1 Literature Review

1.1 Introduction

This chapter will examine haematological cancers, the nutritional status of patient suffering from these cancers, the distress caused by its side-effects, and possible correlations that exist between them, as mentioned in the literature. The principal aim of this chapter is to discuss the factors which affect patients suffering from a haematological and receiving chemotherapy. It will examine the literature regarding nutritional status and distress levels in chemotherapy patients and see whether any other studies have identified any correlations between these variables. The layout of this chapter is such that it will initially examine studies related to cancer and nutritional status – the physical aspects of cancer – and then proceed to examine distress – the psychological aspect. This is important because nutrition may exert a physical effect, limiting the incidence or the severity of chemotherapy side effects, but it might also have a psychological role as well – reassuring the patient about their nutritional reserves – their ability to cope with the assault of tumour and treatment.

1.2 Search Terms

I used search engines, Google Scholar, Google and Yahoo, and also searched more specialised literature search databases such as Medline, MedicineNet.com, PubMed, PubMed Central, Entrez, epnet.com, National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine (NLM), Scopus, Wikipedia, Biology Online and others. All searches were in English and included such terms as “malnutrition”, “cancer and malnutrition”, “distress”, “cancer and distress”, “cancer and metabolism”, “chemotherapy and metabolism”, “chemotherapy and malnutrition”, “chemotherapy and distress”,

"correlation", "malnutrition and distress". Articles in English, dating 2000 or later (this acknowledging developments in treatment), were given most importance, although the number of articles investigating correlations were very limited.

1.3 Haematological Cancers

This study focuses exclusively on haematological cancers. Haematology encompasses the diagnosis and clinical management of a wide spectrum of blood disorders and for the scope of this chapter, haematological cancers will include "acute and chronic leukaemia, lymphoma, multiple myeloma" (NICE, 2008; R.C.P. London, 2008). Haematological cancers are associated strongly with younger age groups, when men and women who are in their working life prime, there is scope for a great deal of anxiety, and especially that associated with chemotherapy administered. Notionally, the impact of chemotherapy and disease on the young adults' appearance, physical energy and potency could all contribute to distress in these patients and typically affect younger people.

1.4 The Effect of Cancer on a Person's Metabolism

Cancer has a large effect several functions of the body, including its metabolism. Figure 1 shows that cancer and other diseases place an increased demand for energy requirements on a person's body. Haematological cancer itself increases a person's energy demands by 50% (Northwestern University Medical School, 2000). This means that these patients would need more calories than a similar person with the same age, gender, work and build, as the person suffering from the disease, to maintain their normal body functions. Therefore, when one calculates the energy requirements of cancer patients, apart from considering the normal Basal Metabolic Rate, mobility status and protein losses, one has to add an extra 50% caloric

intake above all these factors to satisfy their calorific needs. This in itself, puts the patient in a position where he is more vulnerable to undernutrition. A young male patient who works in a physical work setting and who would normally consume around 2000 calories daily, would need around 3000 calories daily due to his cancer. All these facts add importance to this study, where malnutrition is intimately linked to haematological cancers and hence could be a factor which determines their outcomes and responses to treatment.

