To assess the effectiveness of tailored food recipe in attenuating the progression of cancer cachexia to refractory cachexia in adult female patients undergoing palliative care in India

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TO ASSESS THE EFFECTIVENESS OF TAILORED FOOD RECIPE IN ATTENUATING THE PROGRESSION OF CANCER CACHEXIA TO REFRACTORY CACHEXIA IN ADULT FEMALE PATIENTS UNDERGOING PALLIATIVE CARE IN INDIA

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A thesis submitted in partial fulfilment of the
requirements of the University of Westminster
for the degree of Doctor of Philosophy

November 2016

Abstract

Cancer cachexia negatively impacts patients' capability to undergo chemotherapy and fight infection. Increased energy expenditure and anorexia are key clinical features among cachexia patients leading to body weight loss. Therefore, it is imperative to assess all cancer patients for early signs of undernourishment. Nutrition intervention with counselling may ameliorate undernutrition and metabolic alterations. The aim of this study was to attenuate the progression to refractory cachexia, improve nutritional status and quality of life of female palliative care patients by providing nutrient rich natural food along with counselling. Female cancer patients with symptoms of cachexia were randomly distributed into control and intervention group. Patients were recruited from the Palliative clinic, Oncology department in AIIMS, New Delhi, India; control/placebo groups *(for pilot n= 30 and scale-up n=75)* and intervention groups *(for pilot n= 33 and scale-up n=75)*. In addition to nutritional and physical activity counselling, intervention patients were instructed to consume 100g nutritional supplement (IAtta) on a daily basis with their normal dietary intake for a six month period, during the pilot study. Moreover, during the scale-up study, the intervention group received 100g of *IAtta* while the placebo group received 100g of whole wheat flour for daily consumption. Anthropometric measurements, physical activity level (PAL), dietary intake, quality of life (QoL) and biochemical indices were assessed at baseline, three-month and after six-month period. Study variables were analysed using repeated-measures ANOVA and the Friedman test for multi–comparisons to determine the changes within the groups at different time points (i.e. baseline, mid-intervention and post-intervention). Student t-test/ Wilcoxon ranksum tests were performed on the variables to assess the difference between the intervention and control/placebo groups at baseline (P-value ≤0.05; 95% confidence interval). After six months, patients in intervention group (IAtta group) had significant improvement in PAL ($p<0.001$) and QoL domain (global health status, $p<0.001$ and fatigue, $p=0.001$). Conversely, the QoL in the placebo group did not improve (global health status, $p=0.74$) nor did PAL ($p=0.49$). Body mass index was maintained in both groups (IAtta, p-value 0.121; Placebo, p-value 0.35). Serum albumin levels were significantly reduced ($p = 0.005$) in placebo group patients after six months of intervention.

Nutrition sensitive intervention (IAtta meal) along with counselling (tailored nutrition and physical activity) improves quality of life and nutritional status as well as delays progression of cachexia among female palliative care patients. These findings highlight the need to ascertain the nutritional status of cancer patients and underpin the pivotal role of IAtta as intervention tool to compensate for deficient nutrients. It is therefore suggested to embed IAtta into the Indian palliative care framework to modulate cancer progression.
Keywords: cancer cachexia; palliative care; IAtta; quality of life; nutrition sensitive intervention

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Acknowledgements

I would like to thank all my Supervisors and colleagues who have helped and motivated me throughout my research. I am grateful to Dr. Ihab Tewfik, for his support, guidance and constant attention, Dr. Jane Naufahu, for her support and motivation which helped me immensely, Dr. Sundus Tewfik, for her feedback and constructive suggestions which helped me enhance my work. Thanks to the support staff at Westminster University for being by my side in times of need and throughout my research.

I thank Dr. Sushma Bhatnagar, for her close supervision, timely suggestions and enthusiasm which encouraged me enormously. Dr Rakesh Garg, thanks for your guidance and untiring support. I would also like to thank Dr. R.M. Pandey and his colleagues in Statistics department at AIIMS and the Research scholars at AIIMS for their constant support and help. Thanks to the administrative staff at IRCH, AIIMS for help with patient file documentation and CanSupport Palliative Cancer Care NGO for continuous patient follow-up.

I would like to express my gratitude towards my patients for their time and patience. My food suppliers in India have been very efficient and supportive during the trial.

Graduate School at University of Westminster, thanks for sponsoring my attendance at various international conferences. My dear friends, especially Waqas Ahmad, who have been very helpful and supportive throughout this PhD journey and I cannot thank them enough.

Dr. Mukul Kapoor and Mrs. Anjali Kapoor has been the biggest pillar of support for me during this PhD and thanks to my extended family for their timely help.

Lastly my parents, sister, grandparents and fiancé for motivating, believing in me and for constantly being by my side throughout my research.

Author’s Declaration

I declare that all the material contained in this thesis is my own work and has not been submitted for any other award.

Neha Kapoor

List of Acronyms

AIIDS: Acquired Immuno Deficiency Syndrome
AIIMS: All India Institute of Medical Sciences
APPR: Acute Phase Protein Response
ASPEN: American Society for Parenteral and Enteral Nutrition
BIA: Bioelectrical impedance Analysis
BMI: Body Mass Index
CT: Computed Tomography
CRF: Cancer related Fatigue
CRP: C-Reactive Protein
DEXA: Dual Energy x-ray
EORTC: European Organisation for Research and Treatment of Cancer
EPCRC: European Palliative Care Research Collaborative
ESPEN: European Society for Parenteral and Enteral Nutrition
FFQ: Food Frequency Questionnaire
GDP: Gross Domestic Product
GEE: Generalized Estimating Equation
GIT: Gastrointestinal Tract
HIV: Human immunodeficiency virus
IAtta: Improved Atta (flour)
ICMR: Indian Council of Medical Research
IL-1: Interleukin -1
IL-6: Interleukin – 6
IFN-y: Interferon-gamma
IMS-PAQ: Indian Migration Study - Physical Activity Questionnaire
IRCH: Institute Rotary Cancer Hospital
ITT: Intention to Treat
LMF: Lipid Mobilizing Factor
MET: Metabolic equivalent unit
MENAC: Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia
MNA: Mini-Nutritional Assessment
MRI: Magnetic Resonance Imaging
MST: Malnutrition Screening Tool

MUAC: Mid upper arm circumference
MUST: Malnutrition Universal Screening Tool
mGPS: Modified Glasgow Prognostic Score
NAI: Nutritional Assessment Index
NCCN: National Comprehensive Cancer Network
NICE: National Institute for Health and Care Excellence
NNMB: National Nutrition Monitoring Bureau
ONS: Oral Nutritional Supplement
OPD: Outpatient department
PAL: Physical activity level
PIF: Proteolysis Inducing Factor
PNI: Prognostic Nutritional Index
PG-SGA: Patient Generated Subjective Global Assessment
QoL: Quality of life
QLQ-C30: Quality of Life C30 Questionnaire
RCT: Randomised controlled trial
RDA: Recommended Dietary Allowance
REE: Resting Energy Expenditure
SFT: Skin fold thickness
TBW: Total Body Water
TNF: Tumour Necrosis Factor
TFR: Tailored food recipe
UoW: University of Westminster
WHO: World Health Organisation
% BF: Percentage body fat

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Journals

1. A prospective randomized controlled trial to study the impact of nutrition sensitive intervention on adult females with cancer cachexia undergoing palliative care in India. Integrative Cancer Therapies (2016); April-June: 1-11 [**Impact factor 2.361**].

2. Palliative nutritional care for cancer patients. Palliative Medicine and Hospice Care (2016); 1(3): e4-e9.

3. A public health nutrition intervention to delay the progression of cachexia to refractory cachexia in Indian female cancer patients: A conceptual framework. International Journal of Food, Nutrition and Public Health (2014); 7 (1): 1-11.

Conferences

1. The effectiveness of nutritional sensitive approach to restore physical activity in cachexic female palliative patients: A randomized controlled trial in India. Palliative Care in Oncology Symposium by American Society of Clinical Oncology. **San Francisco, USA** on September 10, 2016.

2. Combined tailored nutritional intervention with counselling to enhance quality of life among Indian female palliative cancer patients. Cachexia and Nutrition conference in Advanced Cancer Patients: A Multidisciplinary Approach by European School of Oncology in **Barcelona, Spain** on 13th -14th March 2015.

3. The impact of tailored nutrition intervention and dietary counselling on quality of life in female palliative cancer patients in India. 22nd International Conference of Indian Association of Palliative Care. **Hyderabad, India** on February 14, 2015.

4. Tailored nutrition intervention and dietary counselling helps body weight stabilization in Indian female cancer cachexia patients. 47th Annual National Conference of Indian Dietetic Association. **Delhi, India** on December 22, 2014.

5. The impact of tailored nutrition intervention and dietary counselling on body weight in female cancer cachexia patients in India. 2014 Palliative Care in Oncology Symposium by American Society of Clinical Oncology. **Boston, USA** on October 25, 2014.

Chapter 1:

Introduction

1.1 Cancer epidemiology in India

The International Agency for Research on Cancer (GLOBOCAN project, 2012) reported approximately 14.1 million new cancer cases and 8.2 million cancer deaths worldwide. Out of these there were a little over 1 million cancer cases and 683,000 cancer deaths in India (Ferlay *et al.,* 2012). The average incidence of cancer worldwide (in age adjusted terms) is 182 per 100,000 people and the incidence in India is slightly more than the half of the world average (i.e. 94 per 100,000 people) (Mallath *et al.,* 2014). The prevalence of cancer at any given point of time in India is about 2.5 million patients (Nandakumar, 2009). Cancer registries account for just 7% of disease prevalence in India however provide the best information to design healthcare expenditures. Though higher cancer incidence is reported from the urban parts of India, the mortality rate is similar in urban and rural parts suggesting that incidence reporting is lower in the rural parts (Goss *et al.,* 2014). The cancer burden in India has been predicted to double in the next two decades, to more than 1.7 million new cases by 2035 and 1.2 million cancer deaths (Ferlay *et al.*, 2012) (Figure 1.1-1).

According to the Indian Population Based Cancer Registries, 174,693 cases were registered from 2012 to 2014 (National Cancer Registry Programme, 2016). Among all Indian states, Delhi registered the highest number of cancer incidence cases, 19,746 (10,148 males and 9,598 females) (Figure 1.1-2a and 2b). Male patients under the age group 15 to 19 years old (10.23%) and 20 to 24 years old (10.58%) while female patients under the age group 20 to 24 years old (10.48%) and 25 to 29 years old (10.18%) were most affected by cancer in Delhi (Figure 1.1-3). Cancers of the mouth, lung, stomach, oesophagus, cervix uteri and breast affect majority of the Indian population. Among Indian males, cancers of lung, mouth, oesophagus and stomach are most common and breast and cervical cancer in females (Figure 1.1-4) (National Cancer Registry Programme, 2016).

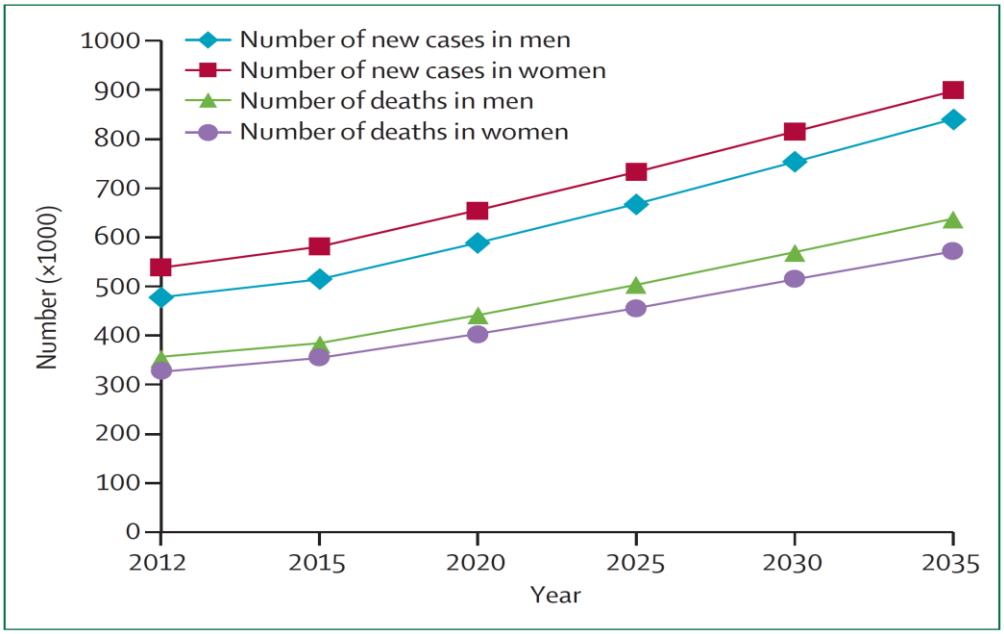
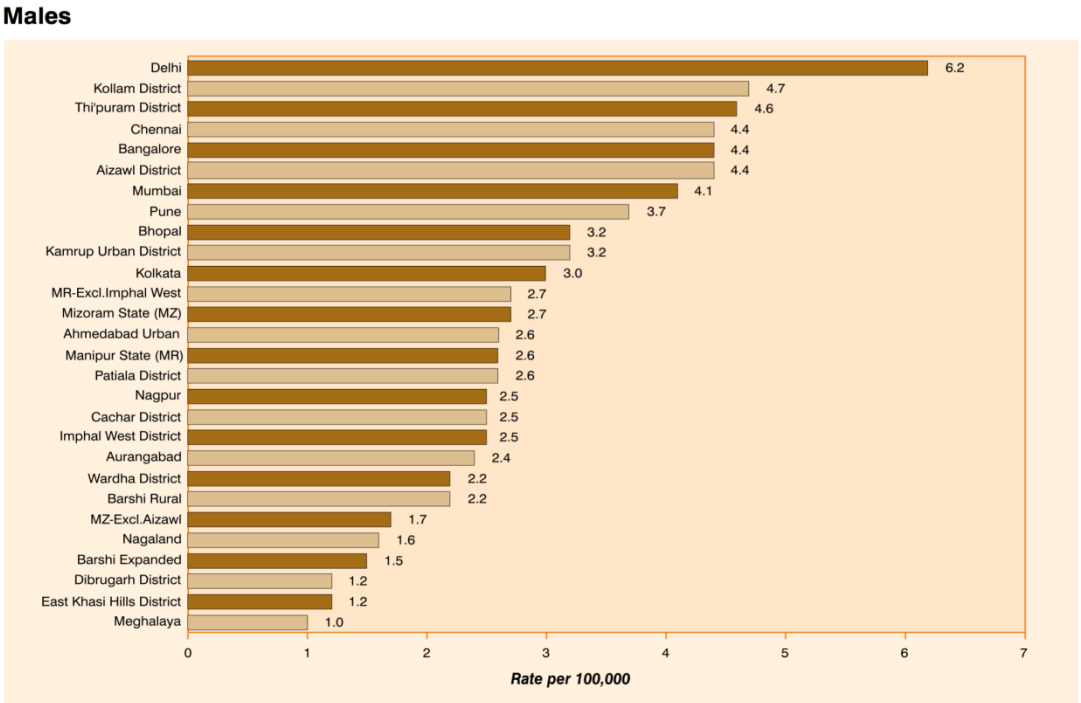
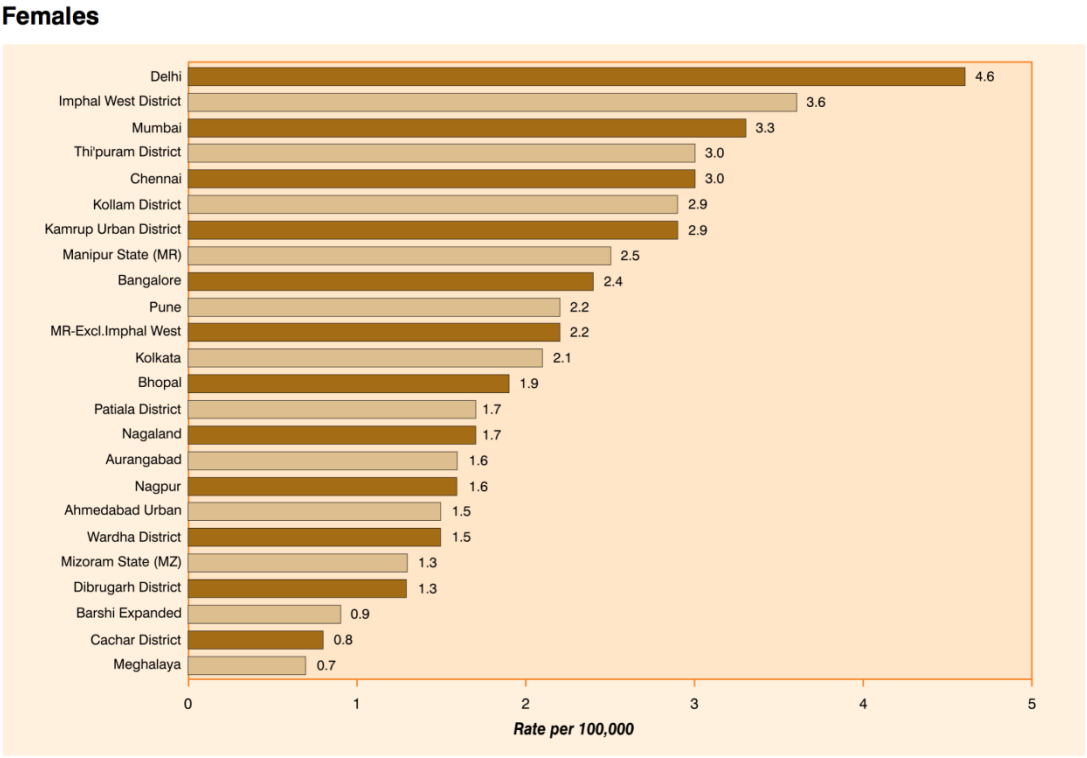


Figure 1.1-1. Predicted cancer prevalence levels in India (Ferlay *et al.*, 2012).



a): Cancer incidence rates among males



b): Cancer incidence rates among females

Figure 1.1-2: Age adjusted cancer incidence rates among males and females according to Indian city they reside (National Cancer Registry Programme, 2016).

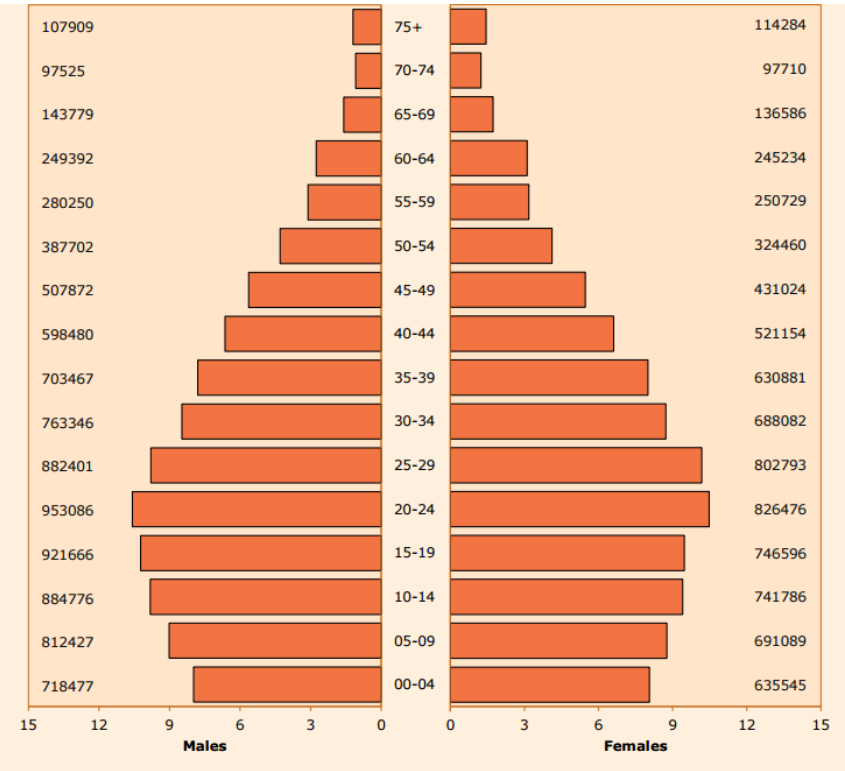


Figure 1.1-3: Cancer distribution among males and females according to age in Delhi (National Cancer Registry Programme, 2016)

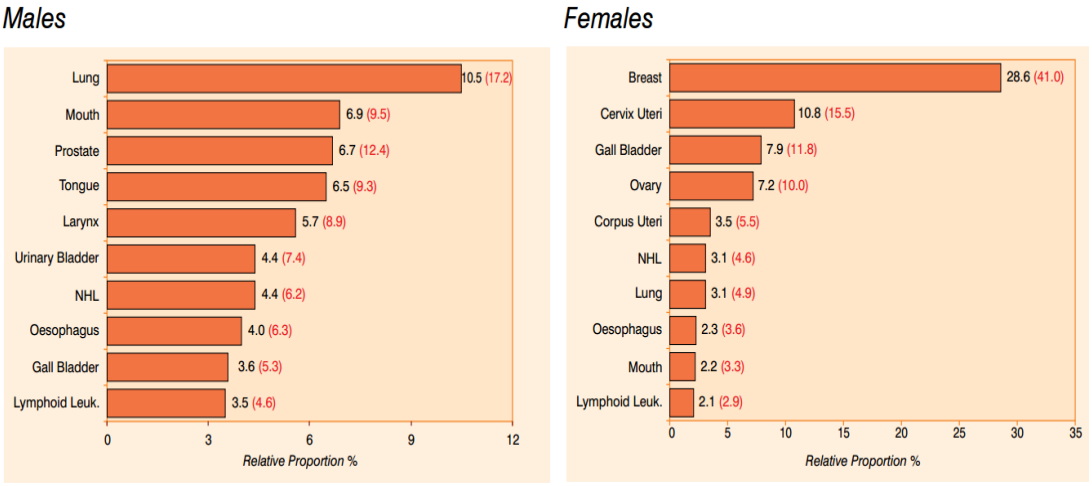


Figure 1.1-4: Cancer site distribution among males and females in Delhi (National Cancer Registry Programme, 2016)

In spite of being the second most populated country in the world, only 3.9% of countries GDP is spent on health care in India. Almost two-thirds of the Indian cancer patients belong to either low or upper-lower socioeconomic strata (Goss *et al.,* 2014). Although majority of the population resides in rural parts, 95% of cancer care providers are established in urban parts (Banavali, 2015). Around 80% of Indian cancer patients are diagnosed when the disease has progressed to an incurable metastatic stage (Fox *et al.,* 2015). Advanced cancer patients face a big economic burden due to the disease prognosis and treatment. Patients undergoing radiotherapy (with or without chemotherapy) spend on an average of 60% of their weekly income towards treatment expenses. India is suffering from a great shortage of health-care providers, data shows that there is just one oncologist per 16000 cancer patients and an availability of 12 healthcare workers per 10,000 population (poor compared to World Health Organisation (WHO) guidelines of 25) (Goss *et al.,* 2014).

The accessibility of reliable cancer treatment is very limited for most Indians (Maroju *et al.,* 2011, p134). Palliative care is a developing field in the Indian national healthcare system. Numbers of palliative care centres are increasing (908 centres) and assistance from trained hospital staff is available, but still there is a vast gap owing to the high incidence of cancer (Suhag *et al.,* 2015; Ministry of Health and Family Welfare, 2012).

Nutrition is considered an important element of palliative care. Patients' nutritional management continues throughout palliative treatment span, in order to enhance

their quality of life and nutritional status (Richardson and Davidson, 2015, p 191). Sadly in Indian palliative care system, nutritional assessment is not practiced by treating physicians and dietician/ nutritionist support is only available for hospitalized oncology in-patients. Indian palliative care guidelines include prescription of dietary supplements in advanced cancer patients to ensure nutritional status management. Commercial dietary supplements (Prosure, Ensure, Resource and Fresubin) are mostly available at urban pharmacy outlets, making it inaccessible (perhaps unaffordable) for the rural patients. Therefore, there is a need to develop sustainable natural food based nutritional supplement using locally available secure ingredients. Palliative care services should consider developing simple care guidelines (that embed adequate nutrition) to empower family members and caregivers for optimum patient management in the household setting.

Undernutrition results in delayed response to therapy among cancer patients, low quality of life, higher healthcare cost and poor survival rate (Lee *et al.,* 2016). Therefore, nutritional intervention can result in favourable treatment response among advanced cancer patients who receive palliative chemotherapy and/or radiotherapy.

1.2 Research hypothesis, aims and objectives

1.2.1 Research hypothesis

We hypothesize that:

- Improved Atta supplementation (Tailored food recipe-TFR) along with nutritional counselling can enhance female cancer cachexic patients' nutritional status and quality of life.
- Supplementation with TFR (Improved Atta-IAtta) can delay the progression of cancer cachexia to refractory cachexia.

1.2.2 Aim

To assess the effectiveness of tailored food recipe (IAtta) in delaying the progression of cachexia to refractory cachexia in adult female cancer patients.

1.2.3 Objectives

The objectives of the study were:

1. To design and optimise a nutritional food recipe (IAtta) for intervention and to ascertain its macro and micronutrient contents.
2. To estimate the nutritional intake of free-living female cancer cachexia patients (baseline data).
3. To appraise the qualitative and quantitative outcomes of 'IAtta' on the health status of free-living cancer cachexia patients (at baseline versus end point) via pilot and scale-up interventions.
4. To evaluate the nutritional role of IAtta in Indian palliative care framework in delaying the progression of cachexia to refractory cachexia in cancer patients.

Chapter 2:

Review of Literature

2.1 Cancer cachexia and classification

The word cachexia is derived from the Greek words kakos meaning bad and hexis meaning state of being or condition, and is a common feature of several advanced diseases such as acquired immunodeficiency syndrome, cancer and congestive heart failure (Argiles *et al.,* 2004). Cancer cachexia has been documented as a recurrent problem and a major reason of morbidity and mortality amongst cancer patients. Worldwide, more than 50-80% of advanced cancer patients suffer from cachexia, and it accounts for mortality in 20% of them (Argiles *et al.,* 2014). Few tumour sites are widely associated with cachexia (like pancreatic, gastric, head and neck) but the same tumour site may exhibit cachexia of varying degree or be absent in different patients (Tisdale, 2009). The prevalence of cancer cachexia in India is not available for documentation.

Cancer cachexia can be described as “a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism” (Fearon *et al.,* 2011).

Weight loss in cachexia is due to wasting of skeletal muscle as well as adipose tissue. In skeletal muscle, due to protein breakdown amino acids are generated, which thereby contribute to fuel hepatic protein and glucose synthesis (Tisdale, 2002). Reduced immunity and mobility are results of skeletal muscle wasting (MacDonald *et al.,* 2003). As weight loss advances to 30% of pre-treatment body weight, death becomes inevitable (Tisdale, 2004). Cachexia negatively impacts patients’ capability to endure chemotherapy and fight infection (Theologides, 1979). Increased energy expenditure and anorexia are key factors among cachexia patients leading to weight loss (Young, 1977; Dhanapal *et al.,* 2011) (Figure 2.1-1).

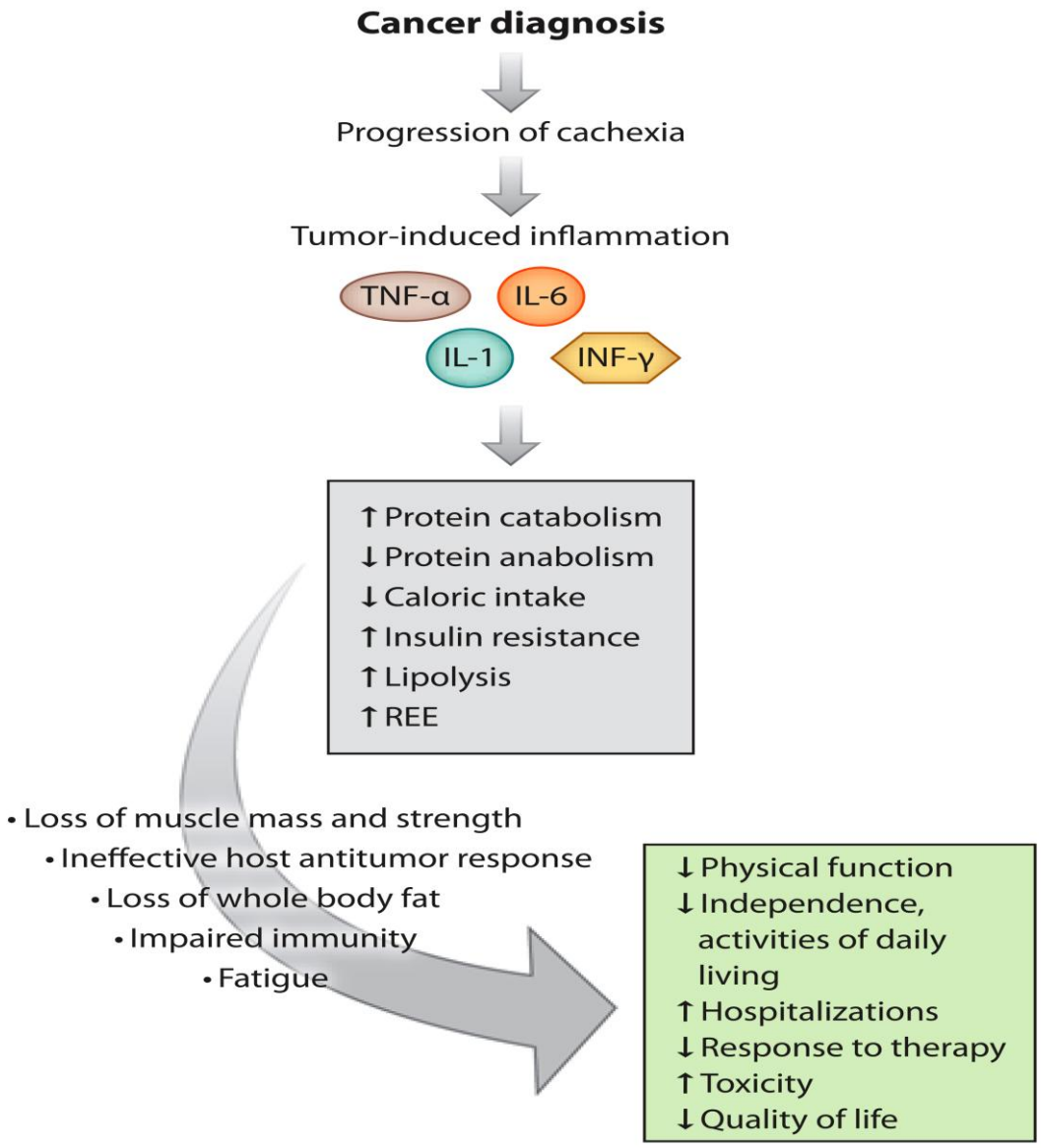


Figure 2.1-1: Cancer cachexia and physiological outcomes (Dodson *et al.*, 2011).

