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# Effects of Early Immunonutrition on Patients with Pelvic Malignancies Receiving Radiotherapy

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## ABSTRACT

**Background:** Immunonutrition controls the response of the body to disease and damage**.** Glutamine acts to maintain the intestinal tract, immune cells and muscle, thus it is important to attack against infections and mucositis, also modifies the inflammatory response. Arginine plays a significant role in cell proliferation, synthesis of protein, endocrine, and immune control. So they help to reduce the degree of toxicities induced by treatment.

**Objective:** This study aimed to evaluate the effects of immunonutrition formula administration on the incidence of acute radiotherapy (RT) related toxicities, treatment interruption, overall treatment time and response to treatment.

**Patients and methods:** This prospective study included 120 patients who met the inclusion criteria (adults > 18 years old, pelvic malignancy; bladder, prostate, cervix, uterus and rectum who received radical dose radiotherapy; adjuvant, neoadjuvant, or definitive, either alone or with chemotherapy or hormonal treatment, and PS 0-2). Patients were randomized into 2 groups: Group 1 received immunonutrition with planned calculated diet and standard treatment, and group 2 that received standard treatment only with standard nutrition.

difference regarding percentage of body weight loss, development of toxicity, time to recovery from toxicity, incidence of hospital admission, and treatment interruption, which were lower in group 1 (P value < 0.0001, 0.022, 0.001, 0.021, and 0.022 respectively). By multivariate logistic regression, group 1, diagnosis of bladder and rectal cancer were independent predictors of toxicity (P value 0.045, 0.026, and 0.001 respectively).

**Conclusion:** Arginine, glutamine, fish oil immunonutrition formula administration could reduce the incidence of radiotherapy-related toxicities, hospital admission, treatment gap and prevent weight loss.

**Keywords:** Immunonutrition, Pelvic malignancies, Toxicity.

## INTRODUCTION

In cancer patients, the clinical outcomes can be efficiently improved by radiotherapy; however, it many times leads to severe side effects including the gastrointestinal tract, genitourinary, hematological, dermatological and sexual side effects, which lead to treatment interruption and prolong overall treatment time [1].

Up to 80% of patients develop gastrointestinal (GI) symptoms when received radiotherapy to the pelvic region. For patients taking long period of treatment of 5–7 weeks, most patients (up to 90% ) develop different degrees of symptoms due to the closeness of the gastrointestinal tract to the pelvic organs. These symptoms include bowel habit change (94%), watery stool (80%), frequency of bowel (74%), urgency (39%) and incontinence of stool (37) % [2]. About 50% of patients treated with definitive external beam radiotherapy to pelvic region develop grade 1–2 genitourinary side effects [3].

The nutritional status of the patients can be affected by toxicity caused by radiotherapy and result in malnutrition**.** Cancer-related malnutrition (CRM) has a negative impact. It has been calculated that more than half of cancer patients die after developing CRM, while in up to 40% of all oncology patients, CRM can be a direct cause of death. > 5% weight loss before starting chemotherapy can be used to predict weak response to therapy and decreased survival, while early intervention with nutrition (before development of refractory cachexia) was shown to be associated with better tolerance to aggressive anti-cancer treatment, improved quality of life, and increased survival [4].

Nutritional pharmacology refers to the use of specific drugs for purposes other than nourishment. There were four nutrients in particular that have been the subject of research: glutamine, arginine, nucleic acids, and essential fatty acids, which can boost immune cells against tumor cells and are known as immunonutrition [5]. Glutamine (GLN) is a non-essential amino acid in healthy persons that becomes conditionally necessary during catabolic stress periods [6]. It is suspected that GLN loss in cancer patients owing to chemotherapy and radiotherapy-related toxicities might cause mucositis, reduced immunity, and cachexia [7]. Therefore, the administration of oral glutamine supplementation can reduce the occurrence of cancer-related cachexia and other debilitating illnesses [4]. Several studies notified that GLN may have protective role on severe diarrhea-induced by radiation [8]. The potential benefits of glutamine supplementation extend beyond gastrointestinal toxicity reduction and immunological modulation to encompass broader facets of patient comfort during cancer therapy [7]. Numerous benefits of glutamine supplementation have been found in studies investigating the impact of this amino acid on nutritional status, quality of life, and tolerance to therapy [10, 9].

Although arginine is a non-essential amino acid, when the body's supply is insufficient to fulfill metabolic needs, it is deemed conditionally essential during metabolic or traumatic stress periods. It is



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important for cell division, protein synthesis, hormone production, immune system control, and other biological processes [11]. It has been demonstrated that arginine and the omega-3 polyunsaturated fatty acids in fish oil have a major impact on infections and wound healing [12].