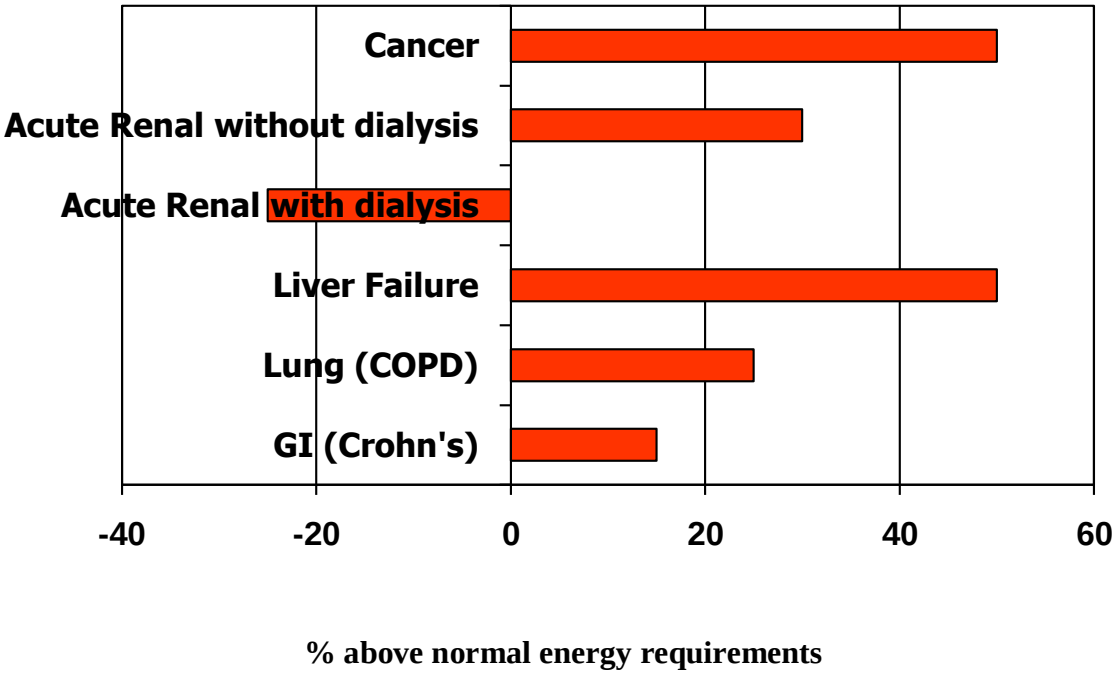

Figure 1 - Changes in Resting Energy Expenditure with Disease (Northwestern University Medical School, 2000)

The Cancer Nutrition Network for Texans (2000) emphasises that malnutrition causes defects in carbohydrate, protein and fat metabolism (see Table 1). The net effect of this is that cancer patients experience a loss of muscle mass and body tissues which, apart from the increased metabolic requirements posed by a patient suffering from cancer, increase the protein malnutrition even more. A person's metabolism is thought to have a direct effect on the amount of calories that are burnt and/or are accumulated within a person's body. Hence the

slow-down in carbohydrate and fat metabolism due to the cancer, together with the increased protein breakdown due to the cancer, as demonstrated in Table 1(see dissertation page 6), places a greater demand on the body's energy requirements. The cancer-related defects outlined in Table 1 will decrease the capability of the patients' bodies to metabolise carbohydrates, fats and proteins and will hence inhibit them from absorbing sufficient amounts of nutrients and calories from their normal diet. Besides that, the increased metabolic uptake of energy by the cancer itself will increase the supply-demand ratio of the patients, and will place the patients at an even higher risk of under-nutrition.

Bozzetti (2001) describes the Resting Metabolic Expenditure according to the type of tumour that a patient has. He reports a 35% increase in metabolism in luekaemia patients and a 22% increase in lymphoma patients. This means that the cancer patients would experience a large loss of nutrients and would also make the amount of nutrients necessary for healthy functioning of their body much larger. Haematological cancers affect fast dividing tissues at a time in adult life when energy demands are already high. It is interesting to note however, that Bozzetti's (2001) reports show that haematological cancers cause less of a demand on the body's need for extra calories, when compared to other cancers. This may mean that haematological cancer patients experience less weight loss than other cancer patients would, although this would need to be investigated in future studies.

Cancer-Related Defects in Carhohydrate Metabolism
• Glucose intolerance • Insulin resistance • Abnormal insulin secretion • Delayed glucose clearance • Increased glucose production • Increased glucose turnover • Variably increased Cori cycle activity
Cancer-Related Defects in Fat Metabolism
• Excess body fat depletion relative to protein loss • Decreased lipolysis, free fatty acids, and glycerol turnover • Hyperlipidaemia • Failure of glucose to suppress oxidation of free fatty acids • Decreased serum lipoprotein lipase activity despite normal insulin

Cancer-Related Defects in Protein Metabolism
• Increased whole-body protein turnover • Increased protein fractional synthetic rates in liver • Reduced fractional synthetic rates in muscle • Increased hepatic protein synthesis • Persistent muscle protein breakdown • Decreased plasma branched-chain amino acids

Table 1 - Cancer-Related Defects in Body Metabolism (The Cancer Nutrition Network for Texas, 2000)

1.5 The Effect of Chemotherapy on Patients' Nutritional Status

Whilst chemotherapy is used to treat haematological cancer, achieving a remission, it carries with it some extra burdens that can make sustaining a satisfactory Body Mass Index (B.M.I[1]). more difficult. These include anorexia, nausea and vomiting, stomatitis and diarrhoea.