Cancer cachexia is classified into three stages: precachexia, cachexia and refractory cachexia (Figure 2.1-2). Involuntary weight loss (≤5% pre-treatment) due to metabolic changes and symptoms like anorexia is classified as pre-cachexia stage. Degree of progression depends upon cancer site, stage, degree of inflammation, nutritional status and response to anticancer treatment. Patients with more than 5% of body weight loss over a six month period or body mass index (BMI) less than 20 Kg/m^2 and/or sarcopenia will be classified under cachexia stage. When patients fail to respond to anticancer therapy with progressive disease leading towards a catabolic stage with continued weight loss, they are classified into refractory cachexia stage. Except for symptom management, no intervention is

advised during refractory cachexia and a survival period of less than three months is expected (Fearon *et al.,* 2011).

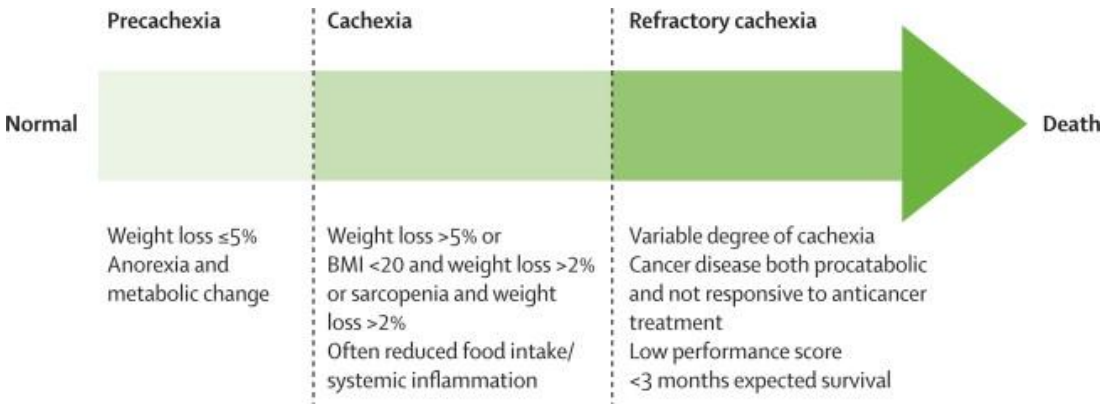


Figure 2.1-2: Classification of cancer cachexia (Fearon *et al.,* 2011).

2.2 Diagnosis of cancer cachexia

Cancer cachexia is a multifactorial syndrome with ongoing metabolic changes making its diagnosis challenging. In 2006, Fearon *et al.,* documented a three factor classification to identify cancer patients suffering from cachexia. Advanced cancer patients experiencing any two of the symptoms of, weight loss of more than 10% compared to their pre-treatment body weight, total calorie intake of less than1500 kcal per day or systemic inflammation determined by C-reactive protein level (more than10 mg/l) were diagnosed with cachexia. While in 2011, a panel of cachexia experts agreed on a common definition and a classification for cancer cachexia. According to the new classification patients experiencing weight loss of more than 5% over past six months, compared to their pre-treatment body weight, or body mass index (BMI) of less than 20Kg/m^2 with continuing weight loss of more than 2% or presence of sarcopenia, are classified as cachectic. Assessment should also include percentage of weight loss, muscle mass, anorexia or appetite loss, reduced food intake, inflammation levels and psychosocial impact (Fearon *et al.,* 2011).

The European Palliative Care Research Collaborative (EPCRC) cancer cachexia guidelines for advanced cancer patients, suggests the following parameters should be assessed (Radbruch *et al.,* 2010):

1. History: Weight change, speed of weight loss, percentage of normal intake.
2. Clinical examination: Body weight, physical strength.

3. Laboratory examination: C - reactive protein (CRP), blood glucose profile.
4. Activity monitoring: Upper limb hand-grip dynamometry, performance status.
5. Body composition: anthropometry (mid-arm muscle area), bioelectrical impedance analysis (BIA).

Weight loss can be assessed by comparing patients' current body weight to their pre-treatment weight using medical records. Increased weight loss is associated with poor therapy outcomes and along with BMI can help in prediction of overall survival (Martin *et al.,* 2015). To measure muscle mass computed tomography (CT) cross-sectional imaging, magnetic resonance imaging (MRI), dual energy x-ray (DEXA) imaging, anthropometry (mid-arm muscle area) and BIA can be used. Muscle depletion is associated with functional impairment and reduced survival rate prediction among cachexic patients. Reduced food intake assessment will require patients' dietary recall using food diaries and food frequency questionnaires undertaken by a trained dietician. This includes quantification of macronutrient and micronutrient intake to identify specific nutrient deficiencies. Appetite loss and anorexia can be determined employing malnutrition questionnaires like PG- SGA (Patient Generated-Subjective Global Assessment), MNA (Mini-Nutritional Assessment), MST (Malnutrition Screening Tool) and MUST (Malnutrition Universal Screening Tool) during patient interaction sessions. Intake data and anorexia assessment will help the practitioner recognize the underlying causes (like nausea, stomatits, mucositis, diarrhoea, constipation) contributing to reduced food consumption. Among inflammation markers, C-reactive protein (CRP) is the most widely accepted marker and modified Glasgow Prognostic score (mGPS) is the most acceptable scale. Inflammation impacts survival and cancer related symptoms. European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 can estimate patients psychological and social functioning (Fearon *et al.,* 2011; Martin, 2016).

2.3 Pathophysiology of cancer cachexia

Nutritional status of patients suffering from cachexia is negatively impacted due to tumour induced alterations in metabolism during cancer (DeWys, 1986). Pro-cachectic factors including proteolysis inducing factor (PIF) and lipid mobilizing factor (LMF) are produced by the tumour cells whilst the production of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin - 1

(IL-1), interleukin – 6 (IL-6) and interferon –gamma (IFN-y) are the hosts' inflammatory tumour presence response. The cytokines are released by the lymphocytes and macrophages of the host immune system. Serum cytokines TNF-α, IL-1 and IL-6 levels correlate with progression of a few tumours. These cytokines inhibit lipoprotein lipase, which in turn restricts fatty acid storage by adipocytes. LMF production promotes lipid breakdown from body fat stores (Tisdale, 2009). TNF-α, IL-1, IL-6 and IFN-y have been shown to activate cancer induced muscle wasting. PIF and pro-inflammatory cytokines lead to protein breakdown by activating the ATP ubiquitin-proteasome proteolytic pathway contributing to muscle atrophy (Acharyya and Guttridge, 2007). During cancer cachexia, reduction in muscle protein synthesis is related to elevated levels of serum PIF. The body's response to cytokine-derived inflammation is called acute phase protein response (APPR). Increased resting energy expenditure is due to extended APPR which further leads to weight loss. During APPR, protein synthesis in the liver is altered as albumin production is substituted by C-reactive protein (CRP), fibrinogen, serum amyloid A, 2-macroglobulin and α-1 antitrypsin production. Released cytokines TNF-α and IL-1 are responsible for loss of appetite and anorexia. Disease progression influences hypothalamus functioning. The cytokines act upon the hypothalamic areas of the brain which control food intake. As fat stores are reduced during cachexia, serum leptin levels decrease which lead to suppression of appetite. IL-1 affects food intake by reducing neuropeptide-Y levels (appetite stimulant) in the hypothalamus (Tisdale, 2009). Cachexia, therefore is related to a set of cytokines and other cachectic factors responsible for wasting. Imbalance between protein catabolism and anabolism aids muscle wasting during cachexia syndrome (Figure 2.3-1).

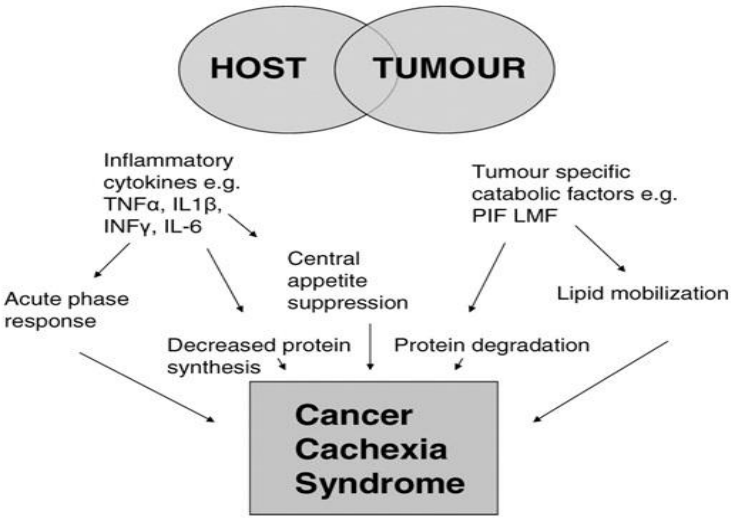


Figure 2.3-1: Pathogenesis of cancer cachexia (Gordon *et al.*, 2005).

Hypercatabolism as a result of systemic inflammation can be measured by assessing serum CRP levels. Serum CRP levels have been correlated to rate of weight loss, onset of cachexia and progression of cancer. Elevated CRP levels (>80mg/L) have been associated with increased mortality risk among cancer patients (Suzuki *et al.,* 2013).

Modified Glasgow prognostic score (mGPS) is a cancer prognostic marker composed of CRP and serum albumin levels. According to mGPS, patients with elevated CRP (>10mg/L) are allocated score of 1, while those with both hypoalbuminemia (serum albumin < 35g/L) and raised CRP are allocated a score of 2 (Table 2.3-1). mGPS is associated with length of survival, skeletal mass index, weight loss, dietary intake, performance score and treatment complications (McMillan, 2013).

Table 2.3-1: Modified Glasgow prognostic scores (mGPS)

mGPS	**Points allocated**
CRP (≤10mg/L) and serum albumin (≥ 35g/L)	0
Elevated CRP (>10mg/L)	1
Elevated CRP (>10mg/L) and hypoalbumenia (serum albumin <35g/L)	2

2.4 Malnutrition and assessment among advanced cancer patients

Malnutrition is prevalent in 40%- 80% of oncology patients worldwide (Paccagnella *et al.,* 2011; Kumar *et al.,* 2010). Multiple factors lead to malnutrition among cancer patients, such as disease progression, therapy side-effects like altered taste perception and emotional changes. Malnutrition results in delayed response to therapy among cancer patients, low quality of life, higher healthcare cost and poor survival rate (Lee *et al.,* 2016). Head and neck cancer patients in eastern part of India have reported high prevalence of malnutrition (76.9%), as well as over 80% of gynaecological cancer patients in western part. (Bhattacharjee *et al.,* 2015; Das *et*

al., 2014). Among advanced cancer patients malnutrition is a strong predictor of morbidity (Lis *et al.,* 2012) (Figure 2.4-1).

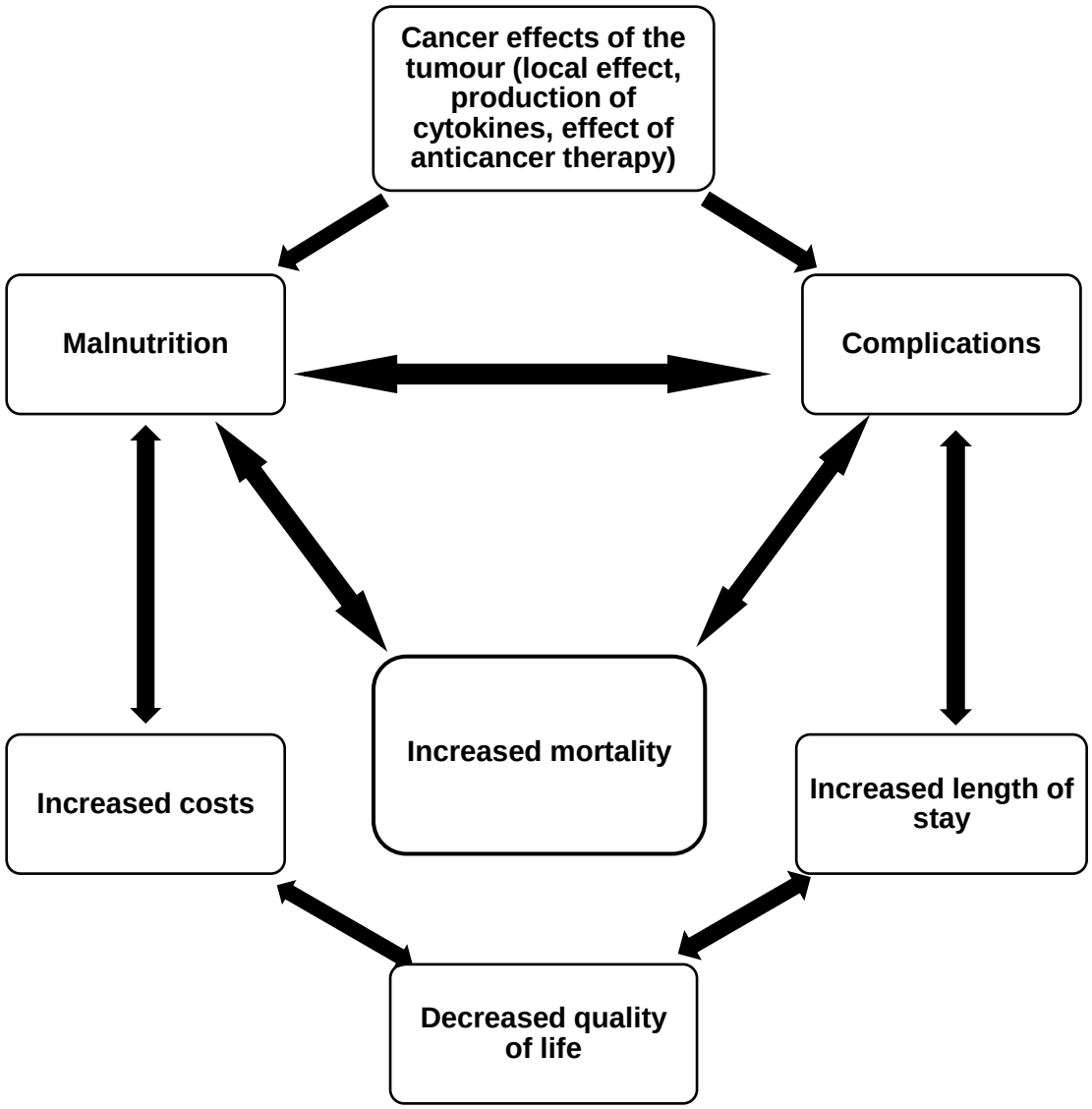


Figure 2.4-1: Flowchart showing mutual relationships between malnutrition, cancer and clinical outcome (adapted from Henry, 2011, p 65).

Body mass index (BMI) less than 20Kg/m^2 is a marker for undernutrition. Presence of oedema or ascites should be assessed before interpreting patient BMI as it may mask the presence of undernutrition, by an increased body weight due to water retention. Upper arm anthropometry is an easy clinical tool to measure skeletal muscle store and has been documented to be less prone to oedema (Richardson and Davidson, 2015, p.194). Sarcopenia (depletion of skeletal muscle) is diagnosed according to established cut-off points (below the 5th percentile for healthy adults).

Using anthropometry, upper-arm muscle area, sarcopenia is identified in men with measurement less than $32cm^2$ and in women less than $18cm^2$. By DEXA, appendicular skeletal muscle index in sarcopenia in men is less than $7.26Kg/m^2$ and in women it is less than $5.45Kg/m^2$. Using BIA, sarcopenia can be defined by whole body fat-free level of less than $14.6Kg/m^2$ in men and in women less than $11.4Kg/m^2$. With the help of CT imaging, lumbar skeletal muscle index of less than $55cm^2/m^2$ in men and less than $39cm^2/m^2$ is categorized as sarcopenia (Fearon *et al.,* 2011).

Prognostic Nutritional Index (PNI) and Nutritional Assessment Index (NAI) are widely used in oncology settings among adults to identify risk of malnutrition (Bhatacharjee *et al.,* 2015). Patient-generated subjective global assessment (PG-SGA) is a nutrition status assessment tool based on the dietary intake, weight change, functional ability, symptoms and physical observation validated for use in cancer patients. On assessment, patients are categorized as well-nourished, moderately malnourished or severely malnourished. A numerical PG-SGA score is calculated, with higher scores indicative of nutritional status decline (Ottery,1996).

Serum albumin is a protein marker and an indicator of amount of lean muscle tissue. It is commonly used to assess patient nutritional status and disease progression. As cancer progresses, patients nutritional status deteriorates and inflammation increases which leads to suppression in albumin synthesis (Gupta and Lis, 2010).

Among oncology patients, undernutrition is often overlooked, despite its high prevalence relationship with treatment outcomes. It should be addressed at the earliest opportunity with the help of dietician assessing malnutrition stage, counselling session to design an individualized nutritional plan according to their food pattern and introducing ONS (Oral Nutrition Supplement) intake daily in addition to normal diet if required. Consulting healthcare professionals should also provide encouragement to the patient, supporting their dietary changes (Lee *et al.,* 2016).

2.5 Symptoms due to disease progression and anti-cancer treatments in advanced cancer

Symptom management has an impact on patients' quality of life and their nutritional status. Optimal symptom management and maintaining patients' independent functionality should be the main focus of the palliative therapist.

Fatigue is commonly reported among chemotherapy and radiotherapy patients. Fatigue is present along with other symptoms like anorexia, nausea, vomiting, dyspnoea, insomnia, anxiety and depression (Yennurajalingam and Bruera, 2015, p. 410). Free-living advanced cancer patients reported significant association between fatigue, anorexia and anxiety (Rhondali *et al.,* 2012).

Changes in food preferences and decline in food intake causes emotional strain between advanced cancer patients and caregivers. Female caregivers express their care for the patient by preparing and serving food. Family members feel rejected by the patient when food is refused. Unnecessary pressure on patient to consume food sometimes becomes a barrier to food intake (Amano *et al.,* 2016).

Cachexic patients frequently experience muscle weakness which leads to increased dependence on the caregiver for basic day-to-day activities. These patients experience psychological distress in the form of anger, frustration, uncertainty, fear, desperation and helplessness. They suffer from social loneliness due to wasted appearance and inability to consume their food (Cooper *et al.,* 2015).

Cancer patients experience chronic pain and opioid therapy is recommended. Opioid induced constipation has been reported by 40% - 80% cancer chronic pain patients on morphine therapy. Constipation negatively affects patients' quality of life (Datto *et al.,* 2016). Opioids such as morphine have significant effects on the reticular system and are capable of inducing sedation, cognitive changes, and fatigue in some patients. In addition, anxiolytics, hypnotics, and other drugs may cause sedation and fatigue (Yennurajalingam and Bruera, 2015, p. 420). The most common opioid-related adverse effects include constipation, sedation, confusion, and hallucinations (Alexander *et al.,* 2016).

2.5.1Chemotherapy and radiotherapy as cancer medical treatment

Anti-cancer treatments like chemotherapy and radiotherapy have a negative impact on patients' nutritional intake. Chemotherapy drugs are known to induce gastrointestinal difficulties like nausea, vomiting and anorexia leading to a decrease in the quality of life. Patients undergoing radiotherapy (depending on treatment site) experience several side effects. Head and neck cancer patients receiving radiotherapy suffer from anorexia, ulceration, xerostomia, mucositis and hypogeusia, while abdomen and pelvis cancer patients experience anorexia, nausea, ulceration, vomiting, diarrhea and enteritis post radiotherapy. These symptoms therefore hinder maintenance of patients' nutritional status (Suzuki *et al.,* 2013).

Immunosuppression among cancer patients due to disease or therapy increases their risk of infections and recovery time. In patients with cancer, myelosuppression due to therapy drugs, excessive bleeding, nutritional deficiency and haemolysis leads to anaemia (Yennurajalingam and Bruera , 2015, p. 416).

2.6 Nutritional requirements of advanced cancer patients

Palliative patients frequently complain of early satiety on consumption of low gastric volume foods. Along with low functional ability, their hunger is lost and diminishes nutrient utilization (Richardson and Davidson, 2015, p. 195).

Kumar *et al.,* (2010) observed a calorie deficit of approximately 250-400 kcal/d among weight losing patients suffering from cancer cachexia. To replete or stabilize skeletal muscle wasting it is advised to maintain protein intake between 1-1.5g/Kg/day (Baracos *et al.,* 2015, p.712).

Research has shown that weight maintenance can be attained at 34kcal/Kg body weight/d (Lundholm *et al.*, 2004), another intervention study has documented that weight stabilisation can be achieved at energy intake of 28.7kcal/Kg body weight/d and protein intake of 1.4g/Kg body weight/d (Bauer and Capra, 2005). Increased

calorie intake by oral nutritional supplements or enteral feeds in patients undergoing oncological treatment has resulted in decreased incidence of complications. (Bozzetti and Mori, 2009).

According to recommendations for cancer patients undergoing chemoradiotherapy by the French Speaking Society of Clinical Nutrition and Metabolism, all patients should undergo nutritional assessment using PG-SGA malnutrition tool at each visit. Undernourished or at-risk patients are recommended to visit nutritional experts and receive counselling session. ONS can be prescribed if necessary. Dietary planning should fulfil energy requirements of 30–35 kcal/Kg/d and protein of 1.2–1.5 g/Kg/d (Senesse *et al.*, 2014). A recent paper by the Italian Society of Medical Oncology suggested that malnutrition among oncology patients should be treated at priority level with structured recommendations from oncologists and nutrition experts. The main aim of nutritional support should be to compensate deficient nutrient intake and improve nutritional status as well as clinical outcomes for every malnourished cancer patient (Caccialanza *et al.*, 2016).

Physical activity is recommended in the management of cancer cachexia. It may boost the immune function and improve quality of life (Ardies, 2002; Radbruch *et al.,* 2010). There are no specific nutritional and physical activity requirements drafted for Indian advanced cancer patients.

Dietary assessment and tailored nutrition advice from a trained dietician can benefit weight losing cachexic patients (Baracos *et al.,* 2015, p.712).

2.7 Multimodal therapy treatment for cancer cachexia

A multimodal therapy approach is considered the most effective for management of cachexia patients. This involves nutritional support (oral nutritional supplement intake), oncological management, anti-inflammatory and anaemia therapy, encouraging physical activity, and multidisciplinary team work approach in order to improve health status of the patient (Fearon, 2008) (Figure 2.7-1).

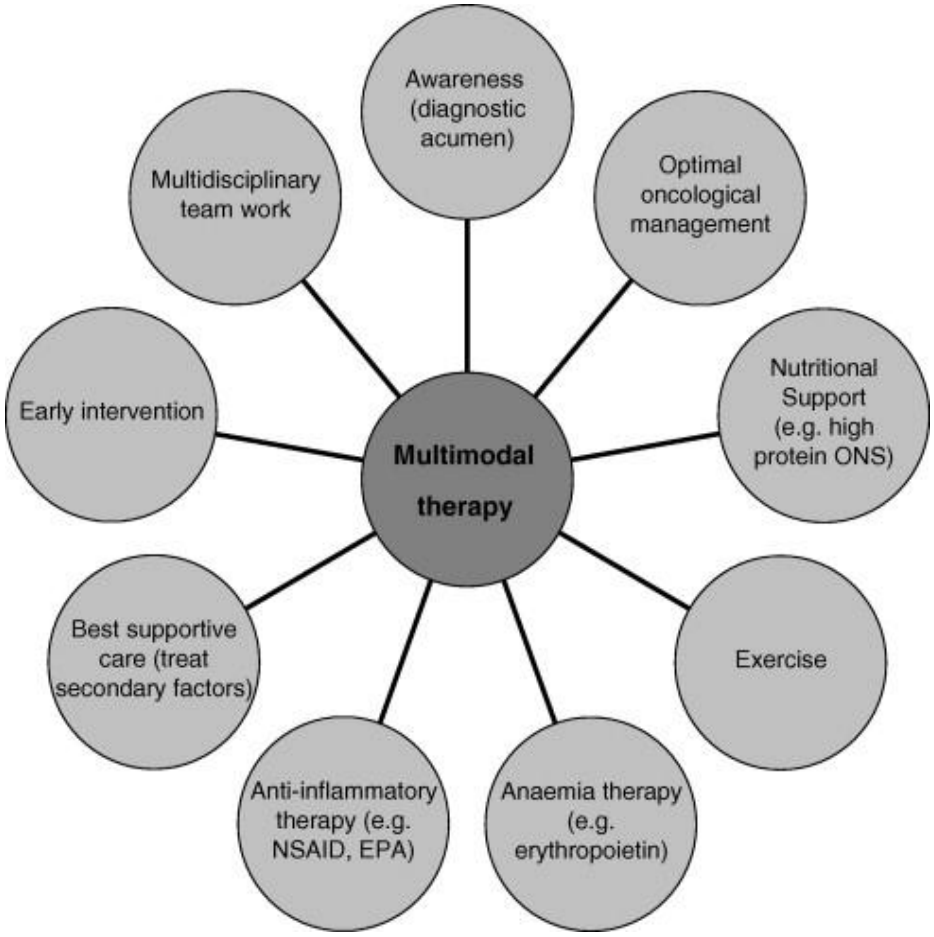


Figure 2.7-1: Multimodal rehabilitation for cancer cachexia (Fearon, 2008).

An individualised treatment approach using a combination of pharmacological and non-pharmacological interventions should be planned for cachexic patients. Expert inputs from a team of dieticians, occupational therapists, psychologists, social workers and nurses in addition to treating oncologist and palliative physician will optimally benefit the cachexic patient. Exercise, nutritional, anti-inflammatory and anti-cancer treatments form the basic components of multimodal cachexia therapy (Del Fabbro, 2015).

A randomized controlled trial incorporated five different arms of treatment including progestational agent in arm one, oral nutritional supplement including EPA in arm two, L- carnitine in arm three, Thalidomide as arm four for its anti-inflammatory property and arm five was a combination of all the four arms. Patients belonging to arm five after four months of treatment performed the best. These patients reported significant increase in their lean body mass, reduction in resting energy expenditure (REE), improvement in appetite and performance status compared to patients of arm 1, 2, 3 and 4 (Mantovani *et al.,* 2010). Multimodal therapy intervention was more effective among advanced gynaecological cancer patients than megestrol

acetate intervention. Patients receiving multimodal therapy for four months reported better QoL and reduced inflammation and oxidative stress than the group receiving megestrol acetate (Maccio *et al.,* 2012). A review by Madeddu *et al.,* (2012) concluded that multimodal intervention is more effective than individual drug or supplement approach for the management of cancer cachexia.

MENAC (Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia) is a multi-centre multimodal intervention ongoing trial since 2014. Advanced cancer patients undergoing chemotherapy are recruited and the effect of multimodal intervention will be studied with the help of parameters such as body weight, muscle mass and physical activity (Karra, 2014).

Every treating oncologist ideally aims at reversing body weight loss and muscle wasting in a cachexic patient however a realistic goal of weight maintenance and symptom control should be the objective. (Suzuki *et al.,* 2013). We therefore propose a nutrient rich natural food (IAtta) intervention along with counselling which has shown weight maintenance in small number of cachexia free-living patients and quality of life improvement (Kapoor et al., 2016)

2.8 Nutritional counselling and supplementation in advanced cancer patients

Nutritional managment is an essential part of palliative care and enhances QoL and patient nutritional status. Decline in nutritional intake leads to fatigue, weight loss and poor functional ability. The dietician has the burden to design tailored nutritional plan keeping in mind patients' diesase trajectory and therapy symptoms (Richardson and Davidson, 2015, p. 192).

Dietary counselling sessions aid the dieteician in understanding patients nutritional difficulties, their requirements and limitation to adhere to drafted nutritional plans. Building a relationship with the patient using good communication skills during consultation sessions results in setting realistic nutritional goals and educating them. Promoting patient and carer involvment during dietary planning may lead towards a tailored efficient care stratergy (Richardson and Davidson, 2015, p. 198).

Oral nutritional supplements (ONS) are intended to be added to patients respective daily diet (Table 2.8-1). Most commonly ONS are administered in liquid form providing 1.5kcal/ml and 0.6g/ml of protein per serving (200-250ml). Compliance with ONS intervention is often poor but has improved in the recent past (Richardson and Davidson, 2015, p. 194). Palliative care patients have often complained of changes in taste and smell. It is therefore advised to offer ONS in different flavours and forms to improve compliance. Daily normal food should be presented in an attractive fashion, small portion size with increased nutrient density and modified consistency (Richardson and Davidson, 2015, p. 194). Advising frequent, small, energy and protein dense snacks will give more food options than ONS prescriptions (Baldwin, 2015).

One literature review has pointed out that dietary counselling in advanced cancer cachexic patients can impact energy intake and body weight (Balstad *et al.,* 2014). A recent systematic review by Lee *et al.*, (2016) on nutritional interventions in cancer patients concluded that nutritional counselling with or without ONS intake improved their nutritional status, reducing malnutrition levels. Nutritional counselling maintained body weight, BMI and PG-SGA change. Studies involving only ONS interventions had insignificant and low improvement in weight gain, BMI and PG-SGA levels among malnourished ancer patients, while a meta analysis by Baldwin *et al.,* (2012), which included 13 RCTs involving malnourished cancer patients, concluded that there was no statistically significant relationship between synthetic ONS intervention and body weight gain. Another review by Baldwin and Weekes (2012) conlcuded that malnourished cancer patients gained more weight on receiving dietary counselling and ONS compared to patients on usual care.

Table 2.8-1: Literature review on oral nutritional supplement (ONS) intervention studies in advanced cancer patients during the last five years (2010- 2015)

Author	Intervention	Variables	Outcome
Dewey *et al.,* (2015)	SG – Prosure (ONS containing EPA) CG – Ensure plus (ONS) Intervention continued for 2 months	Body weight, and QoL	Stabilization of weight loss in both group (p= 0.48) and longer survival in SG (three times longer than CG, p=0.09). No significanct diffrence in QoL between groups after intervention (p = 0.46).
Sánchez-Lara	SG: Protein rich ONS	Body weight, fat	CG had significanct

et al., (2014)	containing n-3 fatty acids Prosure CG- Follow a diet based on 1400-2200Kcal Intervention for 6 months	mass, lean body mass, CRP, serum albumin, EORTC-QLQ30C	weight loss (p<0.001) while body weight maintained (p=0.523) in SG patients. CRP decreased significanctly (p=0.02) in SG and maintained in CG patients. Significanct improvment in global health status, appetite, fatigue (p<0.05) while CG reported no differences after intervention.
Poulsen *et al.,* (2014)	SG: Nutrition counselling. Protein rich ONS containing n-3 fatty acids Forticare offered to palliative oncology patients receiving chemoradiotherapy CG- Nutritional counselling by nurses Intervention up to 3 months	Body weight, nutritional status, dietary intake, QoL	No significant improvment between groups at the end of intervention period. QoL no significant difference between the groups. SG had significant higher energy and protein intake daily compared to CG patients at the end of intervention.
Percival *et al.,* (2013)	SG – Nutrition counselling. Energy and protein rich ONS supplied to malnourished or patients at risk of malnutrition CG- Not includded Intervention for 1 month	Body weight and survival	Body weight was stable in 27%, increased in 42% and decreased in 31% of enrolled patients post intervention. Two third of patients body weight stabilized or increased after one month. No diffrence was observed in survival rate (p= 0.16)
Yeh *et al.,* (2013)	SG: EE- ONS enriched with omega-3 fatty acids, micronutrients and probiotics. Group 1 with BMI<19Kg/m2 (n=12). Group 3 with BMI>19Kg/m2 (n=18). CG: oral nutritional formula Isocal Nestle (doesn't contain Omega 3 and probiotics)	Body weight, BMI, serum albumin & pre albumin	SG group with BMI<19Kg/m2 significantly improved body weight and maintained higher serum albumin & pre-albumin compared to CG (p<0.05).