It has been discovered that immunonutrition reduces the severity of toxicities associated with treatment, such as enteritis, oesophagitis, oral mucositis, and weight loss. Also, improve treatment tolerance and duration of therapy [5].

The aim of this study was to evaluate the effect of early administration of immunonutrition containing formula of glutamine, arginine and fish oil on the incidence of acute radiotherapy (RT) related toxicities, treatment interruption, overall treatment time and response to radical radiotherapy in patients with pelvic malignancies.

## PATIENTS AND METHODS

**Patients:** This prospective study included patients with pelvic malignancies including cancer bladder, prostate, cervix, uterus and rectum who received radical radiotherapy either alone or with chemotherapy or hormonal treatment through the period from January 2022 to December 2022.

**Inclusion Criteria:** Patients with histopathological evidence of cancer rectum, cervix, endometrium, bladder and prostate, who were treated as definitive, neo-adjuvant or adjuvant RT with or without chemotherapy or hormonal therapy, more than 18 years old, performance status 0-2 [13] and with normal CBC and renal and liver function tests.

**Exclusion Criteria:** Patients with contraindication to radiotherapy as: connective tissue disorders (systemic lupus erythematosus, scleroderma) and who refused to participate in the study.

**Methods:** All patients subjected to detailed history (age, sex, special habits, performance status (PS) and comorbidities), clinical examination, and assessment of weight, height and body mass index (BMI) at baseline (BMI = Weight (kg)/Height$^2$ (m$^2$). Laboratory investigations [Complete blood picture (CBC), complete liver and kidney function tests and tumor markers. Prostatic specific antigen (PSA) in prostate cancer, carcinoembryonic antigen (CEA), and CA19.9 in rectal cancer. Radiological [Magnetic resonance image (MRI) pelvis with contrast and computerized tomography (CT) chest, abdomen with contrast and biopsy for histo-pathologic evaluation of suspected lesion.

**Clinicopathological data:** site of disease, histopathological type, and grade were collected.

The included patients were randomized into 2 groups by simple random numbers generated by computer: Group 1 (intervention group) received standard treatment + planned calculated diet with addition of immunonutrition formula (formula of fat 7.2 g/serving from corn oil, medium chain triglyceride and fish oil , protein 15.6 g/serving from casein, arginine, and glutamine) (figure 1). Group 2 (standard group) received standard treatment + standard nutrition only.

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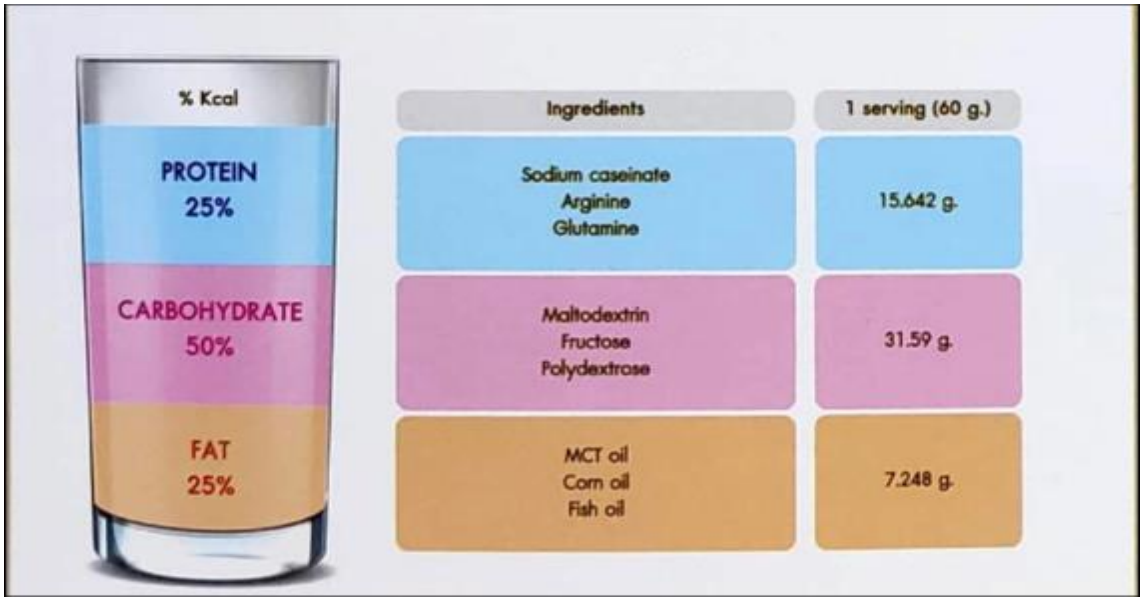


**Figure (1):** Content of one serving of the patient formula

The nutritional supplements were provided with 2 glasses per day (1 glass = 250 mL of 250 kcal), 1 hour before and after radiotherapy session and at week end and holiday.