The goals of chemotherapy could be to achieve a cure, to control disease or to relieve symptoms of the cancer, such as pain and breathlessness (Coward & Coley, 2006). All the metabolic changes mentioned in the previous section (Section 1.4 - The Effect of Cancer on a Person's Metabolism (see dissertation page 2)), together with a diminished dietary intake due to various factors such as the side effects of the chemotherapy, lead to malnutrition (Antoun *et al.*, 2006; Van Cutsem & Arends, 2005). Table 2 (see dissertation page 8) tabulates the most common chemotherapy drugs which are administered to patients suffering from haematological cancers, plus their main adverse effects. Chemotherapy targets rapidly dividing cells, including those of the mouth and digestive tract (The National Cancer Institute, 2002). It can cause anorexia, nausea, diarrhoea, vomiting, inflammation and mouth

[1] A standard measure of nutritional status; a ratio of weight (kilograms) to height squared (metres squared).

ulcers, changes in the taste of food and infections. In agreement with these facts, several studies (Bosaeus, 2008; Renshaw *et al.*,, 2008; BC Cancer Agency, 2007; The Cancer Nutrition Center, 2007; Hutton *et al.*, 2007; Arends *et al.*, 2006; Bozzetti, 2006; Morss Dy, 2006; Brogden, 2004; Slaviero *et al.*, 2003; National Cancer Institute, 2002; Knox *et al.*, 1983) have demonstrated that the inability to maintain nutritional status is a very common problem for persons receiving chemotherapy. The South West Wales Cancer Institute (2007) also confirmed what the previous author stating that up to 80% of people with cancer may be mildly malnourished and that up to 40% have been reported as showing signs of severe malnutrition.

Various authors (Tisdale, 2001 and Davis & Dickerson, 2000, cited in Molassiotis & Foubert, 2006) identify reasons for anorexia in cancer patients, such as "decreased taste and smell of food, resulting in increased sweet and decreased bitter thresholds, and also loss of appetite due to stress or depression. Nausea and vomitting, particularly with chemotherapy, bowel obstruction and dysphagia complicate matters even further" (Molassiotis & Foubert, 2006, p. 634). They also mention early satiety, where patients feel full quickly after eating small amounts of food. Mucositis can result in dysphagia and odynophagia, making eating food or drinking fluids undesirable. Molassiotis & Foubert (2006) report that 40% of cancer patients experience anorexia due to cancer at diagnosis. This factor of malnutrition on diagnosis gives food for thought. It could be that the degree of malnutrition at diagnosis, and maybe even the percentage incidence, could be influenced by several factors. Studies show that age, diet, amount of physical activity, work or other factors could contribute to this percentage.

Immediate reactions	**Chemotherapy Drug**
Haemorrhagic cystitis	Cyclophosphamide
Hypocalcaemia, facial flushing	Mithramycin
Fever and chills	Bleomycin
Early reactions	
Paralytic ileus	Vincristine
Hypercalcaemia	Oestrogen
Psychosis	Cortocisteroids
Pancreatitis	L-asparaginase
Fluid retention	Oestrogen, corticosteroids
Pulmonary infiltrates	Methotrexate, bleomycin
Cerebellar ataxia	5-fluorouracil
Delayed reactions	
Peripheral neuropathy, constipation	Vincristine
Cardiac damage	Daunribicin, cyclophosphamide
Syndrome of inappropriate A.D.H. secretion	Cyclophosphamide, vincristine
	6-mercaptopurine
Cholestatic jaundice	Busulphan
Addisonian-like syndrome	
Late reactions	
Hepatic fibrosis	Methotrexate
Encephalopathy	Intrathecal methotrexate
Osteoporosis	Corticosteroids

Table 2 - Side-Effects of Specific Anti-Cancer Drugs (Fernandez, 1987)