	Group 2 with BMI<19Kg/m2 (n=20). Group 4 with BMI>19Kg/m2 (n=18) Intervention for 3 months		
Ravasco *et al.,* (2012)	SG1: Nutritional counselling SG2: ONS intervention CG: Standard care Intervention continued for 5 years	Weight, PG-SGA, QoL	Nutritional status was maintained in group SG1 while SG2 and CG had severe detoriation in their nutritional status ($p < 0.002$). Intake was lower in SG2 and CG group compared to SG1($p = 0.001$). QoL scores of SG1 were higher/better than SG2 and CG ($p<0.002$).
Weed *et al.,* (2011)	Prosure - EPA-containing ONS Intervention for average 11+0.85 days. (n=38)	Body weight, lean body mass.	At the time of discharge patient showed significant ($p<0.01$) increase in lean body mass.
Baldwin *et al.,* (2011)	G1: no intervention (n=96), G2: dietary advice (n=90) G3:nutritional supplement Scandi shake or Calshake (n=86) G4: dietary advice plus supplement (n=86) Intervention period 1Year	Weight, Hand grip strength, EORTC C30 for QoL.	Significant weight gain ($p=0.002$) from baseline to 12 weeks, independent of nutritional intervention and group allocated. QoL & Hand grip strength no significant difference between group.
van der Meij, B *et al.,* (2010) and van der Meij, B *et al.*, (2012)	SG: Prosure ONS energy and protein dense with EPA+DHA (n=20) CG: Ensure without EPA and DHA Intervention 5 weeks (n=20)	BMI, FFM, MUAC, C Reactive Protein, Serum albumin, leucocytes, serum TNF, serum IL-6. EORTC and physical activity.	SG had better weight and FFM maintenance than CG ($p<0.05$). SG had a greater MUAC than CG but not significant. C-reactive protein, serum albumin, serum TNF, serum IL-6 levels were not different in both the group during

	Period of intervention 5 weeks		intervention. SG tended to have higher level of physical activity after 5 weeks (p=0.05) compared to the CG. Quality of life parameters were noted to be significantly higher (p= 0.04) in SG compared to CG
Trabal *et al.,* (2010)	SG: Prosure ONS energy and protein dense with EPA+DHA and dietary counselling (n=5). CG: Dietary counselling (n=6). Period of intervention 12 weeks	Weight, serum protein, QoL by EORTC QLQ-C30	SG reported statistically significant (p= 0.045) weight gain compared to CG. No significant change in plasma protein and QoL parameters.
van den Berg *et al.,* (2010)	SG – Nutrition counselling. Energy and protein rich ONS supplied if daily diet did not meet intake goals. CG - Standard care. ONS advised when intake was insufficient Intervention for 2 months	Body weight, Malnutrition (assessed by % body weight loss)	SG reported significant decrease in weight loss comapred to CG (P=0.03).Malnutrition level decreased in SG and increased in CG (P=0.02)

(SG= Supplementation group, CG= Control Group, EPA= Eicosapentaenoic acid, DHA= Docosahexaenoic acid, SFT= Skin fold thickness, FFM= Fat free mass, TNF= Tumour necrosis factor, IL-6= Interleukin-6, EORTC-QLQC30= European Organisation for Research and Treatment of Cancer-Quality of Life, QoL= Quality of Life, PG-SGA: Patient Generated - Subjective Global Assessment, SGA= Subjective Global Assessment)

A number of intervention studies have shown a beneficial effect of n-3 fatty acid like eicosapentaenoic acid on advanced cancer cachexia patients, but according to a systemic review by Ries *et al.,* (2011), there is a lack of evidence to support n-3 fatty acid supplementation in cancer cachexia patients. EPCRC guidelines for cancer cachexia patients also state that, there is limited evidence to demonstrate the advantage of n-3 fatty acid administration in advanced cancer patients (Radbruch *et al.,* 2010).

Patient tailored nutrition intervention has resulted in a favourable treatment response among advanced cancer patients. A patient specific nutritional intervention (TiCaCo) under the supervision of trained dieticians and nutritional care experts was tested for 12 months on cachectic malignant patients. According to each patients' calculated energy expenditure, calorie intake goals were finalized. The personalized dietary plan consisted of meals providing 30–35% fat (maximum 10% saturated fat), 50–55% carbohydrates, 10–15% protein and minimum 30 g of dietary fibers daily of the total calories aimed. After the intervention period, patients receving dietary plan had a weight gain of 1.29 ± 3.76Kg while the control group patients (receiving standard hospital care) had lost 5.8Kg. Unexpected hospitalization among control group patients was significantly longer than patients from the nutrition therapy group (37.6 vs. 3.4 days) (DeWaele *et al.,* 2015). Cong *et al.,* (2015), tested a similar approach and planned a nutritional intervention along with dietician and nurses for advanced cancer patients receiving anti-cancer treatment. Nutritional goal set for the study group patients was, energy 30-35kcal/Kg, protein 1.5g/Kg, fat 1.3g/Kg and carbohydrate 3g/Kg per day while the control group patients were treated by physicians (ONS was prescribed if requiered). Nutriitonal status of study group patients' was better compared to control group patients (Pre-Albumin, transferrin and albumin significant difference between group, $p=0.001$, $p<0.001$, $p<0.001$ respectively). Study group patients' maintained their body weight throughout treatment ($p=0.412$) while the control group patients' body weight reduced ($p= 0.001$) (Cong *et al.,* 2015). A diet plan was designed according to an east Indian dietary pattern consisting of local foods providing 2906Kcal, carbohydrate 434g, protein 133g and 81g fat daily for 1 year or until chemoradiotherapy was completed by study group patients (head and neck). Control group patients received a similar dietary plan providing 2104kcal, carbohydrate 380 g, protein 77.7 and 31.6 g fat daily. At the end of intervention period the study group patients had gained 3.5% body weight, protein levels

improved by 33.33% and 45% reported good nutritional status (NAI assessment). SFT improved in both groups on completion of intervention (Bhattacharjee *et al.,* 2015).

According to Prado *et al.,* (2013), if nutritional intervention is introduced in early stages of cachexia it can aid in building body stores. During this observational study, CT images of advanced cancer patients from the start of the treatment until death were studied. Continuous loss of muscle and adipose tissue was observed and the patients were progressively catabolic closer to the time of death (catabolism level increased from 9 month to 1 month before death). Muscle gain was noticed in patients with stable disease or responding to therapy, as well as with symptom improvments during treatment. Increase in skeletal muscle was noticed in few patients within a year before death. Therefore, if nutritional support is rendered to advanced cancer patients during the initial phase of disease (before 90 days of death) anabolism will help in delaying cachexia progression (Prado *et al.,* 2013).
In a community setting with minimum availability of resources, nurses can identify and assess cancer patients suffering from malnutrition as well as provide advice on high energy and protein foods as part of essential dietary counselling (Gillespie and Raftery*,* 2014).

2.9 Advantages of physical activity for advanced cancer patients

In the recent past, palliative cancer patients were advised rest by recommending physical inactivity to reduce energy expenditure (Oechsle *et al.,* 2011). Ambulatory advanced cancer patients have reported average reduction of 40-50% of their physical activity level (Baracos *et al.,* 2015, p.713). Cancer- related fatigue (CRF) is commonly reported among advanced cancer patients. More than 80% of patients receiving anticancer therapy have experienced CRF (Alexander *et al.,* 2016).

The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as follows: ‘Cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning’ (Berger *et al.,* 2010) (Yennurajalingam and Bruera, 2015, p.

410). NCCN recommends activity enhancement as part of non-pharmacological management of CRF.

According to Clinical Practice Guidelines on Cancer Cachexia in Advanced Cancer Patients by the EPCRC (2010), physical activity is strongly recommended in the management of cancer related cachexia. It may help to boost the immune function and suppress inflammatory responses (Ardies, 2002). This could also aid in slowing down decreased physical function and improve quality of life (Radbruch *et al.,* 2010). Lowe *et al.,* (2012) reported a positive association between physical activity and quality of life among fifty advanced cancer patients attending an out-patient palliative care clinic in Canada. Palliative chemotherapy patients have also demonstrated better QoL, with physical activity levels of nine hours or more per week (Oechsle *et al.,* 2011). A systematic review has reported physical activity (walking and cycling) could reduce CRF in patients undergoing treatment for cancer (Cramp and Daniel, 2012). Another systematic review focusing on lung cancer patients recommended CRF screening for all lung cancer survivors and supported exercise intervention for CRF management (Paramanandam *et al.,* 2015).

A study on 188 advanced palliative cancer patients who were enrolled under a 12-week physical activity program (mainly walking) observed strong improvement in fatigue levels and maintenance in body weight (Gagnon *et al.,* 2013). Group exercise session among palliative cancer patients involving physiotherapists, social workers, dieticians, nurses, social workers and physicians was introduced for eight weeks. After completion of the program, patients reported improvement in their nutritional status, symptom severity, performance status, fatigue and physical activity level (Chasen *et al.,* 2013). Advanced cancer patients attending palliative care clinics were recruited for a two month physical activity program involving walk test and grip strength assessment. Following completion of program, patients reported significant improvement in their performance status (walk test), hand grip strength and body weight compared to the patients receiving standard treatment (Oldervoll *et al.,* 2011).

Advanced cancer patients undergoing chemotherapy were enrolled in a supervised multimodal exercise training program for six weeks while the control group patients received conventional medical care. At the end of training, participating patients had

significant improvement in their muscular strength, oxygen consumption, fatigue, physical functioning and emotional well-being (Adamsen *et al.,* 2009).

Breast and colon cancer patients undergoing chemotherapy and receiving supervised physical activity experienced improved fatigue levels, muscle strength, physical functioning as well as less vomiting and nausea (Waart H *et al.,* 2015).

Chemoradiotherapy negatively impacts the oxygen transport cycle in the body and therefore hampers oxygen transport. Head and neck cancer patients on anticancer therapy undergoing six week structured exercise training with walking improved their functional capacity. Exercise improves oxygen transport in the tissues, thus improving function of the peripheral muscles by increasing muscle oxygen uptake. Quality of life improved for these patients while functional capacity decreased by 18% among control group patients who were on standard treatment plan (Samuel *et al.,* 2013).

Performing traditional breathing Yoga exercises (Sudarshan kriya and pranayam) daily for 20 minutes among advanced breast cancer survivors has shown to be helpful in reducing stress and pain perception (Kumar *et al.,* 2013).

Due to fatigue and loss of muscle mass the patients become isolated and experience frustration. Patients therefore should be counselled regarding role of physical activity in correcting muscle wasting. Patients should maintain their routine of household activities and aim for daily walking. Individualised exercise plan from a physiotherapist can further benefit patients (Baracos *et al.*, 2015, p.712). Currently physical activity is overlooked within the palliative health care system in India**.**

2.10 Quality of life of patients living with cancer

Quality of life (QoL) covers multidimensional measures related to health, disease and medical therapy. In palliative medicine QoL is associated with symptom control, physical function, social functioning and psychological fulfilment, existential and spiritual domains (Kassa and Loge, 2015, p.1201). QoL is a patients' view regarding their health according to their satisfaction. Different dimensions of QoL are

dependent on setting/surroundings they are based on, symptom severity, disease coping ability, spirituality, etc. Patients QoL has an impact on their daily activity performance, ability to pursue work and interpersonal relationships (Lis *et al.,* 2012).

To assess QoL among palliative cancer patients, disease specific instruments have been developed like EORTC- QLQ- C30 and Functional Assessment of Cancer – General Version (FACT-G). These instruments cover aspects of physical and social functioning as well as symptoms. According to EORTC, core QLQ-C30 questionnaire can be supplemented with cancer site specific questionnaires. EORTC QLQ C30 is frequently used in Europe while FACT-G is used in the United States. World Health Organization Quality of Life Assessment instrument (WHOQOL) consists of five domains using 100 items (of physical and psychological health, independence levels, social functioning, spirituality and environment). WHOQOL is a generic instrument and therefore in palliative care cancer studies EORTC- QLQ and FACT- G are preferred (Kassa and Loge, 2015, p.1203). Few other QoL assessment tools are Functional Living Index cancer questionnaire (FLIC), Spitzer Quality of Life Index (QLI), Rotterdam Symptom Check List (RSCL), the Medical Outcome Study, 36-item short form (MOS SF-36), EuroQol (EQ-5D), the Cancer Rehabilitation Evaluation System (CARES) and the Symptom Distress Scale (Kapoor *et al.,* 2016).

Studies reveal the following:
The functional domain and symptom scale (loss of appetite and dyspnoea) showed association with ONS intake in malnourished cancer patients (Baldwin *et al.,* 2012). Observations of malnourished cancer patients suggests decline in quality of life with body weight loss (Thoresen *et al.,* 2012; Wallengren *et al.,* 2013). Weight loss greater than 10% has been significantly associated with decreased global QoL, increased fatigue and pain. Nutritional status is positively correlated with QoL. (Lis *et al.,* 2012).

2.11 Dietary pattern of Indians

In India, only 30% of the population lives in urban areas while 70% resides in the rural part. Compared to other countries, the proportion of Indians living in the rural part is the highest in the world (Goss *et al.,* 2014).

Dietary pattern in India is dependent upon the religious and cultural practices as well as family values. The majority of the people in India are vegetarians (10% - 62% for different states). The vegetarian diet consists of variety of vegetables, roots and tubers, fruits, cereals and pulses served with curries using spices and seasoning. Vegetarian diets are low in protein, zinc and vitamin B12 content (Shridhar *et al.,* 2014). Diets also depend on local food availability and agricultural practices (Green *et al.,* 2016). Indians consume home cooked meals three times a day. Among the rural population the food take away concept is uncommon. Women are more likely to be vegetarian compared to men (except in northeast India) (Arnold *et al.,* 2009). In India, the traditional flat bread 'Chapatti' is consumed daily approximately by 50% of urban and rural people along with curry (Bansal *et al.,* 2010). It is made of whole wheat flour, which is called Atta. Cereal and millets form the bulk in rural population diets (National Nutrition Monitoring Bureau, 2012).
According to dietary intake Indian Migrant Study survey (Satija *et al.,* 2015) carried out among factory workers, cereal based diets consisting of whole grains and rice served with potato and other vegetables was the most common. Snacks, milk and its products, nuts, chutney or pickles along with meals was also consumed. The other two patterns observed were, western cereals along with vegetables, fruits and milk products and a pattern based on animal foods. On studying dietary patterns among different regions of India it is seen that meat and fish consumption is popular in East and South part compared to North and West. Also, populations living in North and West part had fruit, vegetables, rice and pulses in their diets while sweets and snacks were common in East and South India (Green *et al.,* 2016). A recent study carried out in the northern part of India among urban low-middle socio-economic adult females also observed that more than half of their study population practiced vegetarianism. Their diet mainly consists of cereals, pulses, roots and tubers (Agarwal and Varma, 2016).

There is a need to develop a natural nutritional supplement meal that can be prepared with minimal training at home using locally available sustainable ingredients. Such a meal can help correct nutritional deficits and improve treatment outcomes among poor cancer patients (Kapoor *et al.,* 2016).

2.12 Nutritional status of Indian adults

The National Nutrition Monitoring Bureau (NNMB) survey (2012) studied the diet and nutritional status of rural Indian population. Intake of green leafy vegetables, milk and milk products and sugar was 50% less than the recommended dietary allowance (RDA) in more than half of the households. Except thiamine, median intake of all other nutrients was lower than the RDA among households. Intake of riboflavin and Vitamin A was less than 50% of RDA by 50%-81% of the households. Adequate intake of protein and energy was 63% among adult males and 71% for non-pregnant and non-lactating adult females. Prevalence of energy deficiency (BMI < 18.5) was noticed in 35% of the adults. Protein intake was 47g/d and energy was 1787 kcal among all Indian households, lower than the recommended amount of 60g/d and 2320kcal/d respectively. Household survey concluded that the average consumption of pulses and legumes was about 31g/d, lower than the suggested level of 40g, in most of the States, while green leafy vegetables and other vegetables consumption was very low at 18g/d and low at 46g/d compared to recommended 40g/d and 60g/d respectively. Except the western state of Gujarat, all states reported low average consumption of milk and its products at 85ml/d compared to the suggested value of 150ml/d. Among micronutrients intake, calcium was 331mg/d, iron 12mg, Vitamin A 124microgram/d, riboflavin 0.8mg/d, Vitamin C 29mg/d and folate 118microgram/d was lower than the recommended intake (National Nutrition Monitoring Bureau, 2012).

Average cereals and legumes intake among non-pregnant and non-lactating adult female was 341g and 28g per day respectively; this is lower than the recommendation. These females reported reduction of 500kcal/d intake and 13g/d of protein intake over a four decade period. Decline in intake of cereals, milk, sugars and nuts was also noticed, while micronutrient intake was less than 50% of RDA among most of them (National Nutrition Monitoring Bureau, 2012).

The survey concluded that there was inadequate intake of energy and proteins and the diet was also severely deficient in iron, riboflavin, folic acid and Vitamin A among the Indian rural population (National Nutrition Monitoring Bureau, 2012).

A study of non-pregnant and non-lactating adult female residing in Rajasthan (northern state of India) assessed the dietary intake using dietary recalls and food

frequency questionnaire. They found 70% of their participants consumed less than 1900Kcal/d along with low (30% less than recommendation) consumption of fruit, green leafy and other vegetables. Therefore, low (22% - 57% of RDA) dietary intake of iron and folic acid was observed, leading them towards anaemia. (Agarwal and Varma, 2016).

2.13 Tailored Food Recipe (TFR) concept for nutrition sensitive intervention

The phrase “Let food be the medicine and medicine be the food” by Hippocrates coined centuries back is the approach nutritionist as well as food scientists are following today. Nutrients in natural foods are bound to plant organelle matrix influencing its digestion and absorption in the gastrointestinal tract. Therefore, methods to deliver natural food to the body in order to maximize the healthy effect of exsisting bioactive compounds within the plant matrix, requires inputs from a team of food scientists, nutritionists, engineers, medical researchers and psychologists. Bioavailability can be defined as nutrients consumed which are accessible and available to support bodily physiological processes or stored in fat cells. Determination of nutrient bioavailability is important while selecting ingredients for development of food recipes to provide health benefit. Basic food processing like grinding and mild heat treatment degrade the food matrix, improving nutrient availability (Sensoy, 2014).

Scientific combination of selected, commonly consumed food ingredients can improve the nutritive value of formulated product known as tailored food recipes (TFR) (Amlogu *et al.,* 2011, 2012, 2013, 2014 a and b, 2016). A TFR can be defined as “a blend of locally available, affordable, culturally acceptable and commonly consumed foodstuffs mixed proportionately, drawing on the ‘nutrient strengths’ of each component of the mix in order to optimise the nutritive value of the end-product without the need for fortification” (Amuna *et al.,* 2004). Nutrients in food naturaly interact with each other and may improve their absorption and impact bodily functions (Zotor *et al.,* 2006, 2015).

Nutrition sensitive intervention works on similar concepts. Designing a nutrition-specific optimum mix of foods to target malnutrition among poor populations can address food security. Nutrition sensitive intervention meals have the potential to

address global malnutrition as well as support the development of enterprises (small and medium-sized) (Ruel *et al.,* 2013).

The TFR and nutritional sensitive intervention concept aims to improve nutritional status in resource-poor environments with limited local food ingredients and to develop a recipe for multiple uses such as health maintenance and therapeutics (Zotor *et al.,* 2015).

Amtewa meal (TFR) has shown delay in progression of human immunodeficiency virus (HIV) to acquired immune deficiency syndrome (AIDS) in Nigerian palliative patients. Patients consuming the meal daily for six months had better nutritional status and improved immunological response at the end of the intervention (Amlogu *et al.,* 2014). Therefore, it is an established fact that TFR (based on Amtewa meal composition) has a positive impact on health status of undernourished immune suppressed palliative patients (Amlogu *et al.,* 2011, 2012, 2013, 2014 a and b, 2016).

2.14 Palliative care for Indian cancer patients

The World Health Organisation (WHO) defines palliative care as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (WHO, 2007). It has been estimated that 80% of advanced cancer patients need symptom management and therefore palliative care plays an essential role in providing patients’ symptomatic relief (Ministry of Health and Family Welfare, 2012). Nine hundred and eight palliative care centres exist in India but 841 of them are based in Kerala (southern state of India). Kerala has incorporated palliative care policies and receives government funding to hold community based care programs. NGO’s in Kerala involve volunteers to provide home based care to palliative patients. After training, volunteers provide psychological, social and spiritual support to patients and their families. However, in the rest of India, majority of the population cannot access quality palliative care treatment, only 1% of suffering patients receive it (Ministry of Health and Family Welfare, 2012).

Studies have concluded that early introduction of palliative care along with anti-cancer treatment extends survival rate compared to patients receiving only anti-cancer therapy (Ministry of Health and Family Welfare, 2012).

Palliative care should be introduced into the cancer patients care plan early in the disease trajectory. For effective patient managment, palliative care should be initiated during diagnosis and continued during treatment and covers bereavement help to the family after patients' death (Ministry of Health and Family Welfare, 2012) (Figure 2.13-1).

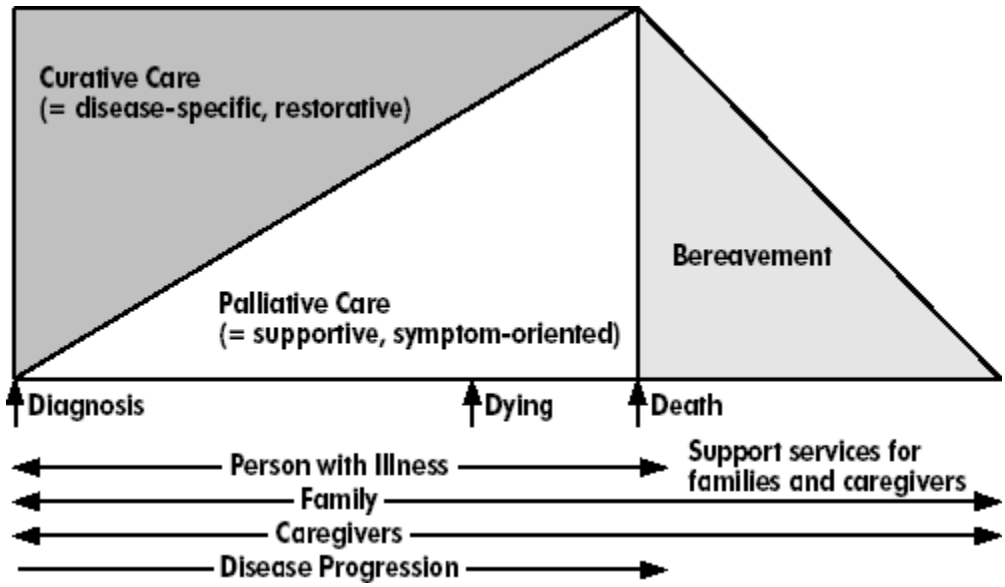


Figure 2.13-1: Cancer patient care model including curative and palliative treatment (adapted from Ferris *et al.,* 2009)

The Indian Association of Palliative Care was formed in 1994 in collaboration with WHO and the government of India. Their main aim is to provide care for patients suffering from life threatening end stage chronic diseases using a multidisciplinary approach and educating health care providers. Few non-profit government organization (NGO) run by volunteers, charities, fundraisers and patient payments are also involved in providing quality care to needy patients (Ministry of Health and Family Welfare, 2012). One such is Pallium India, established in 2003 providing palliative care in 11 states of India funded by National Rural Health Mission. They serve the rural population through community health centres' (Rajagopala, 2015). NGO's established in palliative care have considerable experience and could be used by government to spread awareness in the community (Ministry of Health and

Family Welfare, 2012). The Indian palliative care system involves occasional patient home visits, regular outpatient clinics and an established in-patient facility for severe symptom management. This cost-effective management was developed by Pain and Palliative Care Society (PPCS) and helps in reaching majority of the patients with the limited resources allotted by the Health Ministry (Rajagopala and George, 2015, p.14).

India lacks established guidelines for palliative care services, trained health professionals, training infrastructure, awareness and centres to provide quality treatment for end of life patients (Ministry of Health and Family Welfare, 2012). However, the palliative care manual by Ministry of Health and Family Welfare (2005) does mention general nutrition guidelines (merely six guidelines). There is lack of directions and specificity as regards to quality and quantity of macro and micronutrients to be provided for maintenance of palliative cancer patients' health status.

Palliative care should ideally work towards cancer prevention, early diagnosis and treatment for the suffering population. In a traditional society like India, family members are involved in caring for patients. Palliative care services should develop simple care guidelines to empower family members and caregivers for optimum patient management in the household setting. Developed care guidelines should be according to Indian cultural beliefs, involving family members and using sustainable resources (Rajagopala and George, 2015, p.13).

2.15 Justification of proposed study

The central and state governments spend less than 1.5% of its gross domestic product (GDP) on public health care. Development of better infrastructure and management in cancer care would be difficult if the central and state governments do not increase public health allocated budget and allowances. Increased expenditures on public health care should be India's national policy priority (Mallath *et al.,* 2014).

In spite of established guidelines for diagnosis of cachexia (by EPCRC) in cancer patients, these guidelines are not adopted by majority of the Indian public hospitals

and therefore the medical management of all cancer patients is not optimal. This is the impression one gets after visiting the various hospitals.

Despite, the endorsement of nutritional guidelines for cancer and undernourished patients by many international organisations, such as: ESPEN (Arends *et al.,* 2016; Arends *et al.,* 2006; Bozzetti *et al.,* 2009); NICE (National Collaborating Centre for Acute Care, 2006); ASPEN clinical guidelines in adult anticancer treatment (August *et al.*, 2009); EPCRC (Radbruch *et al.,* 2010); Australian guidelines for nutrition management of cancer cachexia in Adults (Bauer *et al.,* 2005) and SFNEP non-surgical anticancer treatment guidelines (Senesse *et al.,* 2014), the nutritional guidelines for Indian cancer cachexia patients are currently absent with no specific recommendations for free living cachexia patients. There is no such documentation available, hence this is being stated.

It has been documented that nutritional intake of cancer patients is calorie deficient and they suffer from micronutrient deficiencies (Balasubramaniyan *et al.,* 1994; Singh *et al.*, 2005; Goyal, *et al.,* 2006; Naidu *et al.,* 2007). In the absence of energy dense nutrient rich supplements in their diets, the nutritional requirement of these patients are not met and this puts them in jeopardy (Thoresen *et al.,* 2002). In spite of these known facts nutrition is ignored in the palliative care framework of Indian cancer patients.

Interventions with synthetic oral nutritional supplement (ONS) drinks (based on energy and protein dense supplemented with omega-3) among advanced cancer patients have shown body-weight gain, increased lean body mass and better quality of life (See table 2.8-1). However, scientific appraisal is required with respect to their bioavailability, sustainability, food security and suitability for vegetarians.

2.16 Originality of the research

Development of ‘Improved Atta’ of this current study is multidimensional. IAtta addresses the following issues:

Vegetarianism: The majority of Indian population is vegetarian, therefore it was important to include only vegetarian ingredients (for instance, the IAtta supplement

consisted of roasted horse gram, roasted barley flour, roasted soybean flour, amaranth spinosus and flax seeds in dry powder form). Most of the commercial ONS contain fish oils which is not acceptable among most of the Indian population therefore a vegetarian option for omega 3 fatty acids like flaxseeds (in IAtta), if added in diets of undernourished cancer patients is likely to improve their nutritional status.

Bioavailability: IAtta is made up of 100% natural local ingredients and therefore bioavailability will be higher than the commercial ONS (Buchman, 2006; Ball, 2006; Rude and Shils, 2006; King and Cousins, 2006; Wood and Ronnerberg, 2006).

Sustainability: All ingredients used in IAtta are locally produced and very easily available at most grocery stores in the urban as well as the rural areas. Commercial ONS are mostly available at urban pharmacy outlets, making it inaccessible for the rural patients.

Food security (local produce and readily available and low costs): Grains like barley and soybean, pulses like bengal gram, oilseed like flaxseed and amaranth green leafy vegetable are grown in most parts of India. As these products are produced in the country, it is quite affordable and available round the year in most grocery stores. Thus IAtta accessibility for patients from rural as well as urban background is feasible.

Cancer patients who are at nutritional risk have shown better quality of life when their diets are supplemented with ONS (Baldwin *et al.*, 2012). It has been suggested that advanced cancer patients receiving nutritional supplementation (along with exercise counselling) may improve physical strength (Payne *et al.*, 2013). In the Indian palliative care system, nutritional status of cancer patients is not usually assessed. Only hospitalised cancer patients have dietetic consultations. Doctors' advise patients, in a generic fashion, during consultation merely to eat healthy food and frequent meals. If nutrition (i.e. counselling and intervention program) is added to the multi-dimensional approach to treat palliative cancer patients in India, they are likely to experience better QoL and be less dependent on the caregivers.