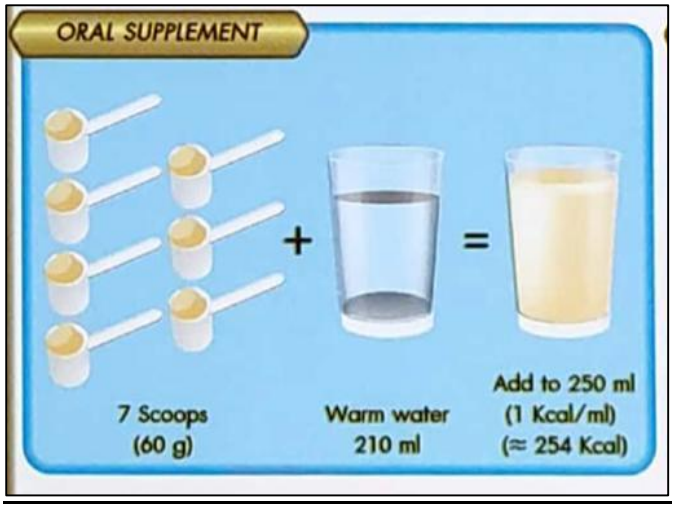


**Figure (2):** Preparation of the formula.

All patients were treated with radical dose of 3 D conformal radiotherapy conventional fractionation schedule with or without concurrent hormonal or chemotherapy or after neoadjuvant chemotherapy or hormonal therapy (androgen deprivation therapy (ADT), and the prescription dose for prostate cancer was 74 Gy in 37 fractions, concurrent with ADT, for cancer rectum was 45 Gy / 25 fractions with a boost of further 5.4 Gy / 3 fractions with concurrent capecitabine (825 mg/m$^2$) twice per day, on each day that RT was given ± neoadjuvant xelox as part of total neoadjuvant therapy and for bladder cancer was 64 Gy / 32 fractions and different radiosensitizers were used including, cisplatin in cisplatin eligible patients or gemcitabine, carboplatin in cisplatin ineligible patients. For cervix and endometrial cancer, whole pelvic RT or extended field RT was delivered with concurrent weekly cisplatin (40 mg/m$^2$). For cervix 45 Gy / 25 fractions, then boost with another 3 fractions up to total dose of 50.4 Gy. For endometrium 45 Gy / 25 fractions. This was followed by brachytherapy (BT) if indicated.

**The study consisted of 3 steps:**

**Step I: pre-radiotherapy nutritional screening and assessment:** before starting radiotherapy included**:** Screening and assessment by Patient-Generated Subjective Global Assessment (PG-SGA) short form tool, which done at diagnosis then weekly during radiotherapy. SGA tool included the patient's medical history (changes in weight and diet, GIT symptoms that occur during the last two weeks and functional capacity) and physical examination (loss of body fat tissue and muscle, edema of ankle and sacrum, and ascites). After history taking and physical examination, the degree of patient's nutritional status was determined: (A): well nourished, (B): moderately malnourished or (C): severely malnourished [14].

**Step II: Intervention phase** started from day one of starting radiotherapy. It included treatment of symptoms that impair food intake and nutritional support. Energy and protein needs were calculated then calculation of nutrient adequacy, recommend the volume of fluid not to exceed 30–35 mL/kg body weight per day, protein intake up to 1.5 g/kg per day. Recommended carbohydrate intake not to exceed 50%–60% of non-protein energy requirements and 40-50% of non-protein calories from fat.

**BMI categories:** Underweight = < 18.5**,** normal weight = 18.5–24.9**,** overweight = 25–29.9 **,** and obesity = BMI of 30 or greater (obesity class I – BMI 30 to 34.9 , class II – BMI 35 to 39.9 , class III – BMI greater than or equal to 40 (also defined as severe, extreme, or massive obesity) [15]**.** In patients with BMI category normal**,** actual body weigh was used. In underweight patients, ideal body weight is calculated then energy requirement is calculated. In men, ideal body weight = 50 + [0.9 × (Height (cm) − 154)], in women: 45.5 + [0.9 × (Height (cm)–154)] [16]**.** In obese and over-weight patients, the adjusted body weight was calculated using the following equation: Adjusted body weight = Ideal weight + (0.4 [Current weight – Ideal weight]) [17]. The protein portion must be increased to 20-30% of the total energy intake. Recommended carbohydrates portion to be 40-50% total energy intake, and recommend fat portion to be 30-40% [18].

**Dietary advice:** Low fiber, low residue diet was designed. Every patient underwent nutritional counseling from the start of RT and received personalized dietary regimen by specialized dietitian, and regular consultation was also provided weekly during RT and at the time of follow-up visits (1 month and 3 months after the end of RT).

