minimally invasive resection of tumours.
- 2 cycles of SPDT therapy.
- 2 cycles of Chemotherapy.
- 1 session of Radio Seed implanted in lung.
- 9 sessions of NK immunotherapy.

The patient had experienced the following side effects:

- Chemotherapy: Fatigue, Anaemia, bone marrow suppression (White Blood Cell and Blood Platelet declined).

• SPDT: Skin rash with pain.

• Radio Seed implantation: Chills, Feeling sick, Diarrhoea.

• NK Immunotherapy: Fatigue, short of breath.

It should be particularly pointed out that:

• It took him too long, about one year and two months, for him to commence cancer treatment, other than three courses of minimally invasive resection of tumours surgery that may result the progress of cancer.

• His cancer had progressed to stage 4 when he attended the research study hospital for cancer therapies.

• The side effects from treatment impacted on his life performance and possible downgraded his immunity capacity as well.

• The NK immunotherapy seems to have played a key role in his treatment along with the combination of chemotherapy, radio-seed implantation and SPDT.

• The treatment history did not show any effectiveness response from surgery nor from the systemic therapies.

• From this case, it is found that the causal factor is the extended period of delay in commencing cancer treatment other than minimal resection of tumours by surgery. It justified that the surgery could not help him to effectively remove the invisible cancer cells.

• The causal factors of side effects from systemic treatments which impacted his life quality possibly might have made his major treatment of immunotherapy less effective.

The conclusion of the assessment and analysis on this case, indicated that the early diagnosis plus the early treatment is critically important in fighting cancer. Once the cancer metastasis occurs, it becomes extremely difficult to cure.

Chapter 5: Analysis and Discussion

The choices of cancer treatment approach, efficacy assessments and disease prognosis prediction are very complicated and contain many visible and non-visible causal factors dynamically influencing the result. To fight aggressive invasive cancer cells one needs a comprehensive network consideration including the avoidance of negative impacts on other healthy body organs. The decision-making in treating the same type of cancer for different patients is always varied and that depends on the individual's holistic body conditions; the outcome of the same treatment for the same cancer stage on different patients can also often be different unexpectedly.

Because the individual patient's personal physique and general constitution, type of job, life style, psychological factors, dietary habits, other non-cancer diseases, response to the treatment, tolerance to the side effects from treatments, living environment, personal economic status, family member support and care, physical activities, original causes of cancer, and other factors are all playing roles as causal factors dynamically affecting each other.

The assessment of cancer treatment effect including "Complete Response", "Partial Response", "Stable Disease", "No Change", "Progressive Disease" should be considered as part of causal factors among the treatment strategies, not an end point in themselves.

Because the outcome of individual patients in a short period of time may change due to the above causal relationship factors, the patient's prognosis maybe negatively backward, or be positively improved.

Cancer treatment strategy proposals should look at the patient's body as a miniature "universe" where inhabits various "ethnic races"; any associated treatments before, during and after the principal therapy can affect the treatment outcome due to the interaction of causal factors. Such as in the battlefield, prior to the army forces attacking the enemy camp, over-reliance on air bombardment may kill their own latent forces on the enemy site.

Scientists at Imperial College London believe that antibiotics can remove beneficial bacteria from the intestines, thereby weakening the immune system. This

seems to reduce the possibility that immunotherapeutic drugs will enhance the body's ability to fight against cancer [89].

Thus, the decision-making in treating a cancer patient should be a “tailor-made” approach considering every single causal factor that may affect the treatment outcomes. Thus, FCM can be used as a value guiding tool in cancer treatment strategy making.

The clinical data, collected from our research hospital, using SPDT in combination with Western therapies and or complementary therapies in cancer treatment, have been collected and analysed using FCM. The Causal Relationship among the Affecting Factors of patients’ diseases and combination treatments, and their interaction with the result outcomes have been investigated and concluded in a systematic format.

This study is not a Case Study Report, and it is difficult to do a systemic research study and report to present the results from influential relationship factors of each patient with the traditional tools of data analysis and assessment. Therefore, FCM is a suitable tool used in this study which is to do the data analysis and assessment on the effects of SPDT, and/or other therapies in cancer treatment.

In the last thirty years various studies have demonstrated the prognostic value of the Karnofsky Performance Status (KPS), primarily for various cancers, but also for other disease entities [78,80].

The assessment of overall physical functionality as a predictor of overall survival is quite understandably pathophysiological because poorer prognoses are generally associated with increasingly severe symptoms and a greater burden of disease [52].

The patients’ vitality depends on many factors other than merely the KPS, including, but not limited to, Cancer TNM Staging, age, gender, molecular genetic markers, [78,80] Response to Therapy, etc. The causal relationship factors which can be assessed have been included in the FCM analysis of our study.