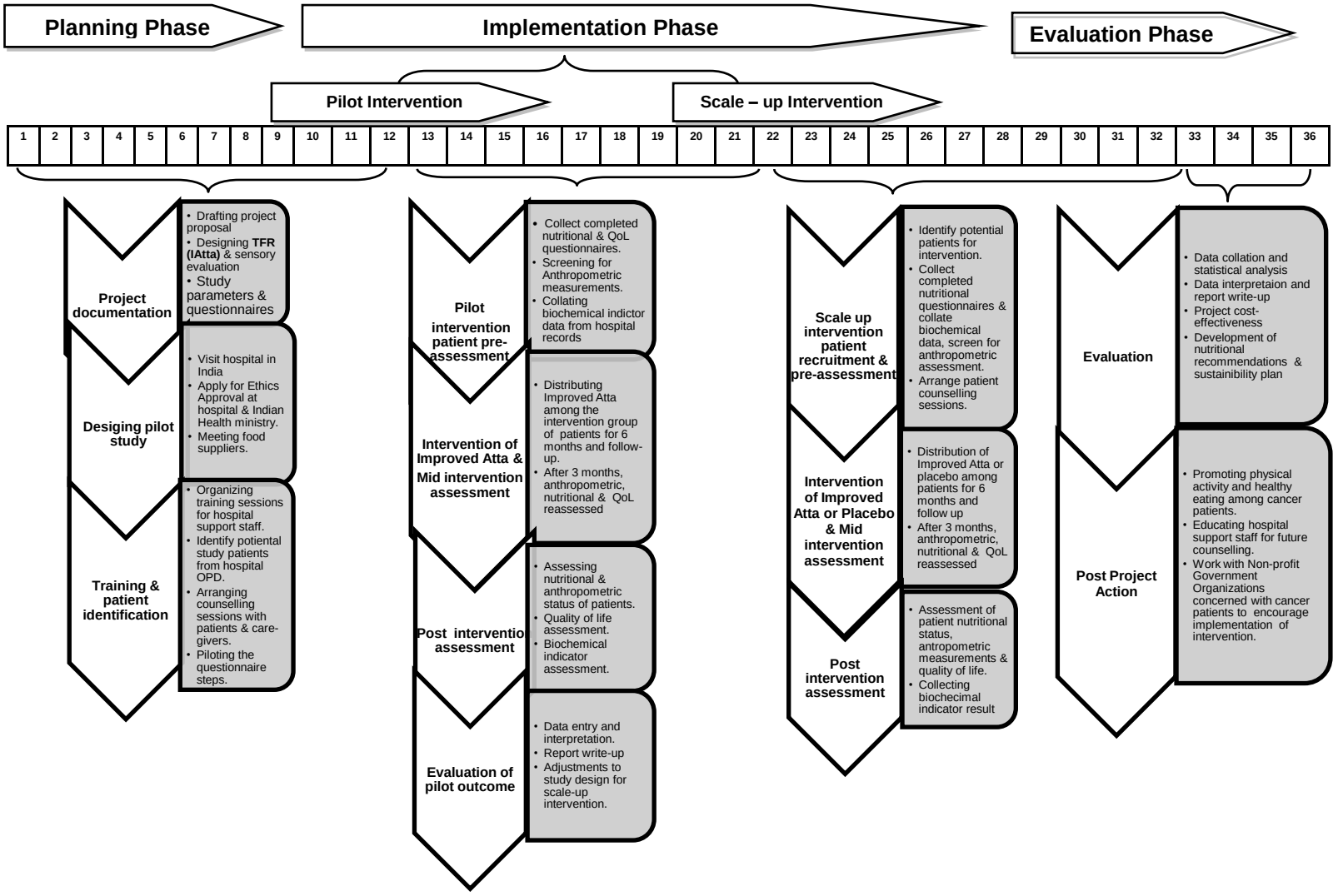
Chapter 3:

Subjects, Materials and Methods

3.1 Introduction

In this prospective randomized controlled nutrition intervention we recruited female free-living cancer cachexic patients who were attending the palliative care clinic for symptom management. Patients with weight loss of more than 5% from pre-treatment weight or BMI less than 20 Kg/m^2 along with haemoglobin level less than 12g/dl and energy intake of less than 1500kcal/d were considered eligible for participation. Patients with gastrointestinal tract disorders, on anabolic steroids, taking synthetic oral nutritional supplements and with life expectancy of less than three months were excluded from participation. We developed a TFR acceptable by the Indian community and easy to prepare according to taste preferences for correction of patients' nutritional status. The intervention was carried out at Dr. BRA Institute Rotary Centre Hospital (Dr BRAIRCH), All India Institute of Medical Sciences (AIIMS), New Delhi, India. The pilot study was carried out between December 2013 and August 2014 and scale-up study between April 2015 and May 2016. Out-patient department (OPD) palliative cancer patients visit Palliative Care experts every fortnight for treatment. During the consultation session the treating Palliative Care Anaesthetist counsels every patient personally to eat small healthy frequent meals and consume pain medication as directed. Patients' nutritional status assessment and Nutritionist/ Dietician counselling session is absent.

3.2 Conceptual framework



3.3 Description of study setting

All-India Institute of Medical Science (AIIMS) was created in 1956 in New Delhi, India. The institute provides comprehensive facilities for teaching, research and tertiary patient-care. It caters to millions of underprivileged Indians who are unable to afford quality healthcare treatment. The study was undertaken at Dr. B.R.A. Institute Rotary Cancer Hospital (IRCH), AIIMS and it is one of the main hospitals providing palliative care to cancer patients in central India. Advanced cancer patients attend Pain and Palliative Care OPD at IRCH, AIIMS every fortnight for regular consultation with the doctor and collect pain medication. During the consultation session the treating Palliative Care Anaesthetist counsels every patient personally to eat according to their food preferences and consume pain medication as directed. Dietician consultation is available only for patients admitted for surgery in the Palliative Care ward.

3.4 Description of Target Population

Females are considered as the inferior sex in the Indian society. Low literacy levels, higher death rate as compared to men and lower sex ratio are the evidence of their lower status in society. The Indian National Nutrition Monitoring Bureau 2012 survey revealed low dietary intake (i.e. 1709kcal/day) among rural and tribal (non-pregnant and non-lactating) women, reflecting poor nutritional status. Energy deficiency among tribal and rural females was 56% and 36% respectively (Roa *et al.,* 2010; Arnold *et al.,* 2009). Half of urban Indian females have been reported to be suffering from anaemia and chronic energy deficiency (Athreya *et al.,* 2010). Also, due to existing traditional and cultural norms in the Indian society their health status is becoming worse, with limited access to healthcare (Roa *et al.,* 2010). The study was therefore designed to reach out and help adult cancer females of low socio economic status.

3.4.1 Sample size calculation for pilot study

The sample size for the pilot study was calculated using nMaster software (2.0 version), considering similar baseline weight in the two groups. After six months of intervention we expected a difference of approximately 10Kg of weight between the

intervention group and control group (i.e. at baseline mean ± SD body weights of both the groups will be 60 ± 15, while at the end of study, intervention group would be 65 ± 15 and control group at 55 ± 15). The study sample size was calculated as 72 with 36 patients per group, in order to study the impact of intervention. This sample size is chosen based on confidence interval (power) of 80% for allowable sample error (precision limit) of 5%, however due to low recruitment rate, the study commenced with total 63 patients.

3.4.2 Sample size calculation for scale- up study

Sample size for the scale up was calculated using nMaster software (2.0 version) to compare the difference in change in mean body weight between the two groups i.e. intervention and control group. Based on the initial observation (pilot project) on limited number of patients, mean ± SD change in body weight during the six months was observed as -0.5±1.5. To detect an improvement of minimum of 1Kg mean body weight as compared to the control group (i.e. mean ± SD in the intervention group as 0.5±2.0) with 95% confidence interval and 80% power we require 50 evaluable subjects in each of the two groups. Considering substantial drop-outs due to mortality and lost in follow-up, we enrolled 75 female cancer cachexia patients in each of the group. Thus, we enrolled 150 female advanced cancer patients in total for the study.

3.4.3 Recruitment of patient

Patients were recruited for pilot and scale up stage of study according to the inclusion and exclusion criteria. Prospective patients were screened and apprised about the study using patient information sheet (Appendix 1). Eligible patients were asked for consent (Appendix 2) and randomized equally into control and intervention group.

Inclusion criteria

- Female, age 18 years and above.
- Diagnosed with advanced cancer.
- Weight loss >5% from pre-treatment weight or BMI<20Kg/m^2.
- Haemoglobin level <12g/dl.
- Energy intake < 1500kcal/d (to be assessed on consultation).

Exclusion criteria

- Incapable to provide written consent.
- Patient diagnosed with refractory cachexia.
- Life expectancy < 3 months.
- Unresponsive to anti-cancer therapy.
- Patient is a pregnant woman or a nursing mother.
- Patient consuming commercial ONS.
- Suffering from secondary illnesses.
- Gastrointestinal tract (GIT) disease which affect nutrient absorption.

All cancer patients receiving chemoradiotherapy, able to consume food orally and digest were likely to be part of the study, subject to the above criteria.

However, the novelty of this project is that every patient on the project received tailored nutrition information from the nutritionist depending on their symptoms and dietary preferences.

3.5 Intervention process

Patients were allocated study codes and a randomisation sheet was generated by using nQuery software (7.0 version) for pilot and scale-up project phase.

Pilot Study: 123 female patients attending Palliative Care OPD were screened for eligibility and of them 63 were randomized equally into two groups i.e. control and intervention group. 30 patients were allocated in intervention group and received IAtta (100g) along with nutritional counselling and 33 patients were allocated in the control group who received only nutritional counselling (Appendix 3, Kapoor *et al*., 2014). Patients in the intervention group collected 14 packets of 100g of IAtta every fortnight during their OPD appointments while the control patients were advised regarding their dietary habits at every OPD visit for 6 months. The study was carried out between December 2013 and August 2014.

Scale-up Study: 329 female patients attending Palliative Care OPD were screened for eligibility and of them 150 were randomized equally into two groups i.e. control and intervention group. 75 patients were allocated in intervention group and

received IAtta (100g) while 75 patients were allocated in the control group and received whole wheat flour (100g, nutritive value table, Appendix 4) for daily consumption (Appendix 5). Patients collected 14 packets of 100g of IAtta/flour every fortnight during their OPD appointments at every visit for 6 months. The study was carried out between April 2015 and May 2016.

Key aspects of the nutritional counselling sessions

Patients were strictly advised to discard any of the dispensed leftover at the end of the day. Adherence to IAtta and flour (during scale-up phase) consumption was measured by patient (and/or caregiver) self–reporting. During follow–up counselling sessions, they were first queried about the number of packets left and accordingly given fresh packs to consume. Patients were advised to eat frequent homemade food. Dietary counselling for 30 minutes was imparted to all patients on each OPD visits by the researcher. Consumption of cereals, roots and tubers, vegetables, legumes, nuts, energy dense fruits, milk products (and eggs for non-vegetarians) was encouraged during these sessions. Weekly phone calls were made to each patient to enquire about their welfare and a manual record of the number of packets dispensed on each visit was recorded.

Depending on the physical status of the patients, low level of physical activity (walking and/or stairs) and participation in daily household chores was encouraged during counselling sessions.

Nutritional, quality of life and anthropometric estimation were assessed at baseline, after 3 months and at 6 months of intervention for all patients.

3.6 Research variables and key indicators

3.6.1 Quantitative variables

Anthropometric parameters: All anthropometric measurements were taken by the same trained investigator throughout the study. The investigator took extra care of the patient, considering their vulnerability while taking measurements. Body

weight and total body water was assessed using Tanita segmental composition scale (BC 545N, dual-frequency 50 kHz and 6.25 kHz). Height was measured using a non-stretchable measuring tape. Body Mass Index (BMI: Kg/m^2) was calculated using weight and height measurements. Mid upper arm circumference (MUAC) was measured using a non-stretchable measuring tape. Four site skin fold thickness (SFT) measurement (i.e. triceps, biceps, subscapular and suprailiac) by the help of scientific Harpenden Skinfold Caliper (0120 by Baty International) was noted to the nearest 0.2mm reading, to calculate percentage body density. Body fat percentage was calculated using body density value in Siri equation (Durnin and Womersley, 1974). Questionnaire used during study is attached as Appendix 6.

Nutritional status parameters: Dietary history was taken by one-to-one interview with the patient by the researcher. Portion size was recorded by showing sample vessels of different sizes (Appendix 7). The FFQ questionnaire consists of 184 commonly consumed food items and was validated among the rural and urban Indian population (Satija *et al.,* 2012) (Appendix 8). Data collected using FFQ was used to calculate the daily macronutrient intake of the patient. Two day 24-hour dietary recall (Appendix 9) data were analysed using DietCal software. DietCal- A Tool for Dietary Assessment and Planning software is based on book “Nutritive Value of Indian Foods” (Gopalan *et al.,* 2012). Patients’ daily energy, carbohydrate, protein and fat intake were calculated using FFQ and recall data. PG-SGA questionnaire (Appendix 10) has been recommended as the nutrition assessment tool for cancer patients by the Oncology Nutrition Dietetic practice group of the American Dietetic Association (McCallum, 2006). SGA questionnaire has been validated among Indian cancer patients to assess level of malnutrition (Shirodkar *et al.*, 2005). The PG-SGA score helped to monitor the deterioration or improvement of patient nutritional status throughout the study.

Physical activity level: Indian Migrant Study Physical Activity questionnaire (IMS-PAQ) was used to assess patients’ physical activity throughout the day (Sullivan *et al.*, 2012) (Appendix 11). Patients’ reported every activity performed with the average amount of time spent for each activity in the questionnaire filled in person. Metabolic Equivalent of Task (MET) was assigned to each activity performed according to Compendium of Physical activity (Ainsworth *et al.,* 2011). The MET in simple terms is energy cost of physical activities as a multiple of the resting metabolic rate. One MET is equivalent to resting metabolic rate of 1Kcal/Kg/hr (Ainsworth *et al.,* 2011), thereby we calculated the average kilocalories

spent by every patient in the whole day. Hence, we were able to estimate patients' total daily energy expenditure.

Biochemical parameters: Cancer patients undergo routine blood tests regularly at the AIIMS. Blood sample collection and laboratory assessment is performed by trained phlebotomist and laboratory technicians following strict aseptic procedures at AIIMS. Haemoglobin, serum albumin and serum CRP levels were planned to be assessed at the start and end of the study. During the pilot study phase, serum CRP analysis was not a routine test in the hospital and therefore patients were reluctant to have blood drawn for it. Therefore, haemoglobin and serum albumin levels were only available from hospital records for reference during pilot project phase. A few patients got their CRP levels assessed from different departmental laboratories within AIIMS at the start and end of the scale-up intervention phase on investigators request.

3.6.2 Qualitative variables

Quality of Life (QoL) assessment: EORTC-QLQ- C30 questionnaire was used to analyse patients' QoL after personal interview by the researcher (Fayers et. al., 2001) (Appendix 12). Translated version in Hindi was available from the official website. The questionnaire has been validated on Indian population (Bansal *et al.,* 2004; Chaukar *et al.,* 2005; Parmar *et al.,* 2005; Mohan *et al.,* 2007; Madhusudhan *et al.,* 2009).The questionnaire consisted of 30 questions which were divided into five functional scales: physical, role, cognitive, emotional, and social; eight symptom scales: fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, loss of appetite, constipation, diarrhoea, global health status and financial status. A score was calculated for all the 15 domains.

3.6.3 Quality control of research variables

All consented patients were randomized according to their study codes into intervention and control group to remove bias. Patient randomization sheet maintenance and IAtta/flour distribution was done from PhD room by Rakesh Garg (RG) throughout the study and the nutritionist was therefore blinded. Patient

counselling was done in OPD by nutritionist without the knowledge of the group the patient belonged to.

After literature review, research variables were meticulously selected to study the multi-dimensional effect of IAtta on patient health status. Tanita segmental composition scale and Harpenden Skinfold Caliper were calibrated to zero before every measurement was performed. In order to minimize investigator error, all physical measurements were repeated thrice and were taken by the same investigator for anthropometric parameters. Though most of the questionnaires were self-reporting in nature but due to variation in education status and linguistic difficulties among study patient group, they were administered in the form of interviews by the nutritionist at all three time-points (baseline, mid–intervention and post-intervention). Hydration level of each patient was maintained using standardised procedure for optimum use of BIA throughout intervention process.

The above mentioned steps were taken to maintain accuracy in data collection and reporting throughout the study.

3.7 Statistical analyses

All statistical analyses were performed using SPSS software (version 20.0) under guidance of trained Biostatistician's at AIIMS.

Data was expressed as mean ± sd and median (min-max) for normal and skewed data respectively. Quantitative normal data were analysed by using Repeated Measures Anova followed by Bonferroni correction. Quantitative skewed and qualitative data was analyzed by using Friedman test followed by Wilcoxon signed rank test for multi–comparisons to determine the changes within the groups at different time points (i.e. baseline, mid-intervention and post-intervention). Student t-test/ Wilcoxon Ranksum tests were performed on the variables to assess the difference between the intervention and control group at baseline. P- value < 0.05 was considered statistically significant.

For the pilot study baseline parameters body weight, body fat, MUAC, energy intake, physical activity level, global health quality of life and fatigue domain were

adjusted to study the overall difference between groups by using generalized estimated equation (GEE). P-value ≤ 0.05 was considered statistically significant. Intention-to-treat (ITT) analysis was done in the scale-up study for the drop out patients.

Primary endpoints for both the studies were to improve patients' anthropometric status and quality of life. Secondary endpoints were maintaining physical activity, nutritional status and biochemical parameters.

3.8 Project monitoring and evaluation

Project was closely monitored at all stages from planning to evaluation phase. Ethics committee at UoW and AIIMS were consulted in study planning to ensure patient safety, addressing their requirements and considering their vulnerability due to the co-morbidities. Senior faculty at Pain and Palliative Care Clinic, IRCH, AIIMS were closely monitoring study implementation according to the proposed study design. They often held unscheduled patient interviews at OPD to ensure intervention compliance and IAtta/placebo flour acceptance. Patient data collection and storage was also reviewed by them.

Evaluation was divided into four stages: Formative, Process, Impact and Outcome.

Formative evaluation stage – Literature review during project planning phase highlighted that nutritional status of Indian palliative cancer patients is neither monitored nor addressed. Women, being considered the weaker sex in the Indian society (especially rural and tribal areas), were unable to access quality healthcare services. Once diagnosed with advanced cancer and understanding about limited survival time, their nutritional needs are further neglected.

Synthetic nutritional supplements are available in the Indian market but are unaffordable by the low socio-economic strata of the society. Therefore, a need for affordable, vegetarian (vegetarianism is practiced by most of the Indians); energy-protein dense food supplement was observed. AIIMS, providing good quality healthcare to the underprivileged people in central India was the preferred study setting.

Process evaluation stage – Patients attended the Palliative care clinic every fortnight for pain medications and were contacted by the project researcher during these sessions. A diary was maintained regarding their appointment dates and future treatment time plans. It was noticed initially that follow–up rate was falling and leading to dropouts. Thereafter, it was decided to collect two (mobile) contact numbers to remain in constant communication and their schedule for chemoradiotherapy was noted. Once a patient missed their Palliative clinic OPD appointment they were contacted and a counselling session was planned during chemoradiotherapy appointment at the hospital. If during the counselling session the patient mentioned they will be delaying their next appointment (i.e. next appointment after more than 2 weeks), they were offered to carry extra IAtta/ flour packets accordingly.

Impact evaluation stage – In the recruitment phase patient diet history and anthropometric measurements were documented. During each follow–up visit and telephonic communication a 24 hour dietary recall was undertaken by the researcher to understand their dietary intake. Also their body weight along with MUAC was measured and compared with the baseline (or last follow-up reading). Depending on these results further nutritional counselling session was carried out. All baseline parameters were assessed for both groups of patients after three months of intervention (mid-intervention period).

Outcome evaluation stage – At the end of intervention period (6 months of intervention), all baseline parameters were assessed to evaluate impact of IAtta supplementation, flour supplementation and nutritional counselling on intervention group of patients, while the effect of nutritional and physical activity counselling on control group patients was observed during study period. All patients were educated about inclusion of affordable nutritious food ingredients in their daily lifestyle and simple recipes to prepare them.

3.9 IAtta formulation and description

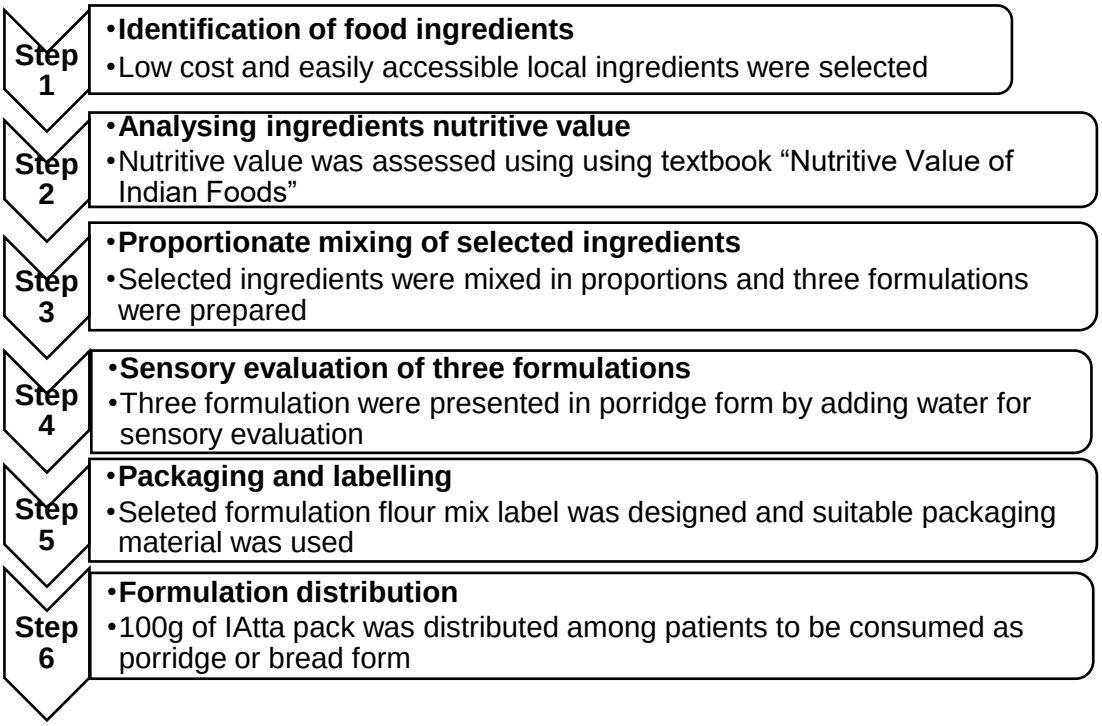


Figure 3.9-1. Stepwise description of IAtta product development

3.9.1 Indian dietary pattern and food secure commodities

Cereals and pulses consumed in flour form by the Indian population were nutritionally evaluated using the textbook "Nutritive Value of Indian Foods" (Gopalan *et al.,* 2012). Among various cereals and pulses listed in the book, wheat flour, barley flour, maize flour and chick pea flour is consumed by the Indian rural population either in the form of breads or porridge. Barley was chosen as the cereal for the formulation because of the high beta glucan levels (3-8 g/100g) and improved immune function efficiency (Arena *et al.,* 2014). Soybean is high in protein (43.2g/100g) and regarded as local food secure pulse (Gopalan *et al.,* 2012; Deshpande and Jha, 2014). According to the National Nutrition Bureau (2012), average Indian diets are low in protein hence soybean and chick pea were considered as potential ingredients for IAtta. Linseeds is the only vegetarian omega-3 source commonly available in Indian markets as well as consumed during winters in savoury items (with jagerry mixed as a sweet) (Joshi, 2009,p62). Among green leafy vegetables; spinach, fenugreek leaves, mustard leaves and amaranth leaves

are generally prepared in curry form and consumed with bread or rice as a meal (Hariprasad *et al.,* 2013). On nutritive value comparison between these leafy vegetables, amaranth leaves had higher amount of iron and Vitamin A and therefore were chosen as an ingredient for the formulation (table 3.1). Green leafy vegetables are consumed by all groups of the society and therefore affordable (Sindhu *et al.,* 2016).

Table 3.9-1: Literature review summary of potential food ingredients locally available in Indian food market place.

Potential IAtta Ingredients	**Roasted gram flour *(Cicer arietinum)***	**Maize flour *(Zea mays L.)***	**Roasted barley flour *(Hordeum sativum)***	**Roasted Soy flour (*Glycine max*)**	**Amaranth leaves (*Amaranthus spinosus*)**	**Spinach leaves *(Spinacia oleracea)***	**Fenugreek leaves (T. foenum-graecum)**	**Flax seeds *(Linum usitassimum)***
Rationale for inclusion & advantages	Affordable source of protein, folate, beta carotene and healthy fatty acids. (Jukanti *et al.,* 2012)	Low protein quality, vitamins and minerals. Good source of carbohydrate and polyunsaturated fatty acids. High in dietary fibre. Affordable cereal compared to wheat and rice (Shobha *et al.,* 2014)	Beta glucan in barley has shown immunomodulatory activity and enhances probiotic activity (Arena *et al.,* 2014).	Enhances the immune system. Soy isoflavons have antioxidant, estrogenic, anti-osteoporotic effect. Consists of total isoflavon 1021.5-1084.3 µg/g (Kumar *et al.,* 2010).	Reported for anti-inflammatory, anti-bacterial, immunomodulatory, antioxidant activity, anti-pyretic, laxative, high concentration of essential amino acid (Tanmoy *et al.,* 2014; Kumar *et al.,* 2010).	Good source of iron and calcium. High in dietary fibre. Contains phytochemicals reported for anti-microbial and anti-inflammatory activity. (Chaturvedi *et al.,* 2013)	Source of iron, silicon, and thiamine. Has hypoglycemic, and hypocholesterolaemic, effects, anti-inflammatory effects (Moradi and Moradi, 2013.	Rich source of alpha linolenic acid, soluble and insoluble fibers, phytoestrogenic lignans and antioxidants. Reported for anti-inflammatory, antifungal, anti-thrombic function (Goyal *et al.*, 2014). Consists of 23g of alpha linolenic acid (per 100g) and biological effect equivalent to 0.4g of long chain omega 3 fatty acids (Morris, 2008; Rodriguez-Leyva, 2010).

3.9.2 Nutritive value of selected ingredient undergoing TFR

The nutritive value of each ingredient was calculated using textbook “Nutritive Value of Indian Foods” (Gopalan *et al.,* 2012). The textbook contains detailed nutritional information of more than 600 Indian food items is and recommended by the Indian council of medical research (ICMR). The dietary fibre content was calculated using usda.gov database as they were unavailable in the textbook.

Each 100 g pack of TFR contained a mixture of roasted horse gram flour, roasted barley flour, roasted soybean flour, roasted flaxseed powder and dried amaranth spinosus powder (figure 3.9-1).

Figure 3.9-1: Tailored Food Recipe (TFR) ingredients

TFR proposed for intervention was named Improved Atta (IAtta). Atta is whole wheat flour in Hindi language. Indians make unleavened bread, sweet porridge as well as savouries using whole wheat flour. Therefore, we named our TFR, Improved Atta to gain patient acceptance and adapt into their dietary pattern. According to the patient preference the flour can be cooked and consumed by them, helping them in nutritional status correction. IAtta (100g/day) will help to meet the macronutrient demands as well as satisfy 30% - 50% of iron, calcium, and vitamin A RDA for adult Indian sedentary female (Department of Health 1991; Indian Council of Medical Research, 2009). IAtta is in line with TFR concept as a complete sustainable, socially acceptable, food secure meal for malnourished advanced cancer patients.

3.9.3 Food safety precautions concerning IAtta

3.9.3.1 Elimination of physical & biological contamination

Gram, barley, soybean and linseeds were first sieved, then physically sorted to remove physical contaminants, roasted to eliminate anti-nutrients and minimize micro-organism growth and then powdered. Thereafter stored in air tight plastic labelled containers, on a raised platform in the food storage room (Figure 3.9-2). Amaranth spinosus leaves were washed twice in potable water to remove excess dirt then vacuum freeze dried and stored in nitrogen gas filled sealed packs (of 1Kg each) to maintain product integrity. All ingredients included were in roasted and dried form to ensure longer shelf life.

3.9.3.1 IAtta dry mixing and packaging in septic environment

IAtta packs were prepared in the hospital kitchen every evening before the patients' appointment the next day. Utensils used during preparation and ingredient mixing were properly washed and disinfected before every use. Kitchen surface in contact with food was cleaned at initiation and adequate personal hygiene was ensured at all stages of IAtta preparation (figure 3.9-3). It was double packed using food grade plastic bags to eliminate moisture and pathogens. Each pack was labelled with use by date and batch number (figure 3.9-4). The caregiver was advised to discard left-over IAtta at the end of the day. Caregivers were counselled to transport the packs carefully, store it away from direct sunlight, protect from pathogens and moisture to avoid contamination making it safe for patient consumption.

Figure 3.9-2: Storage area for ingredients required for IAtta

Figure 3.9-3: Preparation of IAtta

Figure 3.9-4: Packed IAtta 100g (dry weight) food label of packed IAtta showing ingredients, batch number, expiry date and nutritional information

3.9.4 IAtta sensory assessment

Sensory evaluation for IAtta was done among twenty UoW students in the Nutrition laboratory. Three different combination formulations of IAtta (100g) were prepared by adding 20 g of sugar and 150 ml of cold water. The glasses containing the three formulations were labelled with three different coloured stickers and presented with a spoon to the students. Formulation 1(393 kcal/100g) was coded with an orange sticker, formulation 2 (396 kcal/100g) was coded with a green sticker and formulation 3 (398 kcal/100g) was coded with a blue sticker. A sensory evaluation form was distributed among them to complete (Appendix 13). Participants were asked to rate their formulation preferences on the hedonic scale and sip water in-between sample tasting. In total, 88% of the respondents disliked all the formulations, 4% liked formulation 2 and 8% liked formulation 3. IAtta formulation 3 was therefore finalised for the intervention but due to the low acceptance among the tasters it was decided to serve the formulation in a bread form. Unleavened flat breads (Chapattis, figure 3.9-5) were prepared by adding salt and spices and served to 8 UoW academic staff. All academics liked the chapatti and therefore it was decided that patients will be instructed to prepare fresh Chapattis from the IAtta pack.

Patients undergoing cancer therapy frequently complain about changes in taste perception (Steinbach *et al.,* 2009). Therefore, patients and their caregivers were advised to add spices and flavouring in the mixture while preparing IAtta chapattis. This leads to improvement in the appetite and meal acceptance level.

3.9.5 IAtta cost-effectiveness

To develop IAtta flour no sophisticated machinery or equipment was used. All the ingredients of IAtta are readily available in dried, roasted and powdered form in the local markets. Therefore, no prior complex treatment was required to prepare ingredients for the flour mixture. Household utensils like ladles, mixing bowl, kitchen scale and grinder were used to prepare the mixture before filling up 100g food-grade plastic packets of IAtta flour for distribution among patients. The total cost to procure 100g of IAtta flour pack for one patient was as low as £0.20/day.

Figure 3.9-5: Packed IAtta and unleavened bread made from IAtta.

3.10 Ethical Considerations

The project was approved by ethics committee of UoW (App. no.: 12_13_11) and AIIMS (IEC/NP-79/2013; IEC/NP-339/08.10.2014, RP-17/2015). Permission was also obtained from ICMR (IF-25/13-NCD-III) and Indian Health Ministry before starting patient recruitment on the project. The project is registered under ICMR registry and Indian Health Ministry. The project is in compliance with the ethical requirements as laid down by the ICMR. Both trials are registered on www.clinicaltrials.gov vide, identifier no. NCT02350855 for pilot and NCT02561143 for scale-up.