Furthermore, social factors may also be responsible for malnutrition, such as change in eating environment or complications (Grant & Kravits, 2000 and Nitenberg & Raynard, 2000, cited in Molassiotis & Foubert, 2006). Furthermore, Rivadeneira *et al.* (1998) advocate the use of oral nutrition, supplemented whenever necessary with enteral nutrition, to provide more essential nutrients that provide immunologic and metabolic benefits, such as food containing omega-3 fatty acids, glutamine, arginine and RNA. Argilés (2005), Davies (2005) & Van Cutsem & Arends (2005) particularly emphasise that due to malnutrition, the responses to chemotherapy are decreased, chemotherapy-induced toxicity and complications are more frequent and severe, and survival times are shortened. Bosaeus (2001) agrees with them and continues by saying that rather than a reduced dietary intake, in the patients studied – which were a mixed cancer group, the problem was mainly an increased Resting Energy Expenditure (R.E.E.). This will be discussed further in the next section (Section 1.6.1 Malnutrition in cancer patients (see dissertation page 10)). In contrast to what these authors say, the British Medical Journal (1979) states that evidence from experiments on rodents is conflicting and does not answer the doubts as to whether nutritional support improves the clinical outcome of treatment such as chemotherapy. They state there is an idea that "the tumour might be fed rather than the host", and with the evidence presented by studies this query still remains unanswered (British Medical Journal, 1979, p. 912). In agreement with this, Heber *et al.* (2006) state that the provision of excess calories to patients with weight loss at the time of diagnosis did not appear to change median survival in patients with advanced cancer. On the contrary, many patients either maintained the same weight or lost weight despite being given adequate calories by continuous enteral alimentation. These doubts add scope to my research study, which should be able to shed some light on the potential

association between nutritional status and the frequency and extent of patients' adverse effects caused by the treatment.

1.6 Malnutrition

Malnutrition is often defined as a nutritional status with a Body Mass Index (B.M.I.) which is below the normal range, i.e. below 20 kg/m^2, or above 25 kg/m^2 (as defined in the Glossary) and this will be taken as the operational definition of B.M.I. during this dissertation. Whilst people who exceed calorie intakes over requirements and become clinically obese are malnourished in another way, in this study we reserve the term for those with a deficit of food intake needed to protect the body and its needs.

1.6.1 Malnutrition in cancer patients

Wang *et al.* (2002) discovered that 48% of patients experiencing cancer fatigue had serum albumin levels below the reference range (3.5-4.7 g/dL). These patients reported significantly higher levels of fatigue (and hence a greater psychological distress) than patients with albumin levels within the reference range. According to Van Cutsem & Arends (2005), reduced food intake in cancer patients, alterations in their nutrient metabolism and R.E.E. may also contribute to their decreased nutritional status. Hutton, Baracos & Wismer (2007) also found lower energy intakes, higher rates of weight loss and lower quality of life with mild or moderate chemotherapy complaints, giving an indication that nutrition might be associated with chemotherapy-induced distress. Other studies stress the fact that cancer patients often present with anorexia (or cachexia) (Peñalva *et al.*, 2009; Bosaeus, 2008), even due to the adverse effects of the chemotherapy itself, and advocate the use of oral

supplementation and nutritional counselling (Peñalva *et al.*, 2009; Gudny Geirsdottir & Thorsdottir, 2008). Other studies also state that this weight loss has an impact on the patients' treatment prognosis (Steinbach *et al.,* 2009; Renshaw, Barrett & Chowdhury, 2008; Slaviero *et al..*, 2003). No studies were found which contradicted these articles, i.e. all literature read confirmed that the nutritional status of cancer patients was found to deteriorate due to their cancer.

1.7 Distress in patients undergoing chemotherapy

The word 'distress' has various meanings, "ranging from powerlessness, sadness and fear, to depression, anxiety, and panic" (NCCN, 2008) (see Glossary on dissertation page 164), and is experienced by several, if not all, patients undergoing chemotherapy. Although different definitions of distress exist, all include an element of helplessness, suffering, unpleasant feelings and emotions. The definition maintained as operational within this study is one including "a state of helplessness, suffering, unpleasant feelings and emotions, experienced by these patients, hoping it is a temporary condition rather than a permanent one." The patients themselves report different things as being distressing and here we shall concentrate upon the sensation reported.