SPDT is a novel cancer treatment utilizing nontoxic photo/sonosensitizers to be activated by light and ultrasound exposure. It has been clinically proven as a safe, non-toxic effective cancer therapy with minimum tolerable temporary side-effects.

Unfortunately, most of the patients in my research were at Stage 4 or very final stage conditions when they commenced the SPDT treatment and they were necessarily treated in combination with several other therapies during the same course. Hence, it is very difficult to assess and analyse the effectiveness of SPDT therapy independently in this study.

Whereas, quite a few patients repeatedly returned to the hospital, resuming SPDT therapy, travelling between China and Australia. This scenario shows that these patients were satisfied with the treatment and maintained hope. We believe that SPDT is worthy of further investigation as an effective and well tolerated treatment for primary and metastatic tumours including the causal influence relationship with other Western conventional therapies.

Traditional Chinese Medicine (TCM) has been popularly used in the greater China area for thousands of years. In this study, we have found that Chinese herbal medicine is effective in treating cancer patients as an adjunction medicine to support Western medicine.

Cancer treatment should not be limited to getting rid of cancer cells; the preventative management should be considered as the higher priority action. Preventative measures that reduce cancer risk factors, such as smoking, alcohol consumption, poor diet, physical inactivity, overweight and obesity, also help reduce the risk of other chronic diseases, including cardiovascular disease, type 2 diabetes and chronic respiratory disease.

Cancer patients normally have multiple symptoms. Because of the cancer, the patients' health status has deteriorated for some time. Multiple factors interact with each other, forming a complex scenario. When multiple factors interact with each other, the causal relationship therefore is dynamic as well.

Most tumours' development is over a long period of time, while others are rather rapid. During the process of malignant tumour generation, the causal factors of it includes body internal, external environment / acquired factors, prior diseases that can also develop many other causal factors impacting each other during the treatment and recovery. The knowledge of causal reasoning among various factors becomes essential in the analysis and assessment of the treatment effectiveness.

When the patients are treated, the specialists normally adjust according to the patients' status. Such adjustments are based on some causal reasoning that can be represented by FCM. Thus, the FCM modelling we have constructed can facilitate other medical practitioners to use as a medical supportive decision-making system.

Although this study was conducted based on real-life medical data, the accuracy of causal factor weights still requires improvements. Our future work after this thesis will be focused on exercising the results of this study by doing clinical experiment research to avoid these limitations to obtain more practical FCM graphic weights.

Chapter 6: Conclusion

This study has concluded that treating cancer is a whole-body holistic strategy, rather than using one single approach to effect a cure. Cancer patients all have their own backgrounds and so many different causal factors surround the health conditions. While making a proposal of treatment for a cancer patient, one always needs to holistically review individual patient's overall conditions and forecast forthcoming causal factors during and post treatment to facilitate using FCM as a supportive decision-making system.

The FCM causal structure link map can show medical doctors and researchers the relationship between the causal factors and the inference of individual treatment which individual laboratory reports do not give, nor the conventional data analysis reports.

Furthermore, it can be a useful and valuable tool, especially for medical professionals, data analysts, to assist with treatment indication and even for prediction of prognosis accurately.

However, there is a lot more work required for more comprehensive research to achieve further development of FCM models for supportive cancer treatment decision making applications.

Chinese herbal medicine has been used effectively for cancer treatment, however, due to the individualised approach of choosing herbs for different individuals, the evaluation of effectiveness awaits different analytic approaches. FCM has demonstrated its strength in the analytical process.

There are large numbers of clinical research reports showing that SPDT is a safe and significant effective therapy for cancer treatment, Most patients who choose SPDT are in the late stage of cancer, the application of SPDT has been integrated with other suitable therapies for life saving or life extension. FCM analysis has demonstrated the effects of the integrative approach of treatment. It is worthy of further investigation for systematic understanding about SPDT in cancer treatment in the future.

Our study has proved that FCM is a comprehensive front-end medical decision support system that helps health practitioners effectively evaluate the effectiveness of

various combination therapies. FCM has been widely applied in the domain of medical diagnosis, risk or prognosis prediction and treatment evaluation. It is necessary to further fine-tune the FCM maps in order to obtain a more reliable model corresponding to the actual situations with more clinical data and creditable parameters.

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Appendices

Appendix A

Project related Publications

Daniel Lee, Huai Liu, Jia Rong, Hong Xu, and Yuan Miao, "Decision Making for Traditional Chinese Medicine based on Fuzzy Cognitive Map." In: *Proceedings of the 7th International Conference on Health Information Science (HIS2018)*, volume 11148 of Lecture Notes in Computer Science, pages 25-36, 2018.

Daniel Lee, Hong Xu, Huai Liu, and Yuan Miao. "Cognitive Modelling of Chinese Herbal Medicine's Effect on Breast Cancer." *Health Information Science and Systems*, 7(1):20:1-20:11, 2019.