Before enrolment, all participants were explained the purpose of the study, the procedures to be followed and the risks and benefits of participation. A unique patient code was used throughout the study in place of patient name in order to maintain confidentiality. The personal details and medical history information were stored at a secure place. Patient anonymity and project confidentiality was maintained throughout the project. Participation in the project was voluntary and directed towards their welfare.

Chapter 4:

Results – Pilot Intervention

4.1 Introduction

Out of the 63 patients recruited for the study, only 51% of the recruited patients completed the intervention. There were no demographic or clinical differences among the patients who dropped out compared to the ones who finished the study (detailed consort diagram as Appendix 14). The mean consumption of *IAtta* flour among the patients who ended the study after six months of intervention was 45±11.26g/day. No side effects after consuming IAtta *chapattis* were reported by any patient.

4.2 Baseline patient characteristics

Patient baseline characteristics and tumour sites are included under Table 4.2-1 and Table 4.2-2 respectively.

Table 4.2-1: Baseline characteristics of all baseline patients

*Data presented as mean ± SD or median (range)

Baseline parameters	**Intervention group (n=30)**	**Control group (n=33)**	**p-value**
Anthropometric measurements			
Weight (Kg)	39.7 ± 5.7	41.1±7.3	0.402
BMI (Kg/m^2)	17.6 ±1.8	18.6 ±2.5	0.077
MUAC (cm)	20.8 ±2.1	22.2 ±2.4	0.49
Body Fat (%)	20.5±5.2	25.4 ±6.5	0.012*
Nutritional assessment			
Energy intake (kcal)	947.4 ± 327.9	756.7 ± 364.2	0.033*
Protein intake (gm)	30.3±12.0	23.3 ±12.6	0.03*
Fat intake (gm)	28.1±13.1	24.9 ±14.9	0.375
PG-SGA score	7.8 ± 2.2	9.4 ± 2.6	0.010*
Quality of Life Domains (Qualitative assessment)			
Global Health Status score	66.7 (16.7,83.3)	50 (8.3,100)	0.026*
Fatigue score	88.9 (0,100)	100 (0,100)	0.05*
Appetite loss score	66.7 (0, 100)	100 (0, 100)	0.047*

** In the table * denotes significant difference (p≤0.05).*

Table 4.2-2: Tumour site for the recruited study patients

Site of Tumour	Intervention Group	Control Group
Ano-rectum	3	2
Bone	1	2
Brain	0	1
Breast	7	7
Buccal cavity	1	1
Chest wall	1	1
Eyelid	0	1
Female genitourinary tract	12	10
Lung	2	4
Olfactory	1	0
Spine	1	0
Supra renal mass	0	1
Thyroid	1	3

4.3 Anthropometric measurements

4.3.1 Anthropometric results

Patients in the intervention group have shown increase in body weight but this was not statistically significant (p=0.081), while patients in the control group had shown statistically significant reduced body weight (p=0.003) and MUAC (p=0.006) at the end of the study period (6 months) (Figure 4.3-1 and 4.3-2). Body fat (p=0.002) increased significantly in the intervention group patients and decreased significantly (p=0.032) in the control group (Figure 4.3-3). Total body water content was comparable between patient groups at baseline, mid-intervention, and post-intervention (p=0.453, p=0.234, and p= 0.727, respectively) (Appendix 15, Kapoor *et al.,* 2016).

Adjusted analysis concluded significant difference in patients' percentage body fat among the groups (p value 0.001).

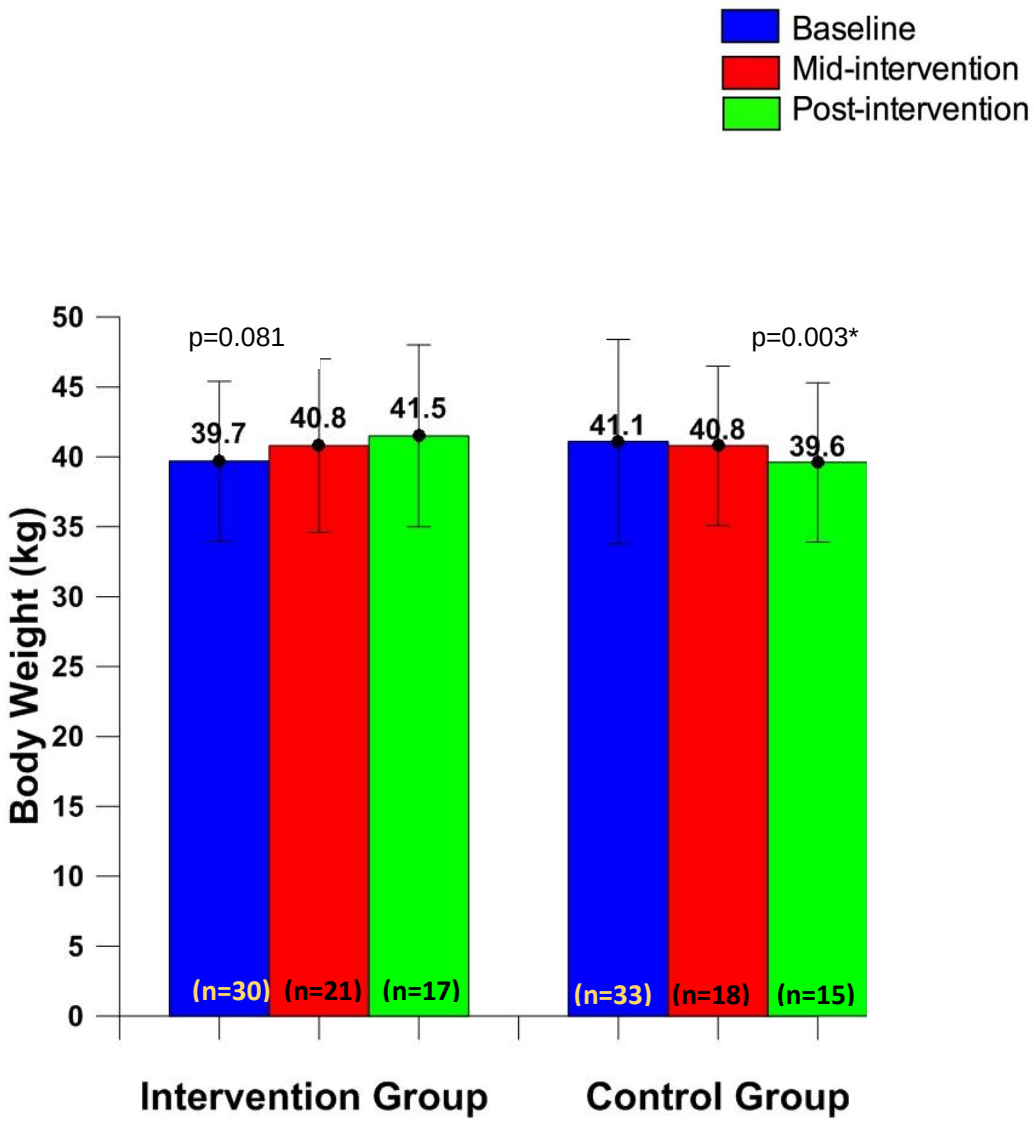


Figure 4.3-1: The bar graph depicts the body weights of patients during baseline, mid-intervention and post intervention.

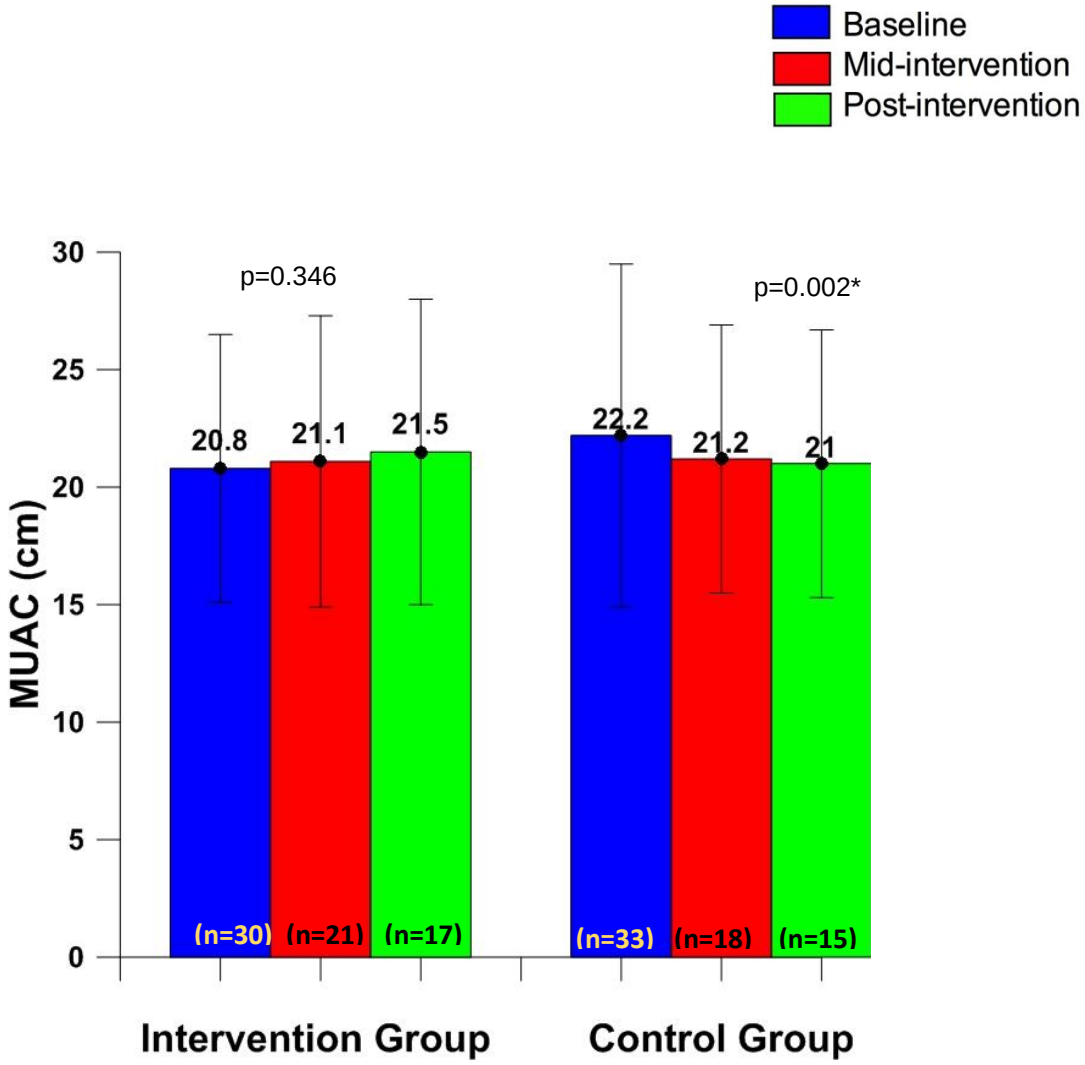


Figure 4.3-2: The graph shows MUAC of both group patients at different time points i.e. during baseline, mid-intervention and post intervention.

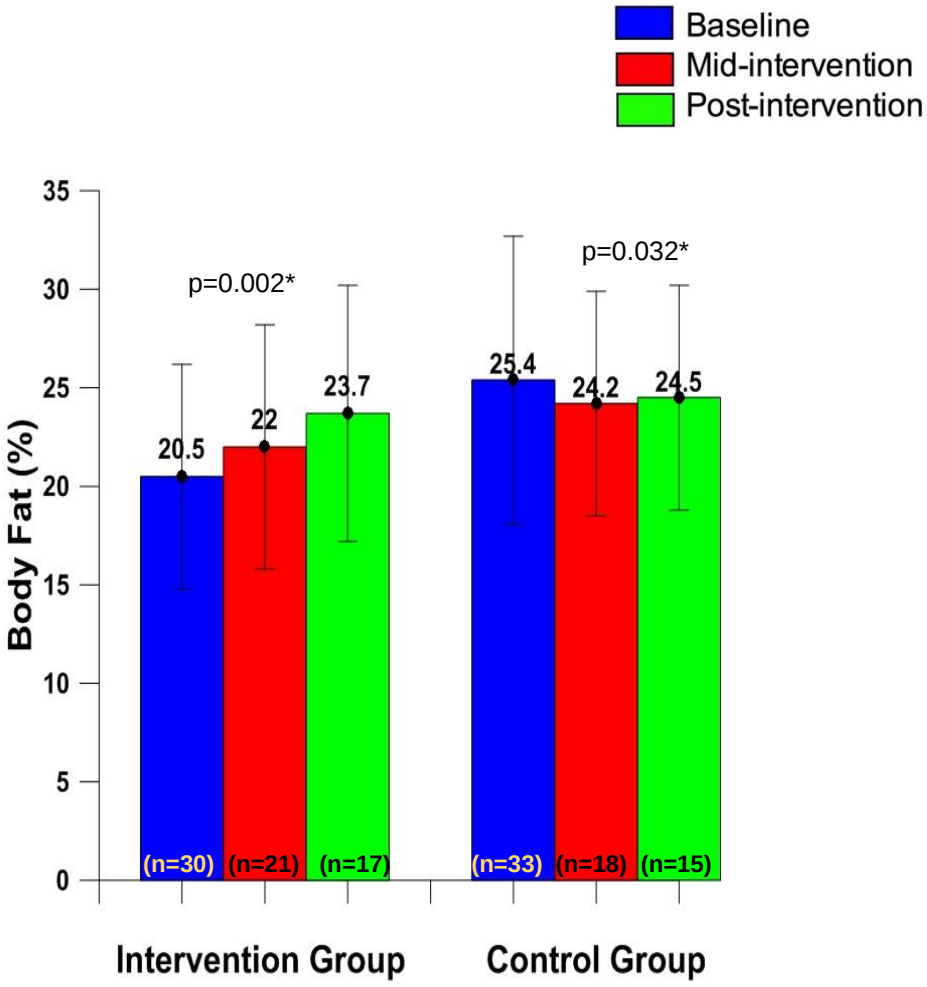


Figure 4.3-3: The graph shows change in % BF between the groups at baseline, mid-intervention and post intervention.

4.4 Dietary intake and nutritional status

At the end of six months significant increase in macronutrients intake i.e. energy (p=0.001), carbohydrate (p=0.001), protein (p=0.001), fat (p=0.006) was observed in the patients eating IAtta assessed using two days 24 hour dietary recall. Using FFQ intervention group patients also showed statistically significant increase in energy (p= 0.006) intake. There was no statistical difference in the PG-SGA score among both the groups during the study period. Baseline parameters on adjustment showed that there was a significant change in energy intake (p= 0.004, by dietary

recall) and PG-SGA score (p<0.001) during intervention (Appendix 15, Kapoor *et al.,* 2016).

4.5 Physical Activity Assessment

Physical activity recall showed significantly reduced activity (p= 0.004) among the control patients after 6 months of start of the study, while the intervention group of patients maintained (p=0.274) their physical activity levels throughout the study (Appendix 15, Kapoor *et al.,* 2016).

4.6 Quality of Life Parameters

Patients eating IAtta showed significant improvement in certain domains of quality of life like fatigue (p=0.002) and appetite loss (p=0.006). A significant decrease in quality of life domains of global health status (p=0.018) and social functioning (p= 0.004) was observed among control group patients. Both the groups reported significant improvement in pain [(p=0.012) in intervention group and (p=0.029) in control group].

On adjusting global health status and fatigue score at baseline, a significant difference in these parameters was seen during the intervention at three months and six months' time points (p <0.001) (Appendix 15, Kapoor *et al.,* 2016).

4.7 Biochemical Parameters Results

Among the employed biochemical indicators, haemoglobin (IAtta group p=0.368 and control group p=0.819) and serum albumin (only control group p=0.368 available), no statistically significant differences were observed within the control and intervention groups or between them.

4.8 Discussion

In the pilot study, IAtta meal supplementation along with nutritional counselling in advanced cancer female patients receiving palliative care improved their quality of life and stabilised body weight.

Patients consuming IAtta for the duration of six months showed clinically increased body weight (increase in body weight by 2.5%) (p=0.081) and body fat percentage (increased by 3.7%) (p=0.002) in contrast to the control group who showed significant reduced body weight (decreased by 8.71%) (p=0.003) and body fat percentage (decreased by 5.2%) (p=0.032). The increase in body fat would be desirable in cachectic patients to support high BMR due to disease progression (Young *et al.,* 1977; Dhanpal *et al.,* 2011). Also, in this study, patients among the control group had reduction of 14.4% of MUAC (p=0.002) at six months as compared to baseline.

The energy intake of all study patients at baseline was lower than the Indian adult female RDA (1900kcal/d) (Indian Council of Medical Research, 2010). There was no significant (p=0.735) change in the PG-SGA score of the intervention group patients at the end of intervention, which is similar to the pattern observed earlier in advanced colorectal cancer patients receiving ONS supplementation (Read *et al.,* 2007).

In advanced lung cancer patients, it has been suggested that exercise and nutrition intervention may have a positive impact on un-intentional weight loss and physical function (Payne *et al.,* 2013). The current study results are in line with the above studies, as patients eating IAtta maintained their body weight as well as physical activity levels. Also patients losing body weight (control group) showed reduced physical activity levels (baseline 30.7$\pm$2.7MET's and at six months 28.0$\pm$2.5 MET's) at the end of the study period.

Observations in malnourished cancer patients suggests decline in quality of life with body weight loss (Wallengren *et al.,* 2013; Thoresen *et al.,* 2012). A similar trend was observed in this study, patients eating IAtta exhibited improvement in fatigue (p=0.002) and appetite loss (p=0.006) domains while weight losing control group

patients declined under the global health status (p=0.018) and social functioning (p=0.004) domains.

4.9 Rationale for progression to scale-up study

Comprehensive nutritional support guidelines are currently absent in palliative care framework for cancer patients in India. The findings of this pilot study underpinned the pivotal role of nutrition intervention in palliative care management. Some employed parameters showed a positive trend, however these can be translated into significant improvement of body weight and quality of life when IAtta has been consumed for a longer period of time and applied to a larger sample. Therefore, these results qualify for a wider intervention study in adult female cancer patients. This will also help to understand the impact of IAtta in sustaining patients' daily lifestyle. Nonetheless, IAtta is a bio-available product and in-line with the Indian populations vegetarian food habit along with easy ingredient availability, it qualifies for an in-depth study on a wider population of cancer patients.

Chapter 5:

Results – Scale-up intervention

5.1 Introduction

One hundred and fifty patients were recruited for the study, only 39% of the recruited patients finished the intervention. There were no demographic or clinical differences among the patients who dropped out compared to the ones who finished the study (detailed consort diagram as Appendix 16). The mean consumption of *IAtta* flour and whole wheat flour (as *Chapattis*) among the patients who finished the study after six months of intervention was 45.4 ± 11.7g/day and 40.9 ± 18.1g/day respectively. No side effects after consuming IAtta or whole wheat flour *chapattis* were reported by any patient.

5.2 Baseline patient characteristics

Patient baseline characteristics and tumour sites are included under Table 5.2-1 and Table 5.2-2 respectively.

Table 5.2-1: Baseline characteristics of study patients

*Data presented as mean ± SD or median (range)

Baseline parameters	**Intervention group (n=75)**	**Control group (n=75)**	**p-value**
Anthropometric parameters			
Body weight (Kg)	43.3 ± 7.0	42.6 ± 7.1	0.589
BMI (Kg/m^2)	18.81 ± 2.82	18.86 ± 3.20	0.929
MUAC (cm)	22.12 ± 2.72	21.93 ± 2.71	0.677
Body Fat (%)	26.42 ± 5.68	26.65 ± 6.46	0.822
Physical activity assessment			
Physical activity (MET's)	29.67 ± 3.13	28.52 ± 2.03	0.013
Nutritional assessment			
Energy intake (kcal)	768.11 ± 372	688.66 ± 408.75	0.215
Protein intake (gm)	26.06 ± 14.38	21.90 ± 13.31	0.068
Fat intake (gm)	24.94 ± 17.28	24.38 ± 20.27	0.857
PG-SGA score	8.92 ± 1.96	9.25 ± 1.74	0.272

Quality of Life Domains (Qualitative assessment)			
Global Health Status score	29.23 ± 19.44	28.44 ± 19.04	0.804
Fatigue score	92.44 ± 14.86	92.74 ± 15.34	0.904
Appetite loss score	83.55 ± 29.19	86.67 ± 26.85	0.500

Table 5.2-2: Tumour site for the recruited scale –up study patients

Site of Tumour	**Intervention Group**	**Control Group**
Ano-rectum	8	3
Bone	2	6
Endocrine	7	7
Breast	15	10
Head & Neck	10	6
Female genitourinary tract	18	17
Lung	8	13
Other	7	13
Total	75	75

The baseline characteristics among both patient groups were similar for all key indicators. The p-value was non-significant ($p \leq 0.05$) for all anthropometric parameters, physical activity, dietary intake and quality of life domains when assessed at baseline.

Most of recruited patients were receiving chemotherapy and/or radiotherapy at our institute during intervention. Few patients were post-operative when they were recruited (Figure 5.2-1).

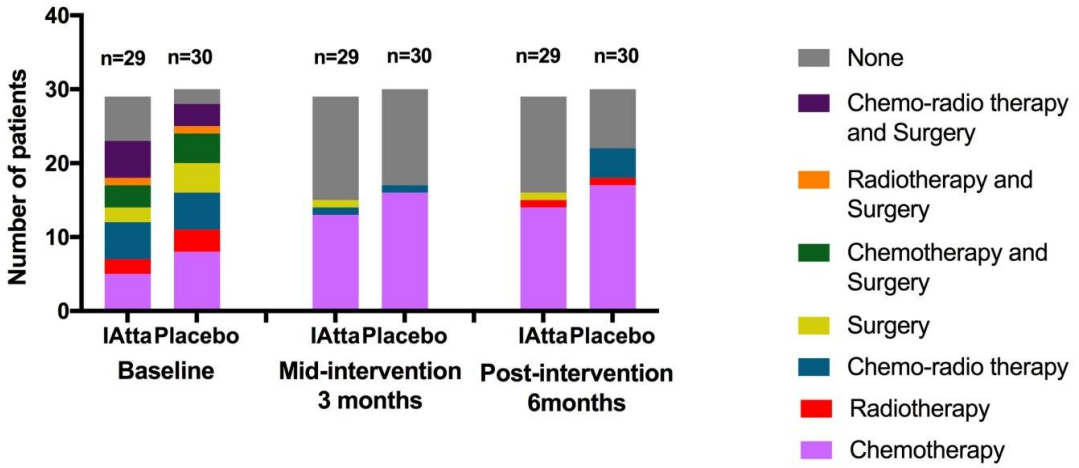


Figure 5.2-1: Therapy received by scale-up patients who finished 6 months intervention.

5.3 Anthropometric measurements

Per-protocol analysis (IAtta group n= 29, placebo group n=30)

Patients in the intervention group (IAtta group) have shown decrease in body weight 43.3±7.0 Kg to 41.6±5.7 Kg (p=0.014), BMI 19.2±2.8Kg/m^2 to 18.4±2.4Kg/m^2 (p=0.015) (figure 5.3-1), total body water (p=0.53) (figure 5.3-2) and MUAC (p=0.068) (figure 5.3-3), were maintained. However, patients in the control group (Placebo group) have shown significant increase in BMI (from 18.8±3.0Kg/m^2 to 19.2±3.3 Kg/m^2, p=0.001) and total body water (p<0.001). MUAC was maintained in placebo group as well after 6 months of flour consumption. Body fat percentage reduction was observed in both the groups at 6 months, IAtta group 26.1±5.7% to 24.9±4.8% (p=0.019) and Placebo group 25.3±6.9% to 23.2±7.9% (p=0.058).

ITT analysis (IAtta group n= 75, placebo group n=75)

According to ITT analysis, body weight (IAtta, p-value 0.111; Placebo, p-value 0.63) and BMI (IAtta, p-value 0.121; Placebo, p-value 0.35) was maintained in both the study groups at the end of intervention. MUAC (IAtta, p-value 0.007; Placebo, p-value 0.001) and body fat percentage (IAtta, p-value <0.001; Placebo, p-value 0.001) reduced significantly in both patient groups after 6 months of intervention. Body water percentage was maintained among IAtta patients (55.6±6.2% to 56±8.2%, p=0.374) and a significant increase was observed among control group patients (54±6.2% to 55.9±6.1%, p<0.001).

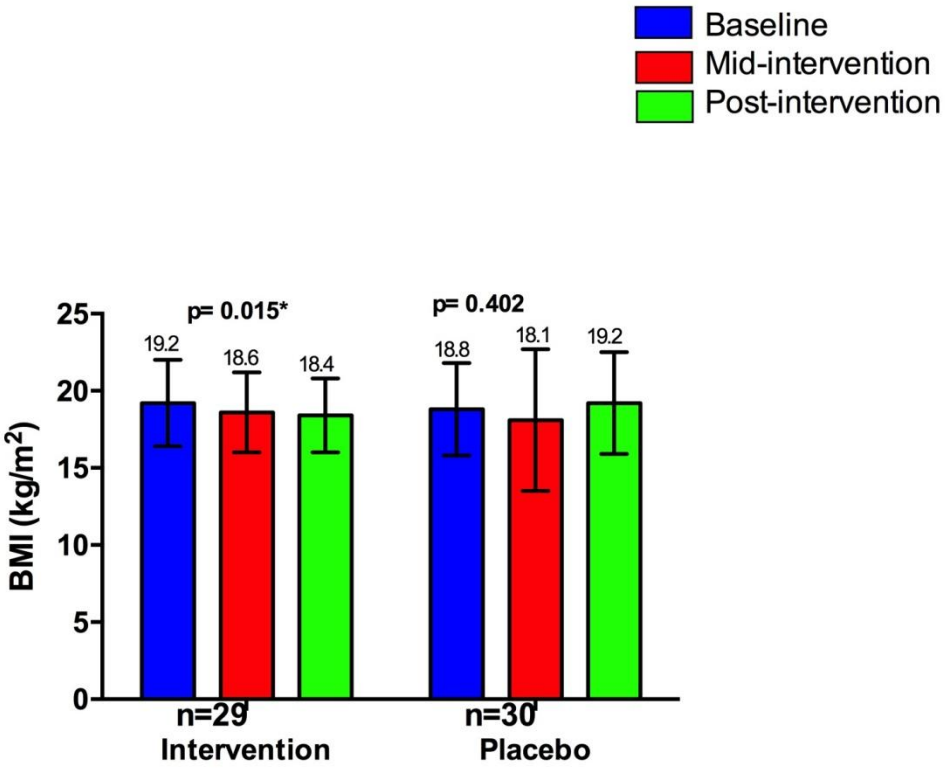


Figure 5.3-1: The graph depicts BMI of patients at baseline, mid-intervention, and post-intervention.

* Data presented as mean ± SD; *P* value ≤.05 was considered statistically significant.

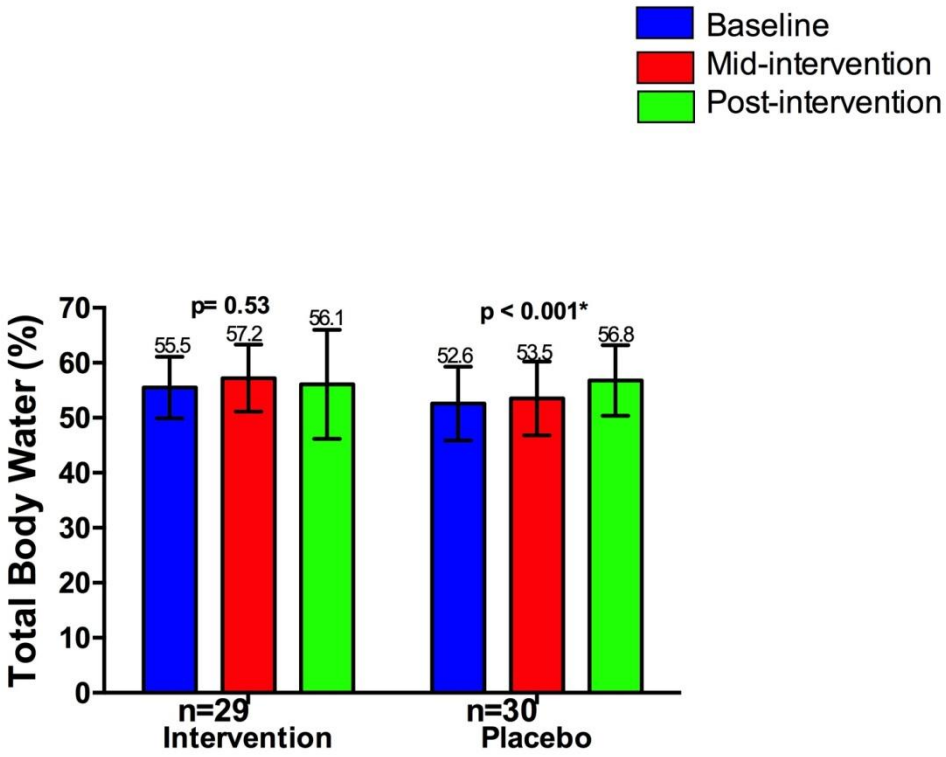


Figure 5.3-2: The graph shows TBW of patients at baseline, mid-intervention, and post-intervention.

* Data presented as mean ± SD; *P* value ≤.05 was considered statistically significant.

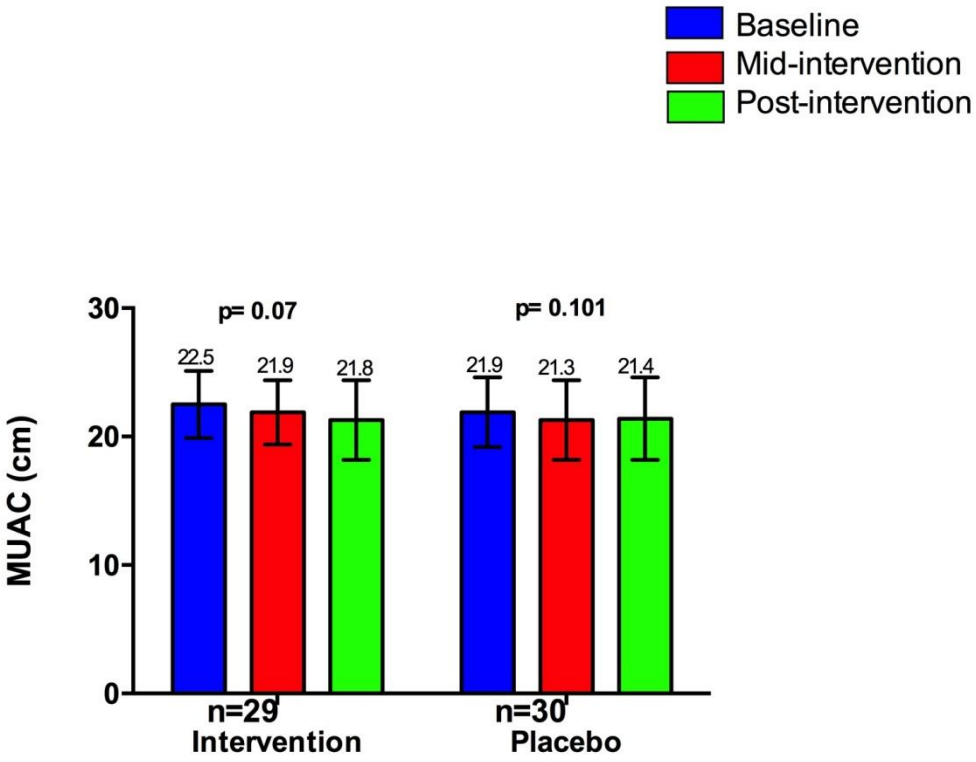


Figure 5.3-3: The graph depicts MUAC of patients at baseline, mid-intervention, and post-intervention.