**Physical therapy** included physical activities of daily life like motivating patients to walk daily in order to decrease hazards of atrophy due to inactivity [19].

**Step III: Follow up phase:** Patients were monitored weekly for the development of side effects and evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version **5** [20]. Concurrent treatment received, starting date and end of radiotherapy date, periods of interruption of treatment were recorded for each patient. Initial response to treatment was assessed according to RECIST criteria [21]. Post-treatment MRI pelvis was done at least 1.5 months after RT, then every 3 months. Cystoscopic bladder evaluation was done in cases of bladder cancer 3 months after radiotherapy. PSA assessment in prostate cancer was recorded every 3 months. End of treatment BMI and percentage of weight loss or gain were recorded.

**Ethical Approval:** A written consent from all patients and approval from the Ethical Committee of Faculty of Medicine, Menoufia University, Egypt (IRB number 4/2022 ONCO 33) were obtained. The Helsinki Declaration was followed throughout the study's conduct.

***Statistical analysis***

SPSS version 26.0 was installed on an IBM compatible personal computer, which was used for data collection, tabulation, and statistical analysis. Qualitative data were reported as number (N) and percentage (%) in descriptive statistics, and quantitative

data were expressed as mean ± SD. Analytical statistics, such as the Student's t-test (t), were used to compare quantitative variables between two normally distributed data groups. For non-normally distributed data groups, Mann-Whitney's test (U) was employed for the same purpose. The $X^2$ test was employed to investigate the relationship between the qualitative factors. Fischer's exact test was applied if any of the anticipated cells had fewer than five. P-values were considered statistically significant if they were ≤ 0.05.

## RESULTS

This study included 120 patients, each group included 60 patients. There was no significant difference between both groups regarding the demographic and clinicopathological data (Table 1). The mean age for group 1 was 58.83 ± 13.06, and for group 2 was 60.85 ± 10.09.

The majority of patients were males in both groups (73.3 % in group 1, and 63.3% in group 2). The mean BMI at baseline was 25.92 ± 5.65 for group 1, and 24.65 ± 3.87 for group 2. Regarding histopathology, adenocarcinoma was the most common subtype with 68.3% in group 1 vs 63.3% in group 2. Rectum was the most predominant site in group1 (33.3%) vs bladder in group 2 (31.7%).

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**Table (1):** Demographics and clinicopathological data of both groups

| Variable | | Intervention Group (n=60) | | Standard Group (n=60) | | Test of significance (χ2) | P value |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| **Age (years)** | Mean ± SD | 58.83 ± 13.06 | | 60.85 ± 10.09 | | t= 0.947 | 0.346 |
| | Range | 20 – 79 | | 23 – 80 | | | |
| | Median (IQR) | 62.5 (55 – 67) | | 63 (55.25 – 67.75) | | | |
| **Sex** | Male | 44 | 73.3 | 38 | 63.3 | $x^2$ = 1.386 | 0.239 |
| | Female | 16 | 26.7 | 22 | 36.7 | | |
| **Smoking** | Yes | 12 | 20 | 16 | 26.7 | $x^2$=0.745 | 0.388 |
| | No | 48 | 80 | 44 | 73.3 | | |
| **Comorbidities** | None | 40 | 66.7 | 45 | 75 | $x^2$=6.646 | 0.467 |
| | DM | 5 | 8.3 | 2 | 3.3 | | |
| | HTN | 4 | 6.7 | 6 | 10 | | |
| | DM&HTN | 4 | 6.7 | 4 | 6.7 | | |
| | Cardiac | 5 | 8.3 | 1 | 1.7 | | |
| | Renal | 0 | 0 | 1 | 1.7 | | |
| | COPD | 1 | 1.7 | 0 | 0 | | |
| | HCV positive | 1 | 1.7 | 1 | 1.7 | | |
| **BMI (kg/m$^2$) (baseline)** | Mean ± SD | 25.92 ± 5.65 | | 24.65 ± 3.87 | | t= 1.434 | 0.154 |
| | Range | 16.6 – 43 | | 19 – 35 | | | |
| **BMI categories** | Underweight | 1 | 1.7 | 0 | 0 | $x^2$=4.368 | 0.498 |
| | Normal weight | 36 | 60 | 41 | 68.3 | | |
| | Overweight | 11 | 18.3 | 12 | 20 | | |
| | Class I obesity | 10 | 16.7 | 5 | 8.3 | | |
| | Class II obesity | 1 | 1.7 | 2 | 3.3 | | |
| | Class III obesity | 1 | 0.8 | 0 | 0 | | |
| **PS** | 0 | 5 | 8.3 | 8 | 13.3 | $x^2$=4.412 | 0.421* |
| | 1 | 50 | 83.3 | 49 | 81.6 | | |
| | 2 | 5 | 8.3 | 3 | 5 | | |
| **Type** | Squamous cell carcinoma | 4 | 6.7 | 5 | 8.3 | 0.350 | 0.839 |
| | Transitional cell carcinoma | 15 | 25 | 17 | 28.3 | | |
| | Adenocarcinoma | 41 | 68.3 | 38 | 63.3 | | |
| **Site of disease** | Bladder | 17 | 28.3 | 19 | 31.7 | x2=0.681 | 0.954 |
| | Prostate | 14 | 23.3 | 15 | 25 | | |
| | Cervix | 5 | 8.3 | 6 | 10 | | |
| | Endometrium | 4 | 6.7 | 4 | 6.7 | | |
| | Rectum | 20 | 33.3 | 16 | 26.7 | | |