1.7.1 Distress in chemotherapy patients

People with cancer have to deal with issues and situations that are very frightening and very challenging (Zainal *et al.*, 2007; Breitbart, W.S., 1995). A number of studies have focussed on nausea and vomiting experienced by the patients. Gralla, Grunberg & Messner (2009)

state that most patients receiving chemotherapy experience these side-effects. The Cancer Treatment Centers of America (CTCA) (2008), from patient experiences reported by the patients themselves, reports nausea (and associated vomiting) as "one of the most feared side effects of chemotherapy" and emphasises that it can make daily activities – such as bathing, preparing meals, working and spending time with friends and family more difficult. CTCA (2008) continue to state that these side effects can cause dehydration, malnutrition, fatigue, loss of appetite, difficulty concentrating, sleep disturbances and emotional distress and can disrupt the treatment regime and this is confirmed by findings of Gralla, Grunberg & Messner (2009), Grosvenor, Bulcavage & Chlebowski (1988) and Fernandez (1987). Gralla, Grunberg & Messner (2009) add that the side-effects also reduce the patients' quality of life and their outlook towards life.

Bernhardson, Tishelman & Rutqvist (2009) studied patients receiving chemotherapy who experienced taste and smell changes. They reported that nearly one-third of the participating patients reported both high levels of distress and detrimental impact of the same on their daily life. Pandey *et al.* (2006) studied distress, anxiety and depression in 117 cancer patients undergoing chemotherapy and obtained the results tabulated in Table 3 (see dissertation page 13). This shows that the highest distress levels were related to what they describe as emotional distress (showing the highest minimum distress score of 10 and maximum score of 43 and an average score of 25.4), followed by spiritual distress (distress score of 10) and family-specific distress (average score of 9.68). Although the results of this study are important, the tool they used had been translated into Malayalam for their study and had been validated purposely for the study, and these might have influenced the accuracy of the tool and the results obtained.

The distress, anxiety and depression scores					
Distress inventory V2	**Mean**	**SD**	**Median**	**Min**	**Max**
Emotional distress	25.4	7.56	25	10	43
Spiritual distress	10.0	3.64	9	5	25
Social distress	9.23	2.79	9	6	19
Medical distress	4.39	0.78	4	4	8
Activity of daily living	2.8	1.8	2	1	5
Family specific distress	9.68	6.11	11	0	23
Total distress (DIC 2)	24	9.06	22.7	7.14	63.64
Anxiety	3.33	3.5	2	0	14
Depression	4.07	3.24	3	0	16

Table 3 - The distress, anxiety and depression scores (Pandey *et al.*, 2006).

Pandey *et al.* (2006) continue to specify that 30-50% of the subjects showed moderate to high levels of distress before the start of the treatment and at the end of the treatment. This was also found in separate studies carried out by Trask *et al.* (2003) and Larsson *et al.* (2004), who had similar results.

Iop, Manfredi & Bonura (2003) stated that fatigue is known to be the commonest side-effect of chemotherapy, and mention a percentage of 82-96% of patients who experience it during their treatment. In fact, this problem is "the most common and distressing problem of cancer patients after treatment" (Dimeo *et al.*, 2003; Smets *et al.*, 1993, cited in Dimeo *et al.*, 2003; Vogelzang *et al.*, 1997, cited in Dimeo *et al.*, 2003). Hofman *et al.* (2007) quoted various studies that found that up to 80% of patients treated with chemotherapy experienced fatigue (as defined in the Glossary, Section F). In about one-third of the patients this continued for months and even years after completion of treatment. This compromised their general activity and work, enjoyable life and personal relationships as was associated with the use of

opioids, performance status, blood transfusions, gastrointestinal symptoms and sleep disturbance (Wang *et al.*, 2002).

1.7.2 Causes of chemotherapy-induced distress

Zainal *et al.* (2007) state that the causes of distress in cancer patients undergoing chemotherapy "could be normal responses to the threat of illness, uncertainty, side-effects of chemotherapy agents, loss of control or an underlying psychiatric disorder such as depression and anxiety" (Zainal *et al.*, 2007). Fernandez (1987) highlights several adverse effects of chemotherapy which cause varying degrees of distress in cancer patients. A summary of the different side-effects caused by specific anti-cancer drugs can be found in Table 2 (see dissertation page 8).