* Data presented as mean ± SD; *P* value ≤.05 was considered statistically significant.

5.4 Dietary Intake

Patients in both groups reported significant improvement (p<0.001) in their PG-SGA score by the end of intervention according to per protocol as well as ITT analysis. Both group patients maintained their PG-SGA level as moderately malnourished according to per-protocol analysis (IAtta p=0.226, Placebo p=0.923) as well as ITT (IAtta p=0.174, Placebo p=0.284).

Per-protocol analysis (IAtta group n= 29, placebo group n=30)

According to dietary data collected using two day recall and FFQ, IAtta group patients who finished the intervention reported significant improvement (p<0.05) in macro-nutrient intake after six months. Patients in placebo group (n=30) maintained (p>0.05) their energy, protein, fat intake at the end of intervention by employing two

day recall as well as FFQ. Placebo consuming patients reported significant increase in carbohydrate intake [105.2g (12.8, 270.2) to 114.7g (31.8, 261.0), p=0.039].

ITT analysis (IAtta group n= 75, placebo group n=75)

ITT analysis showed in IAtta group of patients, using two day dietary recall, documented significant increase in energy [677.1kcal (239.8, 2007.1) to 779kcal (239.8, 2521.5), p=0.032], carbohydrate [103.5g (19.8, 255.8) to 115.9g (26.8, 255.8), p=0.015] and fat [21.7g (4.5, 100.5) to 27.8g (4.5, 108.2), p=0.011] after six months of intervention. Protein intake was maintained in both groups of patients (IAtta p=0.089, Placebo p=0.082) by two day dietary recall. Placebo group reported increase in energy [579.4kcal (148.3, 2155) to 692.4kcal (175.1, 1968), p=0.05] and fat [17.7g (0.33, 99.3) to 23.6g (1.1, 99.7) p=0.001] intake after six months of intervention by two day dietary recall. According to FFQ, IAtta patients maintained their energy (p=0.1) and protein (p=0.135) intake while their fat consumption increased significantly (p=0.024). Placebo group patients maintained (p>0.05) their nutrient intake throughout the intervention (by FFQ analysis). Even though placebo patients maintained their protein intake (p=0.082), at the end of six months intervention they reported significant increase in their body water percentage (p<0.001).

5.5 Physical activity assessment

Analysis using per protocol as well as ITT concluded that IAtta group had significant increase in their physical activity after 6 months of intervention (p<0.001 and p= 0.001 respectively). According to per protocol analysis, patients consuming IAtta increased their MET's from 30.3 ±3.4 (at baseline) to 31.2 ± 3.7 (after six months).

Placebo group patients maintained their physical activity throughout intervention according to per protocol analysis (p=0.49) and ITT (p=0.955) (Figure 5.5-1).

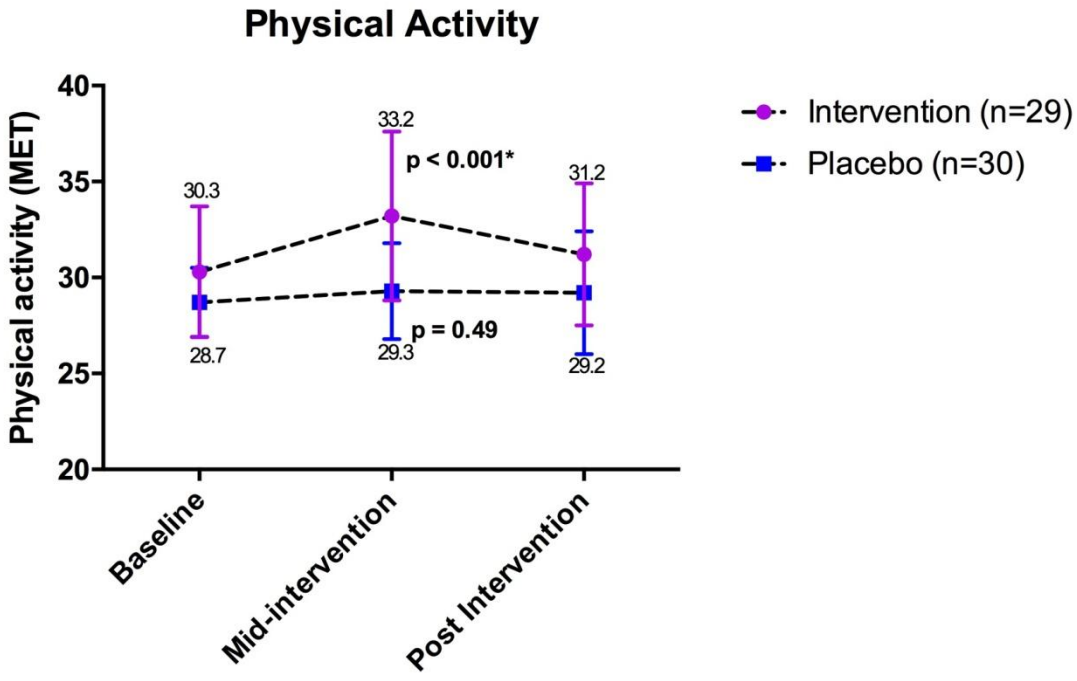


Figure 5.5-1: The graph shows physical activity of patients at baseline, mid-intervention, and post-intervention.

* Data presented as mean ± SD; *P* value ≤.05 was considered statistically significant.

5.6 Quality of life parameters

Per-protocol analysis (IAtta group n= 29, placebo group n=30)

Per protocol analysis reported that IAtta patients improved (p≤0.05) their global health status, fatigue, pain and nausea and vomiting by the end of intervention. Appetite improvement was noted in both group of patients (IAtta p<0.001, Placebo p=0.026). Placebo group patients maintained their global health status [37.5(0, 75) to 41.6(0, 83.3), p=0.74], fatigue [100 (33.3, 100) to 88.7 (55.6, 100) p=0.07], pain (p=0.64) and nausea and vomiting (p=0.25) throughout the intervention time. Both group patients reported significant reduction in social functioning after six months of intervention [IAtta (50(0,100) to 0 (0,100)) p=0.001, Placebo (50(0,100) to 4.67 (0,100)) p=0.041]. Physical functioning was maintained in both group of patients (IAtta p=0.343, Placebo p=0.683) during the intervention period .

ITT analysis (IAtta group n=75, placebo group n=75)

ITT analysis results were in line with the per-protocol results as discussed above .

5.7 Biochemical Indices

Per-protocol analysis (IAtta group n= 29, placebo group n=30)

Placebo group patients reported significant decrease (p=0.029) in their serum albumin levels between baseline (4.1±0.5g%) and three month follow-up (3.9±0.4g%), while by the end of intervention the serum albumin levels were 4.0±0.5g% (p=0.059, overall). Serum albumin levels were maintained (p=0.877) throughout intervention for the IAtta group patients. Haemoglobin levels (IAtta p=0.1, Placebo p=0.46) were maintained throughout study in both groups.

ITT analysis (IAtta group n= 75, placebo group n=75)

According to ITT analysis also, haemoglobin levels (IAtta p=0.664, Placebo p=0.141) were maintained throughout the study in both groups. Serum albumin levels were significantly reduced (4.0 ± 0.7g% to 3.8 ± 0.7g%, p=0.005) in placebo group patients after six months of intervention .

C-Reactive protein (CRP)

CRP levels were analysed in sub-group patients from intervention group (n=14) and placebo group (n=17). CRP levels were clinically increased among placebo group patients [from 5.4mg/L (0.9, 98) to 13.6mg/L (1.4,154), p = 0.097] and decreased among IAtta patients [7.7mg/L (0.4,43.4) to 6.75 mg/L (0.9,66.9), p = 0.177] after six months of intervention).

Modified Glasgow prognostic score (mGPS) was calculated using serum CRP levels and serum albumin in sub-group patients from intervention group (n=14) and placebo group (n=17). Patients who had both a serum elevation of CRP (>10 mg/L) and hypoalbuminemia (<3.5 g/dL) were allocated a GPS of 2. Patients with only one of the abnormal values were allocated a GPS of 1, and patients who had neither were allocated a GPS of 0 (Figure 5.7-1 and 5.7-2).

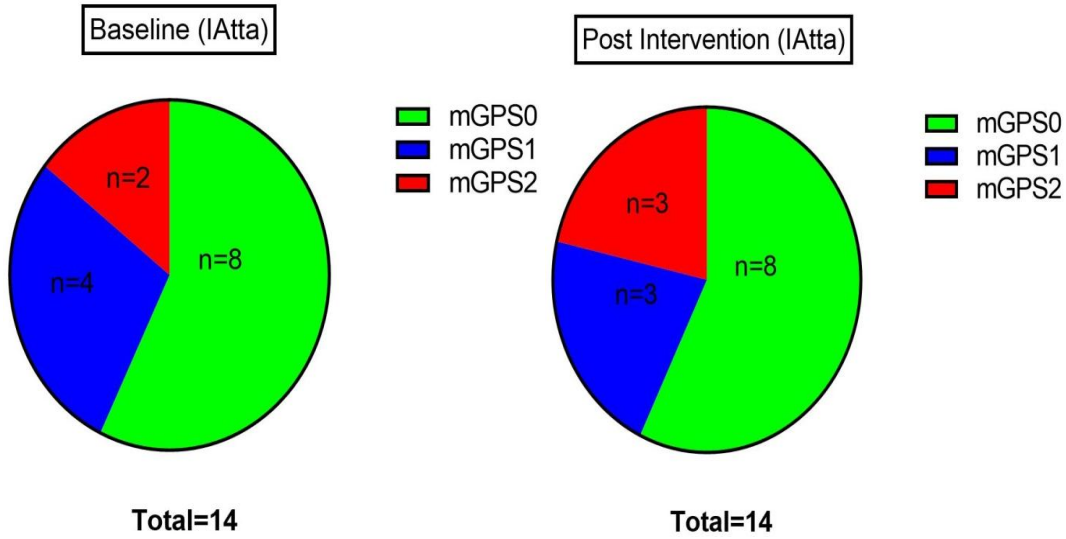


Figure 5.7-1: Intervention group patients categorised according to their respective mGPS at baseline and post-intervention time-points

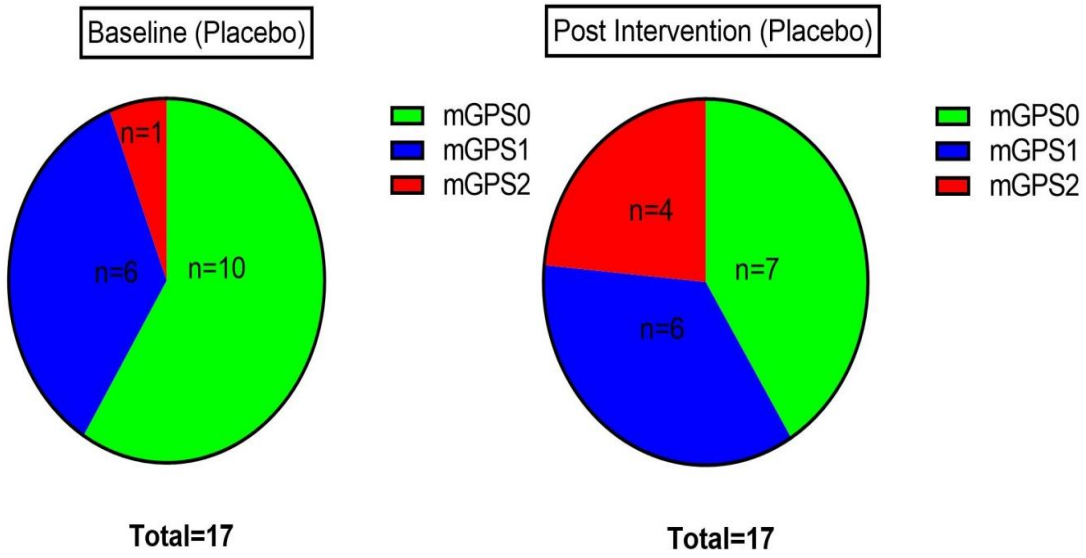


Figure 5.7-2: Placebo group patients categorised according to their respective mGPS at baseline and post-intervention time-points

After six months of intervention there was no significant difference in mGPS within groups when assessed at baseline and after six months of intervention (IAtta: 0.57±0.76 versus 0.64±0.84, p=0.765; Placebo: 0.47±0.62 versus 0.82±0.81, p=0.112).

5.8 Discussion

In the current study, IAtta meal supplementation along with nutritional counselling resulted in improved physical activity and quality of life compared to patients consuming whole wheat flour.

Results were analysed using per protocol as well as ITT method. ITT gives a pragmatic approach to trial results. It is a conservative form of analysis as it considers noncompliance patients leading to dilution of treatment effect. According to a review comparing various guidelines, ITT principle should be employed while analysing trial results. ITT analysis should be viewed as the primary test and per protocol as a supporting test. Treatment effect is considered profound when both types of analysis are in line (Gupta, 2011). According to ITT and per protocol analysis, body water increased significantly ($p<0.001$) after six months intervention in placebo group patients while it was maintained ($p=0.374$) in IAtta group. Similarly physical activity was significantly ($p=0.001$) improved in IAtta patients after six months of intervention along with improved domains (health status, fatigue and appetite; $p<0.001$) of QoL. Serum albumin levels as well were significantly reduced ($p=0.005$) in placebo group at the end of intervention. These results signify the superiority of IAtta compared to whole wheat flour routine intake among cachectic cancer patients.

Cachexia is a multi-factorial syndrome and is often associated with oedema in patients (VanCutsem and Arends, 2005). BIA is a non-invasive and user friendly body composition technique. BIA has been validated among advanced cancer patients for estimation of TBW (Davis *et al.,* 2009). A recent review concluded that using the same BIA equipment under controlled conditions repeatedly for TBW measurement is valid among incurable cancer patients (Haverkort *et al.,* 2015).

Anti-cancer treatment among advanced cancer patients frequently leads to anaemia. Patients undergoing repeated intensive chemotherapy sessions suffer from higher anaemia risk (Rodger *et al.,* 2012). Baseline assessment depicted most of the patients were receiving anti-cancer therapy and were anaemic ($Hb<12g/dl$). The reduced haemoglobin levels were maintained in both the groups (IAtta, $p=0.664$; Placebo, $p=0.141$) throughout the intervention. One of the main reasons

that we did not notice any impact of IAtta on haemoglobin levels of patients could be regular blood transfusion in all cancer patients prior to planned therapy sessions.

Albumin forms about 50% of the total blood proteins. Albumin modulates colloidal osmotic pressure and determines intravascular volume. More than 50% of albumin is present in the extravascular region. Serum albumin depicts long term protein status with a half-life of 14 to 20 days. Presence of oedema is often a symptom of low serum albumin concentration. Reduction in albumin levels is commonly observed in cancer, hepatic failure, zinc deficiency, inflammation, nephritic syndrome, trauma and burns. Inflammation state (in cancer) leads to reduction in albumin levels as body prioritises production of acute phase proteins and limits production of other body proteins. Presence of weight-loss and muscle wasting in patients can be overlooked due to oedema (Donna, 2012; p 257). IAtta group patients, however did not report oedema, this could be explained on the basis of maintained blood serum albumin throughout the intervention. Malignancies result in a variety of pathological changes resulting in adverse effects on the normal homeostatic processes. In addition to the treatment modalities and their side effects, the malignant process also contributes to the disruption of the physiological processes. The control of extracellular fluid is influenced by various proteins, sensors, hormones and organs (Fazzari and Singh, 2016; p 85). In malignancies apart from the decreased serum albumin levels leading to extravascular fluid increase, other factors also play a role. These are mainly due to inflammation affecting the vascular endothelial barrier and leading to increased permeability. The presence of oedema is multi-factorial and is related to the tumour, serum protein levels and the chronic inflammatory state (Fazzari and Singh, 2016; p 85-88).

Body fluid is present in three main compartments namely the capillaries, lymphatic and the interstitium, in addition to the veins and arteries. The interstitial space is made up of interstitial fluid and extracellular matrix. There is interplay of dynamics depending on signalling molecules affecting the collagen and glycosoaminoglycans which is present in a gel like phase. This allows the interstitium to take in water. Physiologically, the amount of water depends on the permeability of the capillary endothelium. Pathologic processes in the form of colloid osmotic pressure changes or factors affecting capillary permeability lead to an increase in the amount of water in the interstitium. Capillary permeability is impacted by various cytokines and cytotoxins in various malignancies leading to an increase in amount of interstitial

fluids. Reduced colloid osmotic pressure also causes increase in interstitial fluid. This colloid osmotic pressure depends on the albumin level and hypoalbuminemia leads to increased interstitial fluid. Increased interstitial fluid is clinically seen as oedema. Oedema is therefore seen in malignancies due to the interplay of cytokines, cytotoxins and hypoalbuminemia (Fazzari and Singh, 2016; p 85-88).

Our results indicate that there is no significant difference in the body weight (IAtta group p=0.111, Placebo group p=0.63) of two groups after six months of intervention. However, when we studied the TBW by BIA in both the groups we noticed that the placebo group showed a higher TBW (baseline 54±6.2% versus post-intervention 55.9±6.9%, p=0.001). Albumin levels in both the groups revealed that the placebo group (baseline 4.0±0.7g% versus post-intervention 3.8±0.7g%, p=0.005) had significantly lower levels compared to baseline. This lead to the probable conclusion that the body weight maintenance in the placebo group (p= 0.63) was a function of water retention rather than improvement in other parameters (muscle mass and body fat). The IAtta group had better albumin levels (baseline 4.0±0.7g% versus post-intervention 3.9±0.7g%, p=0.239) compared to the other group. Hence it may be concluded that the non-significant difference in weight is because of the poor nutritional status as indicated by serum albumin levels and resultant water retention in the form of clinical oedema. Other underlined factors may also be responsible for oedema among these patients, which requires in-depth research for better understanding. IAtta patients were anaemic throughout the intervention period; however they did not report oedema.

To our knowledge this is the first study to report oedema in cachexic cancer patients with significant reduction in serum albumin levels after six months of consumption of whole wheat flour.

Chapter 6:

Discussion

6.1 Introduction

The main aim of the study was to delay progression of cachexia to refractory cachexia in female cancer patients by providing nutritional support as a part of the palliative care system. Patients suffering from cancer cachexia experience increased protein catabolism leading to loss of lean body mass, which is irreversible by nutritional support (Fearon *et al.,* 2011). Our objective was to stabilize and improve nutritional status of our study population. Once patients enter the stage of refractory cachexia they fail to respond to anti-cancer therapy and their survival time is less than three months (Fearon *et al.,* 2011).

The discussion is subdivided into five main categories:

6.2 Anthropometric measurements
6.3 Dietary intake and nutritional status
6.4 Physical activity
6.5 Quality of life parameters
6.6 Biochemical indicators
6.7 Limitations

6.2 Anthropometric measurements

In the pilot study (n=63), control group patients showed a mean body weight loss of 8.71% and scale-up study (n=150) placebo patients maintained their body weight ($p=0.263$) at the end of intervention (6-month period). Patients in IAtta group maintained their body weight after six months of intervention in both the studies. TBW was also measured in both the study groups. During pilot study, TBW content was comparable between patient groups at baseline, mid-intervention (3-month), and post-intervention ($p=0.453$, $p= 0.234$, and $p=0.727$, respectively). In scale-up study (n=150), only the placebo group reported significant increase of 9.8% in their TBW ($p<0.005$). In placebo group the key reason for higher TBW (baseline 54±6.2% versus 55.9±6.1%) could be reduction in plasma albumin levels (baseline 4.0±0.7g% versus 3.8±0.7g%) leading to disturbance in the water distribution between blood and tissues.

Placebo group patients' diet was supplemented with plain whole wheat flour whereas the IAtta group was consuming the specially formulated flour mix with high protein content (26g/100g). Analysis (ITT) of the dietary protein intake during scale-up study did not show any significant difference within the groups after six months of intervention. Comparison of the protein intake between the groups after six months supplementation was however statistically significant (p=0.01). This indicates that the intervention group consuming IAtta had better dietary protein intake (IAtta included soybean which is a good source of protein consisting all essential amino acids). Furthermore, this was reflected and corroborated by stabilized serum albumin in IAtta group patients (baseline 4.0±0.7g% to post–intervention 3.9 ± 0.7g%, p=0.239) and placebo group patients reported significant reduction in albumin levels (baseline 4.0±0.7g% to post–intervention 3.8±0.7g%, p=0.005) (similar to phenomenon reported by Gupta and Lis (2010)). Serum albumin levels influence the total body water through a process of water retention. The reduced albumin levels in the placebo group influenced the body weight through water retention (figure 6.2-1).

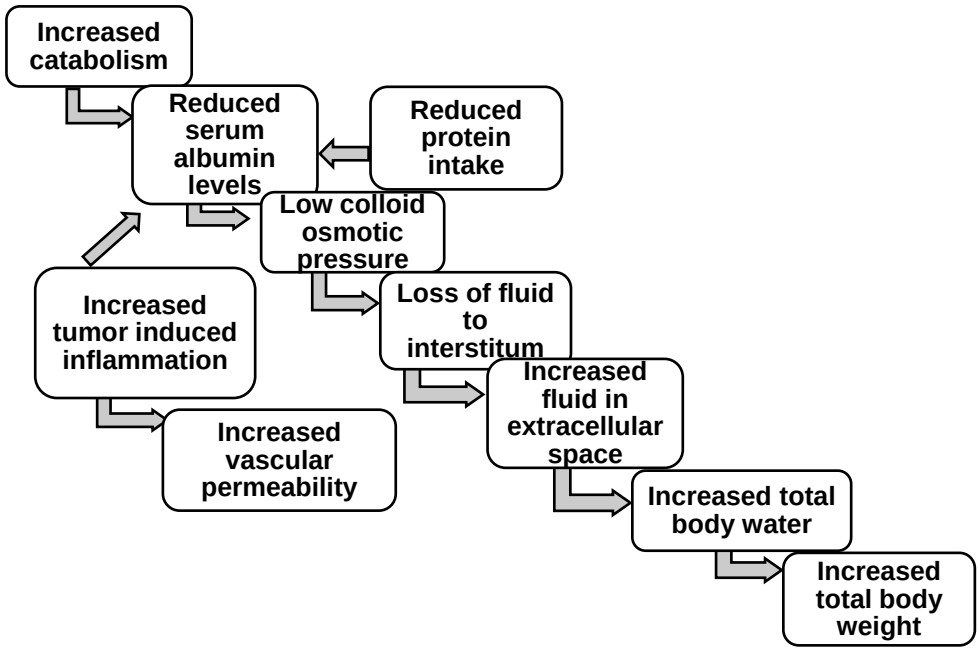


Figure 6.2-1: Cascade phenomenon observed among scale-up cachexic female patients during intervention (adapted from Fazzari and Singh, 2016; p 93).

An increase in body fat percentage (baseline 20.5± 5.2% versus post-intervention 23.7 ± 5.3%, p=0.002) was noticed among the small number of IAtta consuming patients however the same trend was not seen (baseline 26.1± 5.7% versus post-intervention 24.9 ± 4.8%, p=0.019) in the scale-up study. Significant difference was observed in MUAC between the groups in the pilot study (IAtta group p=0.346 and in control group reduction, p=0.002) while the same parameter declined significantly in both the groups in the scale-up study (IAtta group, p = 0.007 and placebo group, p=0.001).

As regards body weight, there was no improvement in nutritional status of cancer patients who are at nutritional risk even after significant increase in energy and protein intake for three months of intervention. This has been reported in an earlier study (Uster *et al.,* 2013). In this study patients, in nutrition therapy group reported stable performance status compared to patients under usual hospital care. In the same RCT, Uster and colleagues (2013) noticed that patients with higher albumin at the end of intervention had better muscle strength (hand- grip strength). Our results are in-line with Uster *et al.,* (2013) as patients did not gain body weight during intervention and reported physical activity maintenance and/or increase compared to controls. In addition to this, IAtta patients reporting higher albumin levels (3.9 ± 0.7g% versus placebo 3.8 ± 0.7g% post-intervention) also continued with their daily activity and reported better health status (QoL). Body weight maintenance (p=0.479) was also reported among cachexic patients with mixed tumour cancers receiving ONS (Prosure and Ensure plus) for two months (Dewey *et al.,* 2015). Cancer patients (mixed tumour site) receiving chemotherapy and/or radiotherapy were randomized into either nutrition therapy group (ONS with dietary counselling dietician) or usual care group (counselling by staff nurse) for up to three months by Poulsen *et al.,* (2014). No significant difference in body weight, body fat, TBW and muscle mass was noticed between the groups even though the therapy group reported significant increased protein intake at the end compared to usual care group. In the present scale- up study, no significant difference in body weight, body fat and muscle mass between groups was evidenced even though significant (p=0.01between groups after six months of IAtta/placebo supplementation) increased protein intake in IAtta consuming patients was reported. Poulsen and colleagues (2014), enrolled patients receiving anti-cancer therapy with palliative as well as curative intent. Protein intake at baseline by patients in both the groups was higher (46-89g/d) than our study patients (IAtta 26±14.4g/d and placebo

21.9±13.3g/d). The above mentioned reasons (mixed treatment population and protein intake) could be the main factor for their study patients to report no changes in serum albumin and TBW levels. One of the main limitations from Poulsen *et al.,* (2014) study was the values for muscle mass, body fat and TBW at baseline and post-intervention were not stated for comparison review. The intervention period in our study was six months compared to three months in the Poulsen *et al.,* (2014) study. The presence of oedema in our placebo study group could be the result of increase in inflammatory levels (clinical increase in CRP and mGPS, section 5.7). Weight maintenance (p=0.412) has been observed in advanced oesophageal cancer patients receiving anti-cancer therapy, on tailored nutrition intervention program along with maintained serum albumin levels (p=1.00) on completion of planned radiotherapy (Cong *et al.,* 2015). Control patients under physician care reported significant weight loss (p<0.001) and reduction in serum albumin ($p \leq 0.001$) (Cong *et al.,* 2015), these results are in line with our trial results.

The progressive significant reduction in body fat (assessed using SFT) and muscle mass (assessed by MUAC) in both group of patients observed during scale-up study is due to extended catabolic phase experienced by cachectic patients. Tumour progression leads to disruption in protein synthesis and degradation cycle in order to retain muscle mass. Fat tissue depletion during cachexia is a common feature which further leads to skeletal muscle depletion (Porporato *et al.,* 2016). Intervention initiated in cachectic patients in their early phase of disease can lead to muscle gain (Prado *et al.,* 2013). CT imaging observations among advanced cancer patients has shown progressive muscle reduction from 9 months until death (Prado *et al.,* 2013). Most cancer patients in India are diagnosed in their advanced stage of cancer due to limited healthcare access (Goss *et al.,* 2014). Basal metabolic rate, individual tumour site, response to anti-cancer treatment and catabolism level could be the main contributory factors for the patients not maintaining their body muscle level. Per-protocol analysis for IAtta scale-up concluded MUAC maintenance in both the groups. Therefore, the impact of IAtta on muscle mass maintenance was noticed; however as per statistical ITT analysis it was not significant (p=0.007). Another fact is that the patients during the study could not consume the entire (100g) dietary supplement (IAtta) provided. IAtta (per pack 100g) would have given them additional 25g of protein. As per observation the average protein intake was less than 30g/d (among IAtta scale-up patients). Keeping in view the high catabolic demands during malignant conditions it is likely that higher protein intake may have significant beneficial effect on nutritional status and cachexia progression.

6.3 Dietary intake and nutritional status

Research has shown that disease progression in malignancy leads to increase in BMR (Young *et al.,* 1977; Dhanpal *et al.,* 2011). Therefore, the energy intake of patients should be higher to maintain their nutritional status. The energy intake of all study patients at baseline was lower than the Indian adult female RDA (<1900 kcal, Table 4.2-1 and 5.2-1). IAtta (each pack 100g/day) would give three flat breads (on average) providing approximately 400 kcal. The mean consumption of *IAtta* flour among the patients who finished the study after six months of intervention was 45.4 ± 11.7g/day. Scale-up study patients receiving IAtta or placebo reported a significant increase (compared to baseline) in their daily energy, protein (only IAtta group) and fat intake at the end of the intervention, which was greater than their average consumption (Section 5.4). The key reason could be nutritional counselling imparted at each visit (one visit every fortnight) as well as during telephonic follow-ups. Studies have reported significant improvement among advance cancer patients' nutritional status with nutritional counselling (Baldwin and Weekes, 2012; Balstad *et al.,* 2014; Silvers *et al.,* 2014; Lee *et al.,* 2016). According to Ravasco and colleagues (2012), nutritional counselling improves PG-SGA scores in advanced colorectal patients which could have helped both group study patients (IAtta, $p<0.001$ and placebo, $p<0.001$ during scale-up) to significantly improve their respective malnutrition scores after six months of intervention. According to ICMR (2010), 1.0g/Kg/d of protein is recommended for Indian adults. Literature review suggests weight maintenance in advanced cancer patients can be achieved by 1.5g/Kg/d of protein intake (Bauer and Capra, 2005; Senesse *et al.,* 2014). Each IAtta pack provides 50% of their daily protein requirement (Table 3.9-1). Therefore, at post-intervention, both studies' IAtta patients reported significant increase in protein intake which could have helped them in maintaining and/or increasing their physical activity significantly. These dietetic consumption observations are in line with Sánchez-Lara *et al.,* (2014) RCT on advanced lung cancer patients. In Lara's study (2014), the control group patients were prescribed a diet based on their energy requirements while the study group patients were given Prosure ONS for consumption during cancer therapy. Prosure group patients reported weight maintenance as well as improvement in health status, appetite and fatigue (QoL domains), similar to our study observations. In our study, despite progression of the neoplastic disease, positive impact on patient health status could be the cumulative positive effect of IAtta natural ingredients.

6.4 Physical activity and functionality

In advanced lung cancer patients, it has been suggested that exercise and nutrition intervention may have a positive impact on un-intentional weight loss and physical function (Payne *et al.,* 2013). A statistically significant positive correlation has been concluded between physical activity and quality of life (Oechsle *et al.,* 2011).