There was no significant difference between both groups regarding treatment data (Table 2). The majority of patients received concurrent chemotherapy with radiotherapy (73.3%) in group 1 vs (71.7%) in group 2. Dose of radiotherapy range from 45 – 74 GY and the number of fractions ranged from 25-37 in both groups. Cisplatin was the most common radiosensitizer used in both groups (35% in group 1 vs 40% in group 2). The majority of patients didn't receive neoadjuvant treatment in both groups (60% in group 1 vs 53.4% in group 2). Most patients didn't undergo surgery related to site of the disease in both groups (96.7% in group 1 vs 88.3% in group 2).

**Table (2):** Treatment data of both groups.

| Variable | | Intervention group(n=60) | | Standard group(n=60) | | Test of sig. | P value |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| **Treatment modality** | EBRT alone | 2 | 3.3 | 2 | 3.3 | $x^2$=0.046 | 0.977 |
| | EBRT & ADT | 14 | 23.3 | 15 | 25 | | |
| | CCRT | 44 | 73.3 | 43 | 71.7 | | |
| **Dose of RT/gray** | Mean ±SD | 58.37±10.79 | | 59.27±10.75 | | t =0.459 | 0.647 |
| | Range | 45 – 74 | | 45 – 74 | | | |
| **Number of RT Fractions** | Mean ±SD | 30.55±4.66 | | 30.55±4.66 | | t =1.024 | 0.308 |
| | Range | 25 – 37 | | 25 – 37 | | | |
| **Concurrent treatment used** | ADT | 14 | 23.3 | 15 | 25 | $x^2$=1.875 | 0.759 |
| | Cisplatin | 21 | 35 | 24 | 40 | | |
| | Gemcitabine | 2 | 3.3 | 3 | 5 | | |
| | Capecitabine | 20 | 33.3 | 16 | 26.7 | | |
| | Carboplatin | 1 | 1.7 | 0 | 0 | | |
| **Neoadjuvant treatment use** | Yes | 24 | 40 | 28 | 46.6 | $x^2$=0.574 | 0.449 |
| | No | 36 | 60 | 32 | 53.4 | | |
| **Type of neoadjuvant treatment** | Gemcitabine _carboplatin | 2 | 10 | 3 | 12.5 | $x^2$=4.330 | 0.228 |
| | Capeox | 17 | 85 | 15 | 62.5 | | |
| | Paclitaxel-carboplatin | 0 | 0 | 4 | 16.7 | | |
| | ADT | 4 | 16.7 | 4 | 16.7 | | |
| | Gemcitabine-cisplatin | 1 | 5 | 2 | 8.3 | | |
| **History of surgery related to site of disease** | Yes | 2 | 3.3 | 7 | 11.7 | $x^2$=3.003 | 0.083 |
| | No | 58 | 96.7 | 53 | 88.3 | | |

There was significant difference between both groups as regards percentage of weight gain and weight loss, development of toxicity, time to recovery from toxicity, incidence of hospital admission (Table 3). The mean body weight gain was higher in group 1 than in group 2 (2.32 ± 4.7 vs 0) (P value <0.0001). The mean body weight loss was higher in group 2 than in group 1 (3.28 ± 4.04 vs 0.87 ± 2.11) (P value <0.0001). Incidence of toxicity was lower in group 1 (16.7% vs 35% in group 2) (P value 0.022). Although, there were no significant differences regarding grade of toxicity and type of toxicity, patients in group 2 experienced higher grades of toxicity (grade two and three) than group 1 (p value 0.127). Time to recovery from toxicity was longer in group 2 [ ranged from 6-30 days and 3-15 days in group 1 with mean 13.57 ± 8.22 vs 6.2 ± 5.22 respectively ( P value 0.001)]. Incidence of hospital admission was high in group 2 (**8.3**% vs 0%) (p value 0.021). The duration of hospital admission ranged from 4 – 30 days with mean of 14.6 ± 14.1 in group 2. There was significant difference between both groups as regards treatment interruption (figure 3). All patients of group 1 completed their treatment without interruption however 8.3 % patients in group 2 faced treatment interruption (p value 0.022).