1.7.3 Reducing chemotherapy-induced distress

Gralla, Houlihan & Messner (2009) and Gralla, Grunberg & Messner (2009) examined ways of managing chemotherapy side effects. These authors mention drugs, taking short naps and short exercise sessions to deal with fatigue. They also mention ways of coping through dietary means, by eating and drinking slowly, avoiding sweet, fried or fatty foods, eating cold foods, drinking a sufficient amount of fluids and obtaining proper nutritional advice. Mayo Clinic (2009) and CTCA (2008) agree with the above authors and suggest plenty of fibre and fluids plus light exercise to prevent constipation, eating upright, trying several small meals, planning ahead, creating a comfortable environment, eating bland foods, choosing healthy options, snacking often, not forcing oneself to eat and practicing good mouth care. Hence all these authors advocate the involvement of a nutrition team or specialist to develop an

individualised nutrition plan for each particular patient. To this Bruera (1997) adds that the nutritional counselling should be based on eating high calorie meals of small portions that are pleasant for the patient, and also stresses the importance of involving the patient's family in such decisions. The above authors are all authorities in the field of cancer and are involved in developing guidelines to be used by both patients and healthcare professionals and therefore their suggestions are based on a vast patient experience, which gives weight to their recommendations. Also, as quite a closed population, the Maltese families get very involved in the care of their loved ones and hence, the fact of involving the relatives in the patients' care is crucial and mandatory, as these could be a factor influencing both patient nutritional status and distress.

1.8 Nutritional Status and Distress

Grosvenor *et al.* (1988) conducted a study on 254 patients with different kinds of cancer over a 3-year period, correlating nutritional status with various variables. 67% of these patients showed weight loss, while 33% did not. Nutritional status was measured using anthropometric measures, i.e. similar to the method used in this dissertation, although skinfold was also used in Grosvenor's (1988) study. Inclusion criteria for the selection of patients was similar to this dissertation, i.e. for patients above 20 years of age, however, some patients had received previous chemotherapy while other had not. In this study all patients were first-time receivers of chemotherapy. Grosvenor (1988) found that patients showing weight loss had more side-effects (and distress) and the results they obtained were seen to be statistically significant (level of significances being less than 0.01 for all variables studied). They concluded that GI symptoms potentially influencing weight loss are prevalent early in the course of treatment, regardless of current nutritional status, calorie intake or prior therapy

experience. They found a relationship of various variables in relation to weight change (and consequently nutritional status). These are abdominal fullness (P-value less than 0.001), taste change (P-value less than 0.002), vomiting (P-value less than 0.005), and mouth dryness (P-value less than 0.02). A definition of P-value is provided in the Glossary (dissertation page 164).

In his article on "Nutrition and Mood Disorders", Dr. J. Fuhrman (2009) states that "The ability of the brain to adapt and respond to stress is correlated with nutritional status". He continues saying that high antioxidant intake prevents oxidation tissue stress in the brain. Fuhrman (2009) states that when lipid peroxidation in a person is high, depression is much more likely. Researchers at the University of Sheffield and the Efarnol Research Institute, both in Great Britain, report that they have found a significant association between severity of depression and the levels of omega-3 fatty acids in both the diet and the red blood cell membranes (NaturalNews.com, 2009).

A new study (Amdouni, 2009) has revealed that cancer patients who are malnourished experience significantly greater levels of psychological distress than those who are more adequately nourished. In this study, distress was measured using the same "distress thermometer" used for this research project. Amdouni (2009) found that the score on the distress thermometer was positively correlated with the total score of the patient-generated subjective global assessment (a nutritional assessment tool); the higher the distress, the worse the patients' nutritional status. Hence, these studies, contrary to what previous studies have reported, might indicate that a possible negative correlation between nutritional status and distress might exist. The methodology of this study (Amdouni, 2009) was very similar to that

of this dissertation in that it asked the patients to rate their own nutritional status and distress, and used the same tool, the Distress Thermometer, to assess patient distress. The nutritional assessment tool was different, where they used the Patient-Generated Subjective Global Assessment (PG-SGA) instead of B.M.I. (used in this dissertation).

The following chapter will outline the methodology used during this study.