A group of 80 advanced cancer patients enrolled into a two month palliative rehabilitation program (involving dietitians, physiotherapist, doctors and social workers) in order to correct their dietary intake and improve physical activity (Feldstain *et al.,* 2016). In this study, patients reported improvement in their physical activity level ($p<0.001$) and depression score ($p<0.002$). These results are in line with our study results, as in both studies patients consuming IAtta either reported maintenance ($p=0.274$) or improvement ($p=0.001$) in their physical activity. Palliative cancer patients attending gym sessions along with dietician and physician counselling have reported significant improvement in physical activity as well as symptom severity (Chasen *et al.,* 2013). These results are in accordance with our observations. IAtta patients reported increased activity ($p=0.001$) along with improvement in their appetite, fatigue, nausea and vomiting and constipation (section 5.6). Though both the groups received physical activity counselling in our study, the key factor for improved physical activity in the intervention group could be consumption of nutrient rich IAtta, partially compensating the protein and micronutrient deficit in their diets. Weight-losing advanced cancer patients with lower MUAC have reported reduced functional abilities (functional ability was defined as walking on the treadmill) (Wallengren *et al.*, 2013). A similar trend was observed among control weight losing patients during our pilot study, who reported reduced physical activity levels at the end of the study period ($p=0.004$, Appendix 15, Kapoor *et al.,* 2016).

6.5 Quality of life parameters

Maintenance of cancer patients' nutritional status has been emphasised in ESPEN European Society of Clinical Nutrition and Metabolism and Nutrition in Cancer patients Guidelines. According to these guidelines, treatment goals should be centred towards symptom management (from disease progress and anti-cancer therapy) and improvement of QoL (Arends *et al.,* 2006; Arends *et al.,* 2016). A recent meta-analysis studied the impact of nutrition intervention (ONS and/or counselling) on QoL using EORTC C-30 questionnaire (Baldwin *et al.,* 2015). On comparison with usual patient care, nutrition intervention had a significant positive impact on emotional functioning, appetite, dyspnoea and global health status (Baldwin *et al.,* 2015). QoL domains of appetite, dyspnoea and global health status ($p<0.001$, $p=0.047$ and $p<0.001$ respectively) significantly improved in patients consuming IAtta for six months. In line with the ESPEN guidelines, significant symptom improvement like fatigue, pain, constipation and nausea–vomiting ($p<0.001$, $p=0.047$, $p=0.007$ and $p<0.001$respectively) was also observed in the IAtta patients compared to placebo group.

Advanced lung cancer patients (on palliative chemotherapy) consuming ONS (Prosure) were compared with control patients on standardized diets according to their calorie requirements. Patients consuming ONS maintained their body weight with increased macronutrient intake and significant decrease in CRP levels after six months of intervention (Sánchez-Lara *et al.,* 2014). Both group of patients reported albumin level maintenance throughout the study. Similar to our intervention group patients, significant QoL improvements were reported for domains global health status, fatigue and appetite. Compared to Sánchez-Lara and colleagues (2014) RCT, the key reason for not observing a significant difference in CRP levels could be the small number of samples assessed (due to unavailability of investigations in the same unit). CRF has been reported by 99% of cancer patients from diagnosis to end of life. A review on lung cancer survivors reported CRF as a limiting factor in patients' daily activities and their QoL (Paramanandam *et al.,* 2015). They concluded that exercise can help in management of CRF in lung cancer patients (Paramanandam and Dunn, 2015). Our study patients consuming IAtta were able to increase their physical activity (baseline 29.6±3.1MET versus post-intervention 30±3.3 MET's, $p=0.001$) by the end of intervention and reported significant

improvement in their fatigue levels ($p<0.001$) when assessed using EORTC C- 30 QoL questionnaire.

6.6 Biochemical indicators

Haemoglobin and serum albumin were assessed in both groups of the study. One of the main reasons that we did not notice any impact of IAtta on haemoglobin levels (baseline 9.6±1.7 g/dl versus post-intervention 9.6±1.7 g/dl, $p=0.664$) of patients could be regular blood transfusion in all cancer patients prior to chemotherapy. All patients recruited in the study were anaemic (Hb<12g/dl) and in order to be eligible for chemotherapy, patients undergo blood transfusion regularly to raise their haemoglobin levels. Serum albumin levels were significantly lower among placebo group patients (baseline 4.0 ± 0.7 g% versus post-intervention 3.8 ± 0.7 g%, $p=0.005$) during the scale-up study while the IAtta patients (baseline 4.0 ± 0.7 g/dl versus post-intervention 3.9 ± 0.7 g/dl, $p=0.239$) had maintained their levels after six months of intervention. Malnourished head and neck cancer patients, who were prescribed a dietary plan according to their East Indian food habits, reported significant improvement in their protein status along with increase in serum albumin levels (Bhattacharjee *et al.,* 2015).

CRP levels were assessed (baseline and at six months) among few patients of both the group during the scale-up study. There was no significant difference between as well as within ($p>0.005$) the groups after six months of intervention. However, in the placebo group patients a greater clinical increase in CRP levels (baseline 5.4mg/L versus post-intervention 13.6mg/L, $p=0.097$) was observed after the intervention compared to the IAtta patients. This is an indicator of ongoing inflammatory activity on the placebo group patients (Suzuki et al., 2013, see section pathophysiology of cancer cachexia section 2.3). Nevertheless, the intervention group has shown maintenance in CRP levels (baseline 7.7mg/L versus post-intervention 6.75mg/L, $p=0.177$) along with significant improvement in QoL (global health status domain, $p<0.001$) after six months of intervention. ONS containing n-3 fatty acids was offered to advance lung cancer patients for five weeks supplementation while the controls were given isocaloric ONS. The intervention group patients had better weight maintenance as well as fat free mass, but no difference in CRP levels was observed between groups (van der Meij,*et al.,* 2010). Recent RCT on palliative oncology patients undergoing a rehabilitation program reported significant

improvement ($p<0.001$) in physical activity but CRP levels did not significanctly improve (Feldstain *et al.,* 2016). These results are similar to our study as even though our IAtta patients maintained their body weight ($p=0.111$), CRP level was not significantly ($p=0.177$) different compared to placebo patients ($p=0.097$).

The modified Glasgow prognostic score (mGPS) is a combined indicator for malnutrition and systemic inflammation (McMillan, 2013). Among placebo group patients, mGPS assessment at baseline and post-intervention showed that score had increased by 3.5% while in the IAtta group patients it had increased by just 0.7% (section 5.7). Higher GPS score is associated with reduced survival and is superior to predicting survival compared to markers like white blood cells, platelets and neutrophil count (Polterauer *et al.,* 2010). Increased mGPS has been associated with body weight loss, dietary intake, co-morbidities, poor performance status and treatment complication (McMillan, 2013). A similar trend was observed in our study, where placebo group patients even though receiving treatment for symptom management reported no significant improvement in pain, fatigue, constipation, appetite, dyspnoea, nausea and vomiting (QoL domains).

6.7 Overall discussion

Literature review (Table 2.8-1) has shown very few ONS intervention RCT among advanced cancer continuing follow-up more than three months. One of the uniqueness of this project was the six month follow-up duration of the intervention for all participating patients.

On comparison of the employed parameters between IAtta and whole wheat flour consuming patients, we can conclude that IAtta patients performed better after six months of intervention compared to the placebo patients. In the table 6.7-1below, scale-up study parameter results analysed using ITT has been compared. CRP and mGPS results mentioned were analysed for a few patients using per protocol method.

Table 6.7-1: Comparison of primary and secondary parameters between IAtta and Placebo patients.

Parameter	IAtta	Placebo
Body weight	Maintained (B: 42.1 ± 7.2; A: 41.5 ± 7.1)	Maintained (B: 42.7 ± 7.3; A: 42.9 ± 7.9)
MUAC	Significant reduction (p = 0.007)	Significant reduction (p = 0.001)
Body fat	Significant reduction (p < 0.001)	Significant reduction (p = 0.001)
Total body water	Maintained (B: 55.6 ± 6.2; A: 56 ± 8.2)	Significant increase (p<0.001)
Dietary protein intake	Maintained (B: 22.6 (5.6, 67.9); A: 29.1 (5.7, 86.2))	Maintained (B: 19.7 (3.2, 66); A: 20.8 (3.2, 70.5))
PG-SGA score	Significant improvement (p < 0.001)	Significant improvement (p < 0.001)
Physical activity	Significant improvement (p = 0.001)	Maintained (B: 28.5 ± 2; A: 28.6 ± 0.3)
QoL Global health status	Significant improvement (p <0.001)	Maintained (B: 25 (0, 75); A: 25 (0, 83.3))
QoL Fatigue	Significant improvement (p <0.001)	Maintained (B: 100 (33.3, 100); A: 100 (33.3, 100))
QoL Appetite loss	Significant improvement (p <0.001)	Maintained (B: 100 (0, 100); A: 100 (0, 100))
Serum albumin	Maintained (B: 4.0 ± 0.7; A: 3.9 ± 0.7)	Significant reduction (p = 0.005)
CRP	Maintained (B: 7.7 (0.4, 43.4); A: 6.75 (0.9, 66.9))	Maintained (B: 5.4 (0.9, 98); A: 13.6 (1.4, 154))
mGPS	Maintained (B: 0.6 ± 0.8; A: 0.6 ± 0.8)	Maintained (B: 0.5 ± 0.6; A: 0.8 ± 0.8)

** 'B' denotes baseline values and 'A' denotes post six months intervention values.*

6.8 IAtta comparison with commercial products

Post pilot study, home visit for a patient consuming IAtta was implemented. Informal talks with the caregiver and family members gave us an understanding regarding perception of IAtta. The caregiver informed the investigator that any leftover of IAtta meal was discarded by end of the day. Patient would not share their IAtta meal with other family members as they consider it a part of their daily medication.

Prosure, Ensure, Resource and Fresubin are ONS mostly prescribed by oncologists. The most important factor in commercial ONS intake is limited availability in rural India and its cost. Among the products prescribed, Prosure contains fish oil and therefore makes it unacceptable for the vegetarian Indian population. Commercial ONS's are sweet in taste and therefore acceptance is limited among patients suffering from therapy related taste alterations (Table 6.8-1).

Patients are overloaded with advanced cancer treatment expenses hence they find it difficult to spend for ONS. Commercial ONS is consequently not a sustainable option. With IAtta, patients can avail additional nutrition as per their taste preferences (salty or sweet), while being an indigenous part of their dietary pattern. IAtta consists of local grains, pulses and oilseeds ingredients available at all grocery shops throughout the year. Amaranth spinosus grows throughout India as a weed and is easily accessible (Kumar *et al.,* 2010) (Figure 6.8-1).

Table 6.8-1: IAtta comparison with commercial products

Characteristics	**IAtta** *(Recommended 100g/day)*	**Commercial ONS** *(Recommended two serves per day, one serve = 200-250ml)*
Vegetarianism	√	×
Synthetic Ingredients	×	√
Natural ingredients	√	×
Affordability	√ (£0.2/100g/day)	× (£1.75-2.3/100g)
Sustainability	√	×
Part of Indian staple diet	√	×

FAO's approach for combating hunger involves sustainable agricultural and rural development helping direct access to food for the malnourished (affected people). According to FAO, "Food security exists when all people, at all times, have physical and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life" (World Food Summit, 1996).

Agriculture is the main source of income for more than half of the Indian population, supporting the largest poor population. It contributes to about 14% of Indian GDP. India produces over 260 million tonnes of food grains, 269 million tonnes of agriculture produce and 132 million tonnes of milk (Food Agriculture Organisation, 2016). Majority (83%) of the agricultural land is possessed by farmers in form of small holding (under 2 hectares of land), leading to limited profit from production and becoming most affected from climate change. Rainfall (unequal and /or inadequate), temperature variation and natural disasters affect agriculture produce, threatening food security. These scenarios affect the small landowners living in rural India. Keeping all this into consideration, the IAtta formulation was done in such a manner; that the ingredients will be available all over the year not being affected by monsoon fluctuation.

IAtta can be set up as an innovative model of a nutrition-sensitive intervention in accordance with world food programme mission and Food Agriculture Organisation approach to combat undernutrition among advanced cancer patients.

Palliative care framework for cancer patients in India lacks nutritional support guidelines. From the above results it is evidenced that nutrition plays a pivotal role in palliative care management.

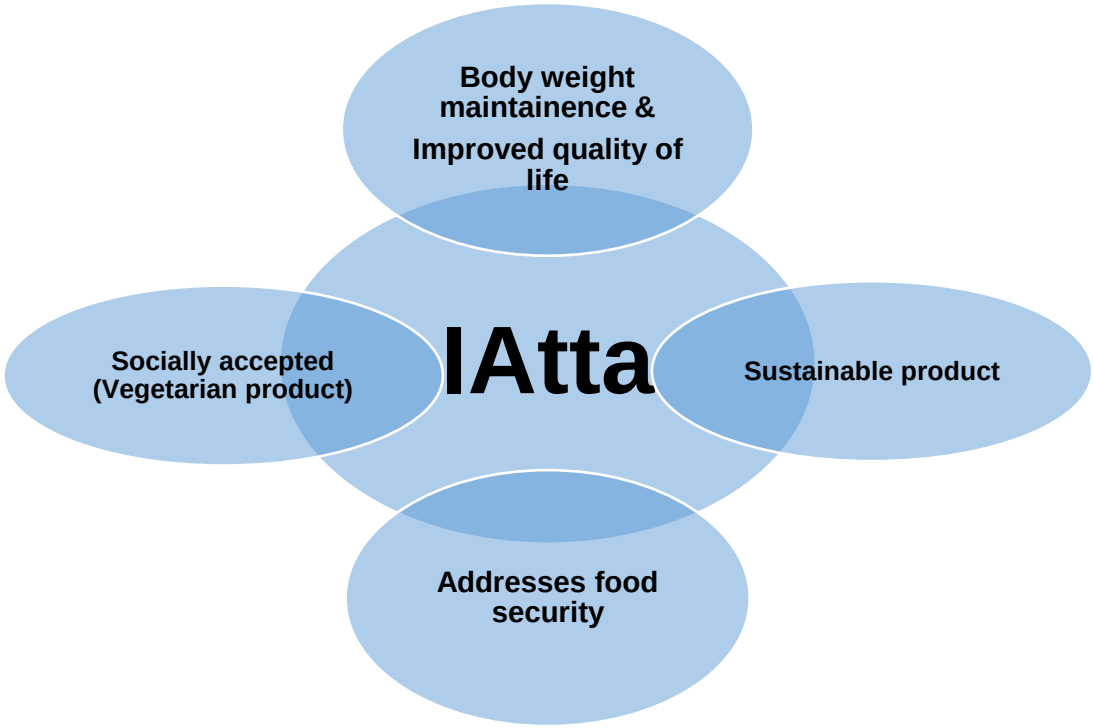


Figure 6.8-1: Multi-dimensional advantages of tailored food recipe - IAtta

6.9 Limitations

There were a number of limitations observed during the current study and they are listed below:

6.9.1 Anorexia and loss of appetite

The key reported causes for low intake of IAtta was anorexia and appetite loss which is commonly observed in cancer cachexia patients.

6.9.2 Gastrointestinal tract complication

Constipation due to medication (morphine to control cancer pain) and vomiting as well as mucositis mostly due to chemo-radiotherapy were some of the main reasons. This would lead to the inability to eat the prescribed amount of IAtta. Treating Palliative Physician prescribe stimulant laxative and stool softener to the patients. Most patients were unable to afford the medication from pharmacy and therefore suffered from severe constipation throughout intervention. Constipation among these patients was associated to abdominal discomfort, poor appetite, impaired nutritional status and interruptions of scheduled anti-cancer treatment.

6.9.3 Drop-out

High patient drop out during intervention was due to co-morbid conditions causing life-threatening complications and long waiting time for anti-cancer therapy sessions. Attrition rate as high as 44% has been reported in palliative oncology studies because of clinical deterioration and mortality among patients (Hui *et al.,* 2013; Visser *et al.,* 2015). Recruiting patients at an early stage of the disease would help in reduction of the attrition rate among palliative patients. Till date there is no biomarker for classification of patients in refractory cachexia stage. Therefore, few drop-out patients could have been in their refractory cachexia stage during recruitment of the intervention.

6.9.4 Financial barrier

Socio-economic compulsions in the form of financial inadequacy also leads to inability of the patient to receive cancer treatment. Caregivers were unable to pay for their fare tickets to reach the hospital. Generic prescription drugs were available free of cost to patients at the hospital. However, as all drugs are not supplied by the hospital and specific drugs were required for symptomatic management of the side-effects. The patients could not afford to procure the same from the market and this led to various conditions like constipation, nausea, vomiting and muscositis impacting intake of prescribed supplement (IAtta).

6.9.5 Appropriateness of used field tool

Tanita segmental body composition machine was used during the study to assess the body fat percentage and muscle mass of the patients. CT imaging or DEXA are considered more accurate tools to identify muscle wasting (Del Fabbro, 2015). As access to regular CT imaging or DEXA was not available, estimation of muscle mass (variable) was excluded from the study.

6.9.6 Biochemical assessment availability

Laboratory facility to analyse CRP levels was not available in the oncology department at AIIMS, New Delhi. Patients had to get their blood samples to a different department at AIIMS for CRP analysis. Due to this inconvenience, only few patients could get their CRP levels analysed during the scale-up study.

Chapter 7:

Author's Critique, Conclusions and Future Work

7.1 Author's critique

During the study, a high patient drop-out rate was experienced. On telephonic conversation with the patient it was understood that financial constraints, travelling long distances for treatment and stay at lodging house arrangements with compromised hygienic conditions were the key reasons for low follow up in cancer care. Gender inequality is commonly observed in many parts of the Indian society. The patriarchal approach, where men are the decision makers for the family, leads to female health issues being frequently neglected. Many female patients were unable to attend follow-up sessions at AIIMS due to their domestic chores and house responsibility.

CT imaging, MRI and DEXA facility (for muscle mass determination) is available at AIIMS. However, due to lack of equipment availability, scans are done once in eight to twelve months or on severe symptom complaints. Though, there has been a sharp increase in cancer patients in India, the infrastructure at hospitals is still not well developed to support optimal treatment. If patients undergo imaging in their early stages of diagnosis, treatment can be planned timely. Also regular scans will aid in monitoring disease progression. Most patients have to wait at least three to four months for a scan appointment (except X-ray) at AIIMS after oncologist referral. This leads to further delay in starting palliative chemoradiotherapy or planning surgery, impacting patients QoL.

Dietary restrictions laid by family members, superstitions, complementary medicine practitioners and religious healers were barriers faced during nutritional counselling sessions. Family caregivers (mostly children, mother or siblings) used to try and force feed the patient causing distress. Lack of knowledge among caregivers regarding disease prognosis and cachexia symptoms was an issue that too needed attention during counselling sessions. Caregivers often suffer from depression like symptoms and altered dietary practices leading to more eating related distress than the patient herself. Telephonic counselling session was imparted to all patients weekly during the intervention and helped in building a healthy relationship with them. These weekly sessions also gave a better understanding about their dietary patterns and might have contributed to better and/or maintenance of QoL. Studies in the past have reported improved nutritional status and QoL in cancer patients receiving telephonic counselling by dieticians (Silvers *et al.,* 2014).

CRP is the most widely accepted inflammation marker for cancer cachexia assessment by western clinical bodies (Suzuki *et al.,* 2013). In India where high percentages of cancer patients are diagnosed at late stages cachexia prevalence should be high (though undocumented). CRP analysis is still not a routine test at the oncology department and our study patients had to pay for the same in a different department.

The most important factor in commercial ONS intake was limited availability in rural India and financial constrains. Taste acceptance was also a factor contributing towards low compliance of commercial ONS. Patients would always correlate commercial ONS with medicines which have side-effects. Their main fear was the well-being of their family on accidental consumption of the same. IAtta was made using natural vegetarian ingredients which they could consume while in company of other family members accompanied by their daily food preparations. The low compliance during our study was mainly due to treatment side-effects and co-morbidities.

7.2 Conclusion

Embedding nutrition supplementation within the palliative care therapy is likely to improve quality of life and stabilise heath status in cancer cachexia patients receiving anti-cancer therapy. Maintenance of inflammatory status among IAtta consuming patients meets the objective of the proposed study. These positive findings qualify IAtta for extensive intervention and to ascertain its position within palliative care framework in India.

ONS available in the market contain synthetic products with limited bioavailability and not affordable by the low socioeconomic status patients. To our knowledge this is the first study to show that a combination of readily available (sustainable) food products can aid in body weight maintenance of palliative free living cancer patients. This study results indicate that if readily bio-available (natural) nutritional supplementation (like IAtta) is offered to cancer cachexia female patients their health status can be maintained along with increased physical activity and they may experience improvement in some aspects of quality of life.

7.3 Future work

A recent systematic review on interventions among cancer cachexic patients (Cuhls *et al.,* 2016), concluded that mineral, vitamin, protein and other types of supplementation had limited effect. Dietary supplementation on the other hand had no adverse effect and therefore impact of food supplementation should be further studied among cachexic palliative cancer patients (Cuhls *et al.,* 2016).

We propose the following suggestions for future work:

- Effect of IAtta consumption on cancer specific sites can be assessed and validated.
- Inclusion of a team of nutritionist/dietician amongst doctors and health professionals in Pain and Palliative Care OPD will be proposed at AIIMS hospital.
- Nutritional guidelines and food recipes to be drafted for Indian cancer cachexia patients and shared with health authorities.
- Sustainability plan: Workshops and training sessions to be arranged for cancer patients receiving palliative care at different health centers in New Delhi to create awareness regarding effectiveness of nutritional intervention in palliative cancer patients. Patients will be empowered to prepare their own meal. They will be guided about ingredient procurement, storage, mode of preparation, cooking, discarding leftover and maintain food hygiene. Caregivers will be included in these sessions to educate them about the disease symptoms and best patient management protocol.
- Rural and tertiary care centres will be approached for an extension of IAtta intervention study.
- NGO's providing patient home visit should be educated about importance of good nutrition in cancer palliative care.
- Workshops and training sessions to be organised for doctors, nurses and health care workers, to educate them regarding the nutritive value of natural food ingredients that can be incorporated in diets of palliative cancer patients. The nutritive value of super foods consumed commonly by the patients to be highlighted in these sessions in order to deliver better nutritional counselling.

Chapter 8:

References and Appendices

8.1 Reference list

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8.2 Appendices

Appendix 1: Patient information sheet

To assess the effectiveness of tailored food recipe in delaying the progression of cachexia to refractory cachexia in adult female cancer patients: A study based in India.

We would like to invite you to participate in this research study. Please read the following details regarding the study and your involvement carefully before you decide to take part. If you require further clarification or have additional questions contact us.

What is the purpose of the study?

Cancer cachexia is a complex disorder marked by progressive weight loss (wasting), in association with anorexia (loss of appetite), asthenia (lack of energy and strength) and altered immune function. Weight loss may be prevented and quality of life may improve by supplementing the patient's diet with energy and protein dense food along with physical activity. Therefore the main aim of this study is to delay the progression of cancer cachexia to refractory cachexia, by nutrition intervention program among free living female patients.

Can I take part in the study?

Yes if you are:

Female, age 18 years and above.

Not pregnant woman or a nursing mother

Suffering from cancer with no gastrointestinal tract defects affecting nutrient digestion and absorption.

Have weight loss more than 5% from pre-treatment weight or Body Mass Index less than 20Kg/m2.

Haemoglobin level less than 12g/dl.

Energy intake less than 1500kcal/d (to be assessed on consultation).

What is expected from me?

You will be asked to sign a “consent form” and a copy of the “information sheet” will be provided. We will seek your permission to access your past medical records. Physical measurements will be taken and you will be expected to complete certain questionnaires regarding your well-being. Depending upon the group you are randomly assigned to, you might be asked to consume the prepared supplement once a day for duration of 6 months along with nutritional and physical activity counselling.

What types of measurements / tests will be performed on me?

On the first day of the study following measurements will be taken:

Weight

Height

Mid-upper arm circumference

Skin fold thickness

This involves measurement of thickness of a vertical fold on the right upper arm, shoulder blade and waist using a Skinfold Caliper.

A series of questionnaires will be completed to provide information regarding your well-being and medical history.

All the above mentioned measurements will be repeated at the end of 3 months and 6 months of participation. Your haemoglobin levels will be monitored by referring to regular hospital medical test reports.

How can I prepare the “IAtta” Chapatti?

A sealed packet will be provided for each day of the study period. The packet will contain roasted horse gram, barley flour, soybean flour, amaranth spinosus and flax seeds in dry powdered form. Please follow the steps below to prepare the Chapatti:

Empty the contents of the packet in a mixing bowl.

Add some water, salt and spices according to your taste.

Gradually knead the dough and add some more water until soft to make balls.

Using the roller make chapattis and heat them on the pan until cooked.

Apply some ghee or butter on top, if required.

Are there any risks of taking part in the study?

There are no risks involved in the study. The ingredients used for IAtta composition are natural vegetarian food items and commonly consumed by the community. All the physical measurements taken are non-invasive.

How will confidentiality be maintained throughout the study?

A unique patient code will be used throughout the study in place of patient name in order to maintain confidentiality. The personal details and medical history information will be stored at a secure place.

What are the advantages of taking part in the study?

The counselling sessions organized for all patients taking part in the study may help to improve your quality of life. If you are randomly assigned in the intervention group you will be consuming the iAtta chapatti which may help you to gain weight or stabilize weight loss and respond optimally to chemotherapy (and other forms of treatment).

What is the procedure to withdraw from the study?

If you decide not to be a part of the study, you are free to withdraw at any time. Your participation in the study is completely voluntary. On withdrawal all your records will be erased and you will be asked to return the unused IAtta powder packets to the investigator.

How will the results be used after the study?

The results would be interpreted and written by the investigator and will be used for research output (but individuals will not be identified). The research output will be available to you upon your written request. If you wish to read a copy of the final report please contact the researcher.

What should I do next to take part in the study?

Please fill in the “consent form” and contact me to arrange for an appointment.

Please note that the decision to participate in this study should be your own and choosing not to take part will not disadvantage you in any way.

For any further questions or information please contact me:

Neha Kapoor: n.kapoor@my.westminster.ac.uk

रोगी सूचना पत्र

अध्ययन का शीर्षकः "महिला कैंसर रोगियों में दुर्दम्य केकेक्सिया हेतु केकेक्सिया की वृद्धि में विलम्ब करने मे पौषणिक हस्तक्षेप के प्रभाव का अध्ययन करना।"

अन्वेषक– नेहा कपूर फोन नं.– +91-9958282099

हम आपको इस अनुसंधान अध्ययन में भाग लेने के लिए आमंत्रित करते हैं। इसमे भाग लेने का निर्णय लेने से पूर्व अपनी सहभागिता एवं अध्ययन से संबंधित निम्नलिखित विवरणों को ध्यानपूर्वक पढ़े। यदि आप और अधिक स्पष्टीकरण पूछना चाहते है अथवा आपके मन में कोई अतिरिक्त प्रश्न है तो इसके लिए आप हमसे संपर्क करें।

अध्ययन का प्रायोजन क्या है?

कैंसर केकसिया एक जटिल विकार है जिसमें भूंख न लगना, कमजोरी (ऊर्जा एवं बल की कमी), परिवर्तित इम्यून प्रकार्य के साथ निरन्तर वजन घटना जैसे लक्षण होते हैं। शारीरिक गतिविधि के साथ ऊर्जा एवं प्रोटीन युक्त भोजन सहित रोगियों के आहार में परिपूरक द्वारा उनके वजन में कमी को रोका जा सकता है तथा जीवन गुणवत्ता में सुधार किया जा सकता है। अतः एव इस अध्ययन का मुख्य उद्देश्य स्वतंत्र जीवन महिला रोगियों में पौषणिक हस्तक्षेप कार्यक्रम द्वारा दुर्दम केकसिया की वृद्धि में विलम्ब करना है।

दुर्दम केकसिया एक ऐसी अवस्था है जिसमें रागी को एण्टी कैंसर थेरेपी हेतु कोई प्रतिक्रिया नही होती एवं उनके जीवित रहने की आशा 3 माह से भी कम होती है।

क्या मैं अध्ययन में भाग ले सकती हूँ?

हाँ यदि आपः

- महिला हैं और आपकी आयु 18 वर्ष एवं अधिक है।

- गर्भवती नहीं है या नार्सिंग माँ नही हैं।
- कैंसर से पीड़ित है परन्तु गैस्ट्रोइंटेस्टिनल पथ दोषों से युक्त नहीं है, पौषणिक पाचन एवं अवचूषण से ग्रसित हों।
- उपचार पूर्व वजन की तुलना में 5% से अधिक वजन कम हुआ हो अथवा वॉडी मास इंडेक्स 20 किग्रा/एम^2 से कम हो ।
- हीमोग्लोबिन स्तर 12 जी/डी एल से कम हो।
- ऊर्जा का अन्तर्ग्रहण 1500 के सी ए एल/डी से कम हो (परामर्श करने पर निर्धारित किया जाए)

मुझसे क्या आशा की जा रही है?

आपसे "सहमति प्रपत्र" पर हस्ताक्षर करने को कहा जाएगा एवं "सूचना पत्र" की एक प्रति आपको प्रदान की जाएगी।

हम आपके पिछले चिकित्सा रिकार्डो को देखने की अनुमति मागेंगे। शारिरिक माप लिया जाएगा एवं आपसे आपके स्वास्थ्य के संबंध में कुछ निश्चित प्रश्नावलियों को भरने के लिए कहा जाएगा । यादृच्छिक रूप से जिस समूह में आपको रखा जाएगा उसमें आपको पौषणिक एवं शारिरिक गतिविधि परामर्श के साथ 6 माह की अवधि के लिए दिन में एक बार तैयार संपूरक को रखने के लिए कहा जाएगा।

मुझ पर किस प्रकार के माप/जांचे निष्पादित की जाएगी?

अध्ययन के प्रथम दिन निम्नलिखित माप किए जाएंगे।

- वजन
- लंबाई
- मध्य–ऊपरी बाँह का घेरा
- त्वचा की मोटाई

इन मापो में स्किनफोल्ड कैलीपर का प्रयोग करके दाएं ऊपरी बाँह पर लम्ब फोल्ड की मोटाई, कंधे की हड्डी एवं कमर का माप लेना सम्मिलित है।,

- आपके स्वास्थ्य एवं चिकित्सा इतिवृत के संबंध में सूचना प्रदान करने के लिए प्रश्नावलियां का एक क्रम पूर्ण किया जाएगा।
- 0.02 सी सी (एक चौथाई चाय के चम्मच से कम) रक्त नमूना लेकर हीमोग्लोबिन मूल्यांकन किया जाएगा।

उपर्युक्त सभी मापों को आपकी सहभागिता के 3 माह एवं 6 माह के अंत में दुबारा किया जाएगा नियमित अस्पताल चिकित्सा जांच रिपोर्टो के रेफर द्वारा आपके हीमोग्लोबिन स्तरो को मॉनीटर किया जाएगा।

आई.ए.टी.टी.ए से संबधित सभी जांचे यूनीवर्सिटी ऑफ वेस्टमिन्स्टर एवं लंदन मेट्रोपोलीटन यूनीवर्सिटी में की जांएगी।

मै आई. ए. टी. टी. ए. चपाती की तैयारी कैसे कर सकती हूँ?