**Table (3):** Body weight changes and toxicity of both groups.

| Variable | | Intervention group (n=60) | | Standard group (n=60) | | Test of sig. | P value |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| **Percentage of body weight gain(Kg)** | Mean ±SD | 2.32±4.7 | | 0 | | U=1080 | **<0.0001*** |
| | Range | 0 – 25 | | 0 | | | |
| **Percentage of body weight loss(Kg)** | Mean ±SD | 0.87±2.11 | | 3.28±4.04 | | U=1170 | **<0.0001*** |
| | Range | 0 – 11.5 | | 0 – 13 | | | |
| **Development of toxicity** | Yes | 10 | 16.7 | 21 | 35 | $x^2$=5.263 | **0.022*** |
| | No | 50 | 83.3 | 39 | 65 | | |
| **Grade of toxicity (n =31)** | 1 | 8 | 80 | 9 | 42.9 | $x^2$= 4.130 | 0.127 |
| | 2 | 2 | 20 | 9 | 42.9 | | |
| | 3 | 0 | 0 | 3 | 14.3 | | |
| **Type of toxicity** | GIT | 3 | 5 | 6 | 10 | $x^2$=6.675 | 0.154 |
| | Genitourinary | 7 | 11.7 | 12 | 20 | | |
| | Fever and neutropenia | 0 | 0 | 2 | 3.3 | | |
| | Anemia | 0 | 0 | 1 | 1.7 | | |
| **Time of toxicity (n =31)** | first week | 0 | 0 | 0 | 0 | FE=4.490 | 0.283 |
| | second week | 0 | 0 | 2 | 9.5 | | |
| | third week | 2 | 20 | 4 | 19 | | |
| | forth week | 5 | 50 | 6 | 28.6 | | |
| | Fifth week | 1 | 10 | 3 | 14.3 | | |
| | Six week | 1 | 10 | 3 | 14.3 | | |
| | Seventh week | 1 | 10 | 2 | 9.5 | | |
| | Eighth week | 0 | 0 | 1 | 4.7 | | |
| **Time to recovery from toxicity(days)** | Mean ±SD | 6.2±5.22 | | 13.57±8.22 | | U=66.5 | **0.001*** |
| | Range | 3 – 15 | | 6 – 30 | | | |
| **Adherence to immunonutrition** | Yes | 59 | 98.3 | ----- | | ----- | ---- |
| | No | 1 | 1.7 | | | | |
| **Hospital admission incidence** | Yes | 0 | 0 | 5 | 8.3 | $x^2$=5.308 | **0.021*** |
| | No | 60 | 100 | 55 | 91.7 | | |
| **Duration of hospital admission in days** | Mean ±SD | ----- | | 14.6±14.1 | | ----- | ----- |
| | Range | ----- | | 4 – 30 | | | |

t = student t test; U= Mann-Whitney test; $\chi 2$ =Chi-square test *P value of < 0.05: statistically significant FE= Fischer's Exact test.

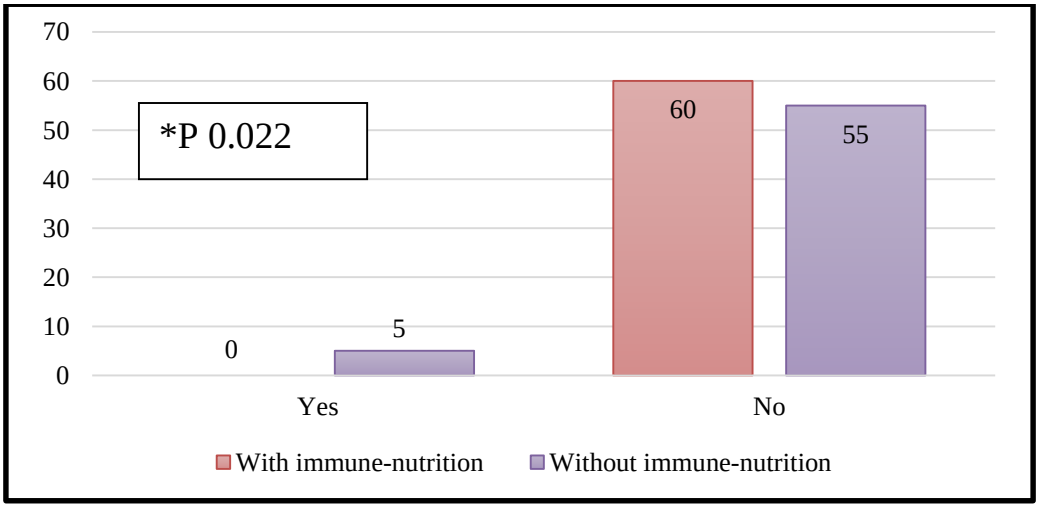


**Figure (3):** Interruption of treatment of both groups.

There was no significant difference between both groups regarding overall treatment time (Table 4).