अध्ययन अवधि के प्रत्येक दिन एक सीलबंद पैकेट प्रदान किया जाएगा। पैकेट में भूना हुआ चने का आटा, भूना हुआ जौ का आटा , सोयाबीन का आटा, सूखा हुआ चौलिया का पत्ता और अलसी के बीज का आटा सूखे पाउडर के रूप में मिलाया है । चपाती बनाने के लिए कृपया नीचे दिये गए कथनो का अनुपालन करें।

- एक परात में पैकेट के तत्वों को डालें ।
- अपने स्वादानुसार कुछ नमक एवं मसलें डालें ।
- थोडा पानी डालें । धीरे - धीरे लोई को गूथें एवं जब तक यह मृदु न हो जाए तब तक और पानी डालकर गूथें जिससे कि गोला बन सकें ।
- बेलन का प्रयोग करके चपाती बनाएं एवं उन्हें तवे पर तब तक गर्म करें जब तक यह पक न जाए ।

क्या अध्ययन में भाग लेने से कोई जोखिम है?

अध्ययन में किसी प्रकार का जोखिम नहीं है। आई. ए. टी. टी. ए. संयोजन के लिए प्रयोग की जाने वाली सामग्रिय प्रकृतिक शाकाहारी भोजन की वस्तुएं है एवं सामान्यत: जनसमुदाय इन्हें उपयोग किया जाता है । यदि अनुसंधान संबंधी कोई क्षति होती है तो रोगी का अखिल भारतीय आयुर्विज्ञान संस्थान वार्ड , नई दिल्ली, भारत, द्वारा उपचार किया जाएगा । और अधिक जानकारी के लिए कृपया अन्वेषकों से संपर्क करें ।

अध्ययन के दौरान गोपनीयता किस प्रकार राखी जाएगी?

गोपनीयता को बनाए रखने के लिए रोगी के नाम के स्थान पर पूरे अध्ययन में एक विशिष्ट रोगी कोड का प्रयोग किया जाएगा । निजी जानकारी एवं चिकित्सा जानकारी को एक सुरक्षित स्थान में रखा जाएगा ।

अध्ययन में भाग लेने के क्या लाभ हैं?

अध्ययन में भाग लेने वाले सभी रोगियो के लिए आयोजित किये जाने वाले परामर्श राजो से आपकी जीवन गुणवत्ता में सुधार लाने में मदद मिल सकती है यदि हस्तक्षेप समूह में आपके यादृच्छिक रूप से रखा जाता है तो आपको आई.ए.टी.टी.ए चपाती खाने के लिए कहा जाएगा जिससे आपको वजन बढ़ाने या वजन मे कमी को स्थिर करने एवं कीमोथेरेपी (एवं उपचार के अन्य प्रकार) हेतु सही प्रकार से प्रतिक्रिया करने में मदद मिल सकती है।

अध्ययन में नाम वापस लेने की क्या प्रक्रिया है?

यदि आप अध्ययन में भाग नहीं लेने का निर्णय करते है तो आप किसी भी समय ऐसा करने के लिए स्वतंत्र हैं। इस अध्ययन में आपकी सहभागिता पूर्णतः स्वैच्छिक हैं। नाम वापस लेने पर आपके सभी रिकार्डो को मिटा दिया जाएगा एवं आपसे प्रयोग नहीं किए गए आई.ए.टी.टी.ए पाउडर के पैकेड को अन्वेषक को वापस करने के लिए कहा जाएगा।

अध्ययन के पश्चात परिणामों का प्रयोग किस प्रकार किया जाएगा?

परिणामों की अन्वेषक द्वारा व्याख्या की जाएगी एवं उन्हे लिखा जाएगा तथा इनका प्रयोग अनुसंधान परिणाम के लिए किया जाएगा (परन्तु व्यक्ति की पहचान प्रकार नहीं की जाएगी)। आपके लिखित अनुरोध करने पर अनुसंधान परिणाम को आपको उपलब्ध कराया जाएगा। यदि आपकी इच्छा अंतिम रिपोर्ट को पढ़ने की हो कृपया अनुसंधानकर्ता से संपर्क करें।

अध्ययन में भाग लेने के लिए मुझे और क्या करना चाहिए?

कृपया "सहमति प्रपत्र" को भरें एवं एपाइटमेंट (नियोजित समय) के लिए मुझसे संपर्क करें।

कृपया नोट करे कि इस अध्ययन में भाग लेने का निर्णय आपका अपना होना चाहिए एवं इसमें भाग नहीं लेने के निर्णय से आप पर किसी प्रकार का प्रतिकूल प्रभाव नहीं पड़ेगा।

Appendix 2: Patient informed consent form

PARTICIPANT INFORMED CONSENT FORM

Protocol / Study number:_ IEC/NP-79/2013

Participant identification number for this trial:

Title of project: To assess the effectiveness of tailored food recipe in delaying the progression of cachexia to refractory cachexia in adult female cancer patients: A study based in India

Name of Principal Investigator: Miss Neha Kapoor Tel. No(s). 09958282099

The contents of the information sheet dated…….that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:

(Signatures / Left Thumb Impression) Place:

Name of the Participant: _____

Son / Daughter / Spouse of:_____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date: Place:

1) Witness – 1

Signatures

Name:

Address:

2) Witness – 2

Signatures

Name:

Address:

सहभागी सुचित सहमति प्रपत्र

इस जाचं के लिए सहभागी पहचान नमबर IEC/NP-79/2013 _____

अनुसन्धान शीर्षक: महिला कैंसर रोगियों में आग रोक दुर्बलता को दुर्बलता की प्रगति में देरी में पोषण हस्तक्षेप के प्रभाव का अध्ययन करने के लिए भारत में आधारित एक अध्ययन

मुख्य अन्वेषक का नाम ____ नेहा कपूर_____ फोन नंबर: 0091-9958282099

मैंने दिनांक_____ के सूचना पत्र में दिये गए सभी तथ्यो को पड़ लिया हैं। मुझे समझ आने वालीं भाषा मैं विस्तारपूर्वक बत्ता दिया है और मैनें तथ्यो को भली भांति समझ लिया है। मैं पुष्टि करता हूँ कि मुझे प्रशन पुछने का अवसर दिया गया है।

मुझे अध्ययन की प्रकृति, उद्देश्य और इसके सम्भावित लाभ/जोखिमों और अध्ययन की सम्भावित अवधि अन्य प्रासंगिक जानकारी के बारे में विस्तार पुर्वक समझा दिया गया है । मैं समझाता हूँ कि इस अध्ययन में मेरी भागिधारी स्वेछिक है और इस अध्ययन से किसी भी समय बिना कोई कारण बताए, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकारों के प्रभावित हए अपना नाम वापिस ले सकता/सकती हूँ ।

मैं समझता हूँ कि इस अनुसन्धान में मेरी सहभागिता से मेरे बारे में एकत्र जानकारी और चिकित्सीय नोटों को एम्स अस्पताल के जिम्मेदार लोगो द्वारा देखा जायेगा। मैं इन व्यक्तियों को अपने रिकोर्ड देखने कि अनुमति प्रदान करता/करती हूँ ।

मैं उपयुक्र्त अध्यन में भाग लेने के लिए अपनी सहमति प्रदान करता /करती हूँ ।

सहभागी के हस्ताक्षर / बाएं अंगूठे का निशान दिनांक
स्थान

सहभागी का नाम

पिता/पति का नाम

पूरा पता

यह प्रमाणित किया जाता हे कि उपयुक्र्त सहमति मेरी उपस्थति में ली गईं हैं ।

मुख्य अन्वेषक के हस्ताक्षर दिनाक: स्थान:

१) गवाह के हस्ताक्षर

नाम

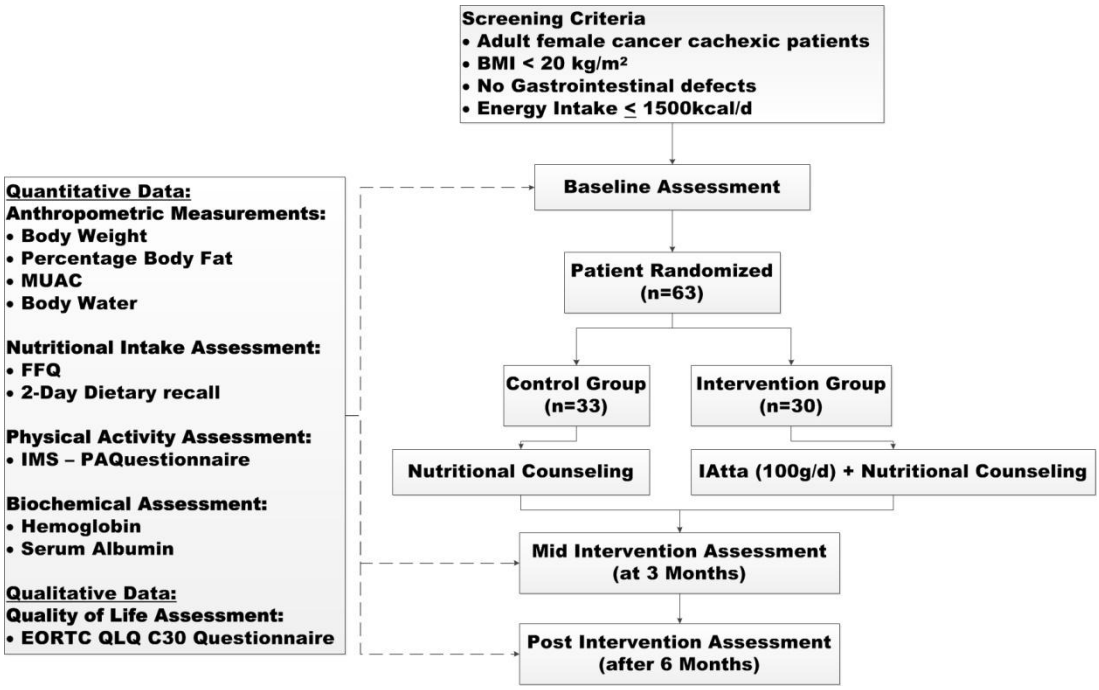
पता

२) गवाह के हस्ताक्षर

नाम

पता

Appendix 3: Pilot study design

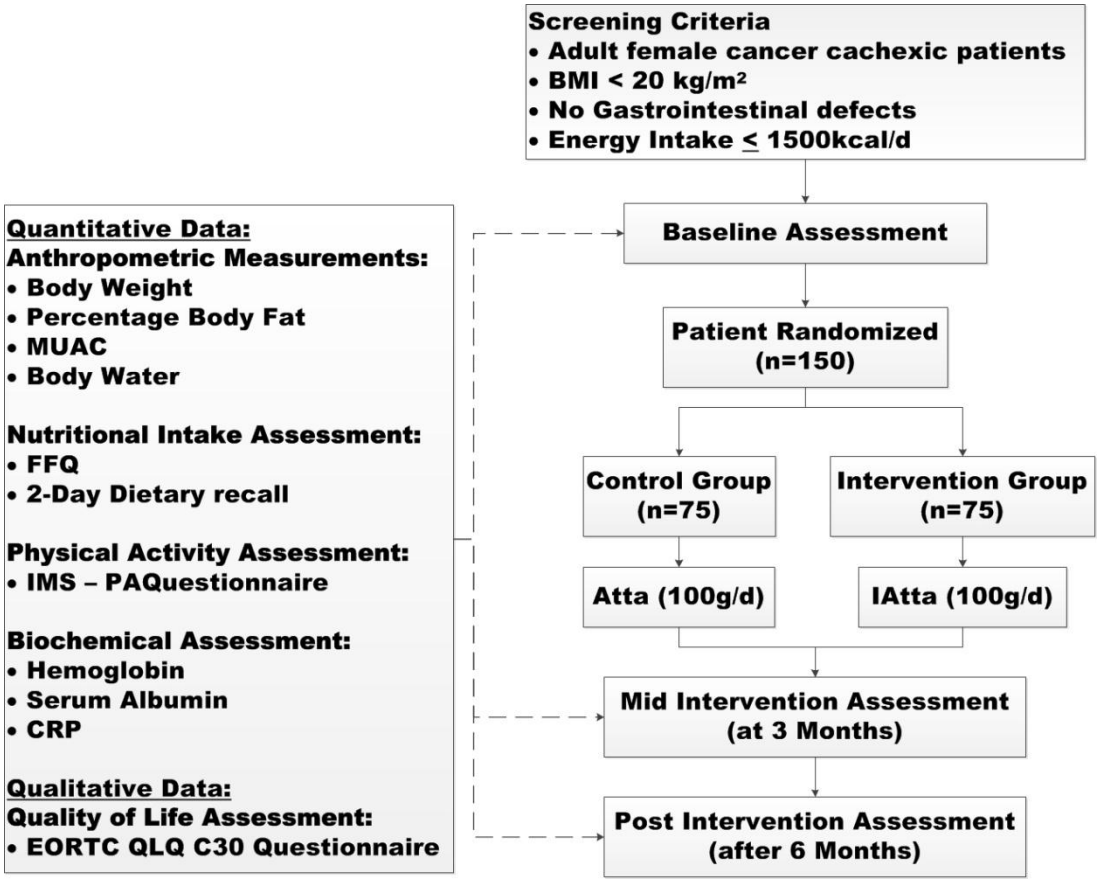


Appendix 4: Nutritive value whole wheat flour

(Gopalan *et. al.,* 2012, p.47)

Energy	Carbohydrate	Protein	Fat	Iron	Calcium	Phosphorus	Vitamin A (Carotene)
341 kcal	69.4 g	12.1g	1.7g	4.9mg	48mg	355 mg	29mg

Appendix 5: Scale-up study design



Appendix 6: Questionnaire used during intervention

To evaluate the effectiveness of nutritional counselling and "Improved Atta" supplementation in delaying progression of cachexia to refractory cachexia in adult cancer patients in Indian population.

Name: Age: Sex:

UHID: IRCH No:

Address:

Mobile:

Weight (Kg): Height (cm): BMI (Kg/m^2):

Diagnosis: Cancer Stage:

History of treatement:

- Radiotherapy:
- Chemotherapy:
- Previous Surgery (Describe):

Biochemical Investigations:

- Hemoglobin /PCV:
- Albumin:
- C-Reactive Protein:

Anthropometry:

	Baseline	**Follow-up**
Body weight (Kg)		
BMI (Kg/m^2)		
Body fat(%)		
Total body water (%)		
Muscle Mass (Kg)		
Physique rating		
Bone mass (Kg)		
BMR(kcal)		
Metabolic age (yrs)		
Visceral fat level		
MUAC (cm)		
Skin fold thickness		
Bicep (mm)		
Tricep (mm)		
Suprascapular (mm)		
Suprailliac (mm)		

Appendix 7: Tools used for dietary recall portion size estimation

Appendix 8: Food frequency questionnaire

* Permission received from Satija *et al.,* (2012) to use the questionnaire for research purpose

	CEREALS	**Portion Size**	**Average consumpt-ion**	**Per Day**	**Per We-ek**	**Per Month**	**Per Year / Never**
1.1	Tandoor roti, phulkas, Chapathis, parathas, naan	No					
1.2	Stuffed parathas	No					
1.3	Ragi roti	No					
1.4	Bajra, maize roti	No					
1.5	Jowar, channa roti	No					
1.6	Poori, bhatura	No					
1.7	Plain rice	Bowl					
1.8	Vegetable pulao/ veg biriyani	Bowl					
1.9	Mutton, chicken pulao/biriyani	Bowl					
1.10	Khichdi	Bowl					
1.11	Idlis	No					
1.12	Plain dosa, masala dosa, uthappam	No					
1.13	Poha	Bowl					
1.14	Dalia	Bowl					
1.15	Oats porridge	Bowl					
1.16	Corn flakes, cereal flakes etc.	Bowl					
1.17	Bread, Toast, Rolls, Buns	No					
1.18	Pizza, Burger	No					
1.19	Noodles, macaroni, pasta etc	Bowl					

2.1	Plain tur dhal sambar / dhal	Ladle					
2.2	Tur dhal sambar / dhal with vegetables	Ladle					
2.3	Channa, rajma, dry peas etc. curry	Ladle					
2.4	Green leafy vegetable curry	Ladle					
2.5	Paneer gravy	Ladle					
2.6	Kadhi	Ladle					
2.7	Bengal gram dhal curry	Ladle					
2.8	Blackgram dhal curry	Ladle					
	CHUTNEYS / SALAD / PAPAD						
3.1	Soups, all types (veg or non-veg)	Bowl					
3.2	Fresh vegetable salad	Tbsp					
3.3	Vegetable Raitha	Tbsp					
3.4	Mango, lime pickle etc.	Tsp					
3.5	Papad	No					
3.6	Chutney (Tomato, Tamarind, Coriander, etc.)	Tbsp					
	NON – VEGETARIAN						
4.1	Chicken curry	Bowl					
4.2	Chicken fry/grilled	No					
4.3	Mutton/ pork curry	Bowl					
4.4	Mutton /pork fry	No.					
4.5	Fish curry	Bowl					
4.6	Fish fry	No					
4.7	Organ meats (Liver,	Tbsp					

	brain, kidney etc.)						
4.8	Prawn, crab, shell fish etc.	Bowl					
4.9	Egg (boiled, poached, omelettes)	No					
4.10	Ham, salami, bacon etc.	Slices					
	MILK & BEVERAGES						
5.1	Tea	Glass					
5.2	Coffee	Glass					
5.3	Plain milk	Glass					
5.4	Flavored milk (horlicks, bournvita etc)	Glass					
5.5	Curd, yoghurt	Bowl					
5.6	Buttermilk/Lassi	Glass					
5.7	Fresh fruit juice(lime, orange etc)	Glass					
5.8	Fanta, pepsi, coca cola etc.	250ml bottle					
5.9	Beer	Glass					
5.10	Wine	Glass					
5.11	Spirits (whiskey, gin, rum)	30ml peg					
5.12	Aam ka panna	Glass					
	MISCELLANEOUS						
6.1	Butter/ cream	Tsp					
6.2	Ghee	Tsp					
6.3	Jam	Tsp					
6.4	Sugar	Tsp					
6.5	Honey	Tsp					
6.6	Jaggery	Tsp					
6.7	Cheese	Cube					

6.8	Ketchup, tomato sauce	Tbsp					
	SNACKS/ SWEETS/DESSERTS						
7.1	Mixture, namkeen, chiwda, khara boondi, dalmoth	Tbsp					
7.2	Nuts (grounduts, cashewnuts etc.)	Tbsp					
7.3	Chips, French fries	Bowl					
7.4	Samosa,bajji ,bonda, cutlet, patties, puff	No					
7.6	Biscuits (sweet, creamed, salted etc)	No					
7.7	Bhel puri, masala puri, other chaats	Bowl					
7.8	Dhokla	No					
7.9	Pav bhaji	No					
7.10	Cakes or sweet pastries	No					
7.11	Payasam, kheer	Bowl					
7.12	Custard, puddings	Bowl					
7.13	Ice cream	Bowl					
7.14	Jamoon, Jilebi, etc.	No					
7.15	Ladoo, barfis	No					
7.16	All Halwas	Tbsp					
7.17	Shakarpara, balushahi, Gujiya	No					
7.18	Indian milk sweet (peda, rasgulla etc.	No					
7.19	Dairy milk, 5 star, kitkat etc. Chocolates	Small Bar					

	FRUITS	**Porti-on Size**	**Average consumpt-ion**	**Pe-r Da-y**	**Per Week**	**Per Mo-nth**	**Per Year/ Never**	**Sea-son-al**
8.1	Banana	No						
8.2	Apple	No						
8.3	Orange	No						
8.4	Sweet lime	No						
8.5	Mango	No						
8.6	Guava	No						
8.7	Grapes	Bowl						
8.8	Pineapple	Slice						
8.9	Papaya	Slice						
8.10	Pomegranate	No						

Appendix 9: 24 hour dietary recall

Questions	**Menu**	**Ingredients**	**Amount in household measure**	**Consistency (Dry/Liquidy/ Thick/Soft/NA)**	**Final Weights *(for investigators use only)***
Did you eat or drink anything after you got up in the morning yesterday? What did you have?					
Did you eat /drink anything else in the morning? *(if working ,then specify; "before going for work")* What did you have?					
Did you eat/drink anything in the afternoon? What did you have?					
Did you eat/ drink in the evening *(if working, then specify; "after coming from work")* What did you have?					
Did you eat/drink anything at night? What did you have?					
Did you eat or drink anything else just before going to bed? What did you have?					
Is there anything else that you ate/drank yesterday which you haven't told me already? What did you have?					

Appendix 10: PG-SGA questionnaire

* Available for use in Bauer *et al.,* (2006)

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking:
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3)_____
☐ other** (1) _____
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)

** Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)

Box 4 ☐

Additive Score of the Boxes 1-4 ☐ **A**

The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements *(See Worksheet 2)*

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

Age _____

Numerical score from Worksheet 2 ☐ **B**

6. Metabolic Demand *(See Worksheet 3)*

Numerical score from Worksheet 3 ☐ **C**

7. Physical *(See Worksheet 4)*

Numerical score from Worksheet 4 ☐ **D**

Global Assessment *(See Worksheet 5)*
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total PG-SGA score
(Total numerical score of A+B+C+D above) ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other __ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

) **FD Ottery, 2001**

Worksheets for PG-SGA Scoring

Boxes 1-4 of the PG-SGA are designed to be completed by the patient. The PG-SGA numerical score is determined using 1) the parenthetical points noted in boxes 1-4 and 2) the worksheets below for items not marked with parenthetical points. Scores for boxes 1 and 3 are additive within each box and scores for boxes 2 and 4 are based on the highest scored item checked off by the patient.

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of the PG-SGA.

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Score for Worksheet 1 ☐
Record in Box 1

Worksheet 2 - Scoring Criteria for Condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1

Score for Worksheet 2 = ☐
Record in Box B

Worksheet 3 - Scoring Metabolic Stress

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Corticosteroids	no corticosteroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroids (≥30mg prednisone equivalents/day)

Score for Worksheet 3 = ☐
Record in Box C

Worksheet 4 - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Rating of deficit in these categories are *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	**0**	**1+**	**2+**	**3+**
Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	**0**	**1+**	**2+**	**3+**

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	**0**	**1+**	**2+**	**3+**

Point score for the physical exam is determined by the overall subjective rating of total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Score for Worksheet 4 = ☐
Record in Box D

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss **OR** Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) **OR** No wt stabilization or wt gain (i.e., continued wt loss)	> 5% wt loss in 1 month (or >10% in 6 months) **OR** No wt stabilization or wt gain (i.e., continued wt loss)
Nutrient Intake	No deficit **OR** Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None **OR** Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit **OR** Significant recent improvement	Moderate functional deficit **OR** Recent deterioration	Severe functional deficit **OR** recent significant deterioration
Physical Exam	No deficit **OR** Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible edema)

Global PG-SGA rating (A, B, or C) = ☐

Appendix 11: Physical activity questionnaire

* Permission received from Sullivan *et al.,* (2012) to use the questionnaire for research purpose

	Now I will ask you questions relating to your daily activity as this will help us to determine how active you are. Please answer these questions with respect to your activities over last ONE MONTH.			
	Work related activity			
1.1	How many days in a week do you work?	☐ [In completed days]		
1.2	On an average, how many hours per day do you spend at work?	☐☐.☐ [In completed half hours]		
1.3	**Of the hours you spend at work, how many hours do you spend in (completed half hours):**			
	(a) **Standing:** Activities such as talk, lab work, supervise, mild cleaning, cattle grazing done standing.	(b) **Sitting:** Activities such as typing, computer work, cleaning grains, eating lunch, driving, ironing, done sitting etc	(c) **Walking**: walking around, strolling	(d) **On activities more strenuous than walking**: Fetch water/ fuel, fooder. weeding, chop wood, ploughing, pounding rice, walking with a load.
	☐☐.☐ [hours]	☐☐.☐ [hours]	☐☐.☐ [hours]	☐☐.☐ [hours]
1.4	**If you spend any time at work on activities more strenuous than walking, please list the activities that you do most in terms of time:**			
	(a)			
	(b)			
	(c)			
	(d)			
1.5	On an average, how many hours do you sleep in a day? ☐☐.☐ [Completed half hours]			
	Apart from work, how do you spend your time (over the last month): Frequency options: [1=Daily; 2=Once a week; 3=2-4 times/week; 4=5-6 times/week; 5=2-3 times/month; 6=Once a month]			
2.1	**Sports / games / exercise (for eg. walking, badminton, jogging, cricket……etc)**			
	(a) Name of activity	(b) Duration	(c) Frequency	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
2.2	**Hobbies involving manual labour (for eg. Carpentry, gardening ……..etc.)**			
	(a) Name of activity	(b) Duration	(c) Frequency	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	
	_____	☐☐☐ [mts]	☐	

	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
2.3	**Household activities (for eg. sweeping, collecting fuel/fodder/water, animal care, cooking, washing child care……. etc.)**		
	(a) Name of activity	(b) Duration	(c) Frequency
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	Apart from work, how do you spend your time (over the last month): Frequency options: [1=Daily; 2=Once a week; 3=2-4 times/week; 4=5-6 times/week; 5=2-3 times/month; 6=Once a month]		
2.4	**Sedentary activities for e.g. Reading, watching TV, prayer, carom, computer games, travelling……. etc.)**		
	(a) Name of activity	(b) Duration	(c) Frequency
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	_____	☐☐☐ [mts]	☐
	Other activities	(a) Duration	(b) Frequency
2.5	Eating (breakfast, dinner)	☐☐☐ [mts]	☐
2.6	Brushing, shaving & bathing	☐☐☐ [mts]	☐
2.7	Dressing	☐☐☐ [mts]	☐
2.8	Socialising (talking outside working hours)	☐☐☐ [mts]	☐
2.9	Travelling to and fro from work	☐☐☐ [mts]	☐
2.10	How do you travel to and fro from work?	_____	

Appendix 12: Quality of life

* Permission received from Fayers *et al.,* (2001) to use the questionnaire for research purpose

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 13: Sensory evaluation questionnaire

Food Product for evaluation: *IAtta*

(100% natural ingredient: Roasted chickpea flour, roasted barley flour, roasted soybean flour, roasted flaxseeds powder & dried amaranth leaves powder)

Please taste the presented formulated three samples and evaluate them according to following characteristics: Aroma, appearance, etc. See table below.

Provide marks between 1 to 5, according to your liking.

1	2	3	4	5
Strongly disliked	**Disliked**	**Acceptable**	**Liked**	**Most liked**

Characteristics	**Orange**	**Blue**	**Green**
Aroma			
Appearance			
Consistency /Thickness			
Texture			
Taste			

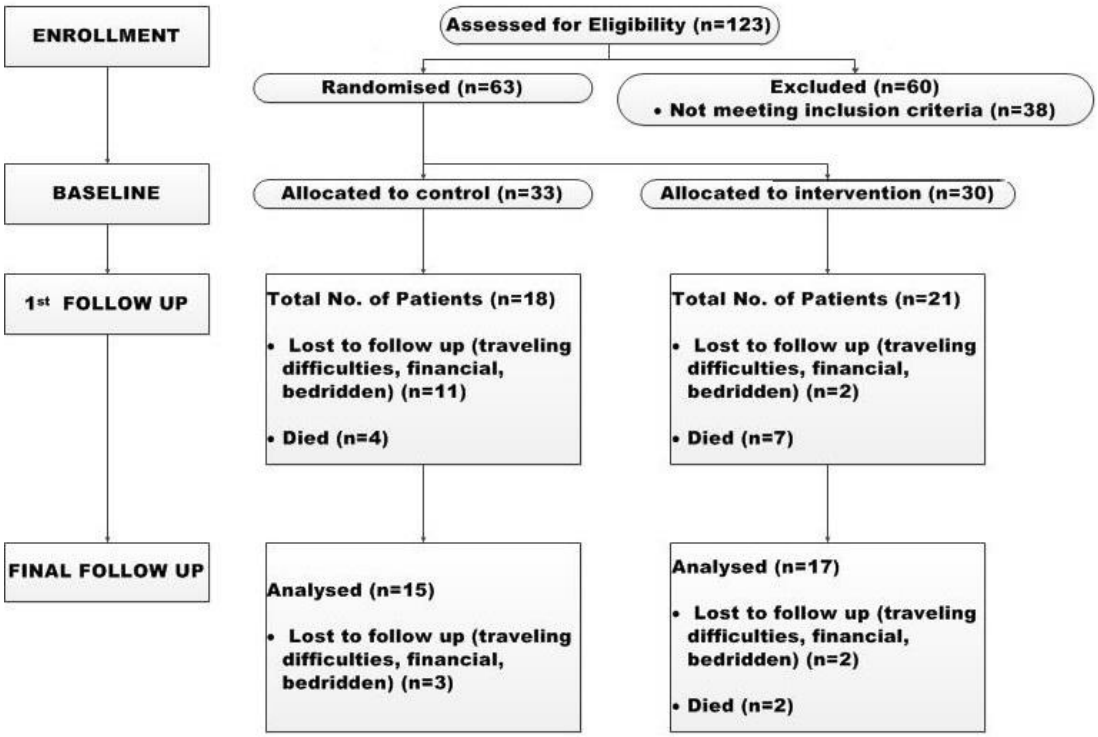
Please re-arrange the 3 formula according to your taste preferences	**Formula**	**Insert your preference here**
	Orange	
	Blue	
	Green	

Comments (if any):

.....
.....
.....
.....
.....

Thank you for your time.

Appendix 14: Consort flow diagram for pilot study



Appendix 15: IAtta pilot study results

* Full text available for free access in Kapoor *et al.,* (2016)

Research Article

Integrative Cancer Therapies
April-June 2016: 1–11

DOI: 10.1177/1534735416651968
ict.sagepub.com
SAGE

A Prospective Randomized Controlled Trial to Study the Impact of a Nutrition-Sensitive Intervention on Adult Women With Cancer Cachexia Undergoing Palliative Care in India

Neha Kapoor, MSc[1], Jane Naufahu, PhD[1], Sundus Tewfik, PhD[2], Sushma Bhatnagar, MD[3], Rakesh Garg, MD[3], and Ihab Tewfik, PhD[1]

Abstract

Purpose. Advanced cancer patients with disease progression develop cachexia. Nevertheless, cancer patients at nutritional risk have shown improved body weight and quality of life with oral nutritional supplements. *Method.* This was a randomized controlled trial in adult female cancer patients (n = 63) attending palliative clinics, with symptoms of cachexia. Eligible patients were randomly distributed into control (n = 33) and intervention (n = 30) groups. Both groups were provided with nutritional and physical activity counseling, but the intervention group received an additional 100 g of Improved

Appendix 16: Consort diagram for scale-up study