**Table (4):** Overall treatment time

| Median treatment time(days) | Intervention group (n=60) | Standard group (n=60) | P value |
|---|---|---|---|
| prostate | 58(56-60) | 59 (56-62) | 0.369 |
| Cervix | 38 (35-42) | 40 (35-45) | |
| endometrium | 38 (35-42) | 38 (35-42) | |
| Rectum | 37 (36-38) | 38 (36-40) | |
| bladder | 48 (46-50) | 51 (48-54) | |

Comparison of both groups as regards pre- and post-treatment weight and BMI was shown in figures (4 & 5). Non-obese patients in group 1 increased in post treatment weight, and BMI (P value 0.001 and <0.0001 respectively). Non-obese patients in group 2 decreased in post treatment weight, and BMI (P value <0.0001 and <0.0001 respectively). Obese patients in group 1 and 2 decreased in post treatment weight, and BMI (P value 0.086, 0.062, 0.229, 0.140 respectively).

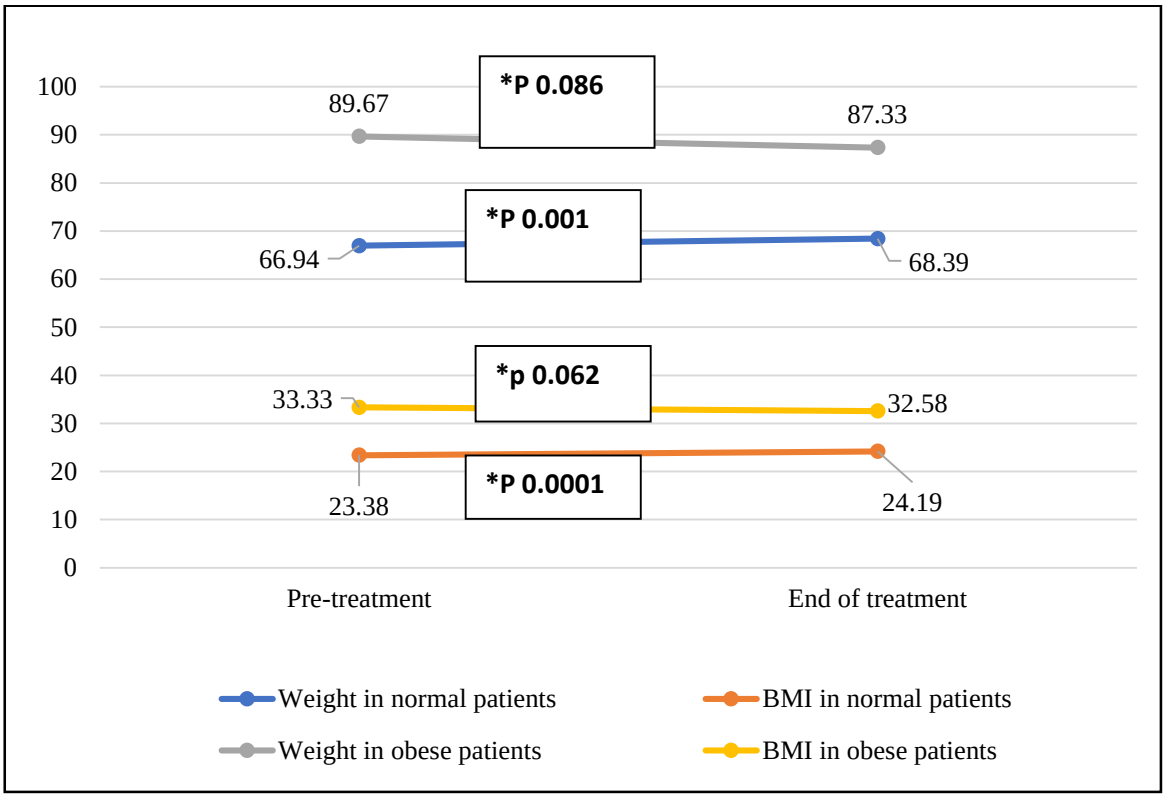


**Figure (4):** Mean body weight and BMI (pre and post treatment) of group 1.

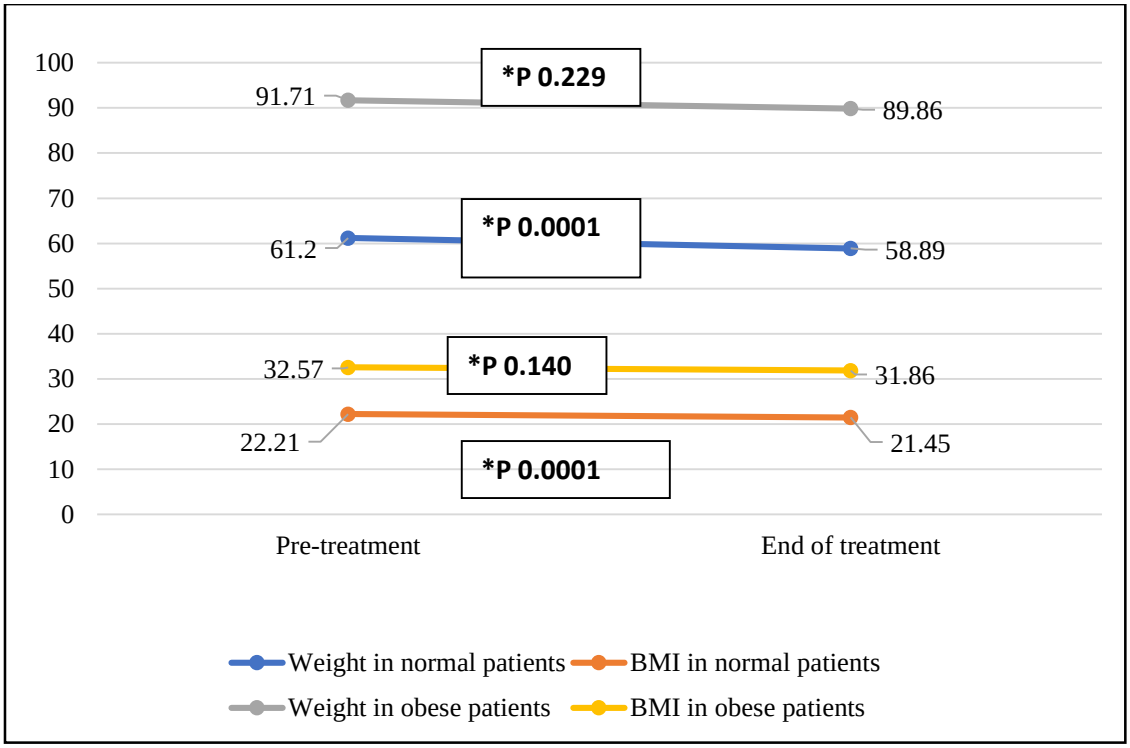


**Figure (5):** Mean body weight and BMI (pre and post treatment) of group 2.

Although there was no significant difference between both groups as regards response (p value 0.213) , 51.7% of patients in group 1 achieved complete response (CR) vs 39.6% in group 2, and 9.4% of patients in group 2 achieved progressive disease vs 3.4% in group 1 ( Table 5). 2 patients in group 1 and 7 patients in group 2 were excluded from response assessment as they underwent surgery before RT and were free postoperatively.

**Table (5):** Response to treatment of both groups

| Response | Intervention group (n=58) | | Standard group (n=53) | | Test of significance | P value |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Stationary | 8 | 13.7 | 8 | 15 | χ2 =12.000 | 0.213 |
| Partial response | 18 | 31 | 19 | 35.8 | | |
| Complete response | 30 | 51.7 | 21 | 39.6 | | |
| Disease progression | 2 | 3.4 | 5 | 9.4 | | |

χ2 =Chi-square test*P value<0.05 statistically significant.

Univariate, and multivariate logistic regression of risk factors associated with toxicity (Table 6) showed that by univariate analysis, there was significant correlation between toxicity and intervention group, adherence to immunonutrition and diagnosis of cancer bladder and rectum. Diagnosis of cancer rectum (P value <0.001) and cancer bladder (P value 0.002) had high risk of toxicity development (Odds ratio, 1.14 and 8.000 respectively), and the factors associated with significant lower toxicity were intervention group (P value 0.024) and adherence to immunonutrition (P value 0.011) (Odds ratio, 0.692 and 0.134 respectively). By multivariate analysis, it was found that intervention group, diagnosis of bladder and rectal cancer were independent predictors of toxicity (P value 0.045, 0.026, and 0.001 respectively).

**Table (6):** Univariate and multivariate logistic regression for predictors of toxicity

| Variables | Odds ratio | P value | CI (95%) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| **Univariate logistic regression** | | | | |
| **Group** | | | | |
| Intervention group | 0.692 | **0.024*** | 0.137 | 0.373 |
| **Age** | 2.610 | 0.138 | 0.930 | 6.030 |
| **Gender** | | | | |
| Male | 1.846 | 0.714 | 0.560 | 5.676 |
| **Diagnosis** | | | | |
| Bladder | 1.140 | **0.002** | 1.041 | 1.477 |
| Prostate | 0.479 | 0.294 | 0.121 | 1.893 |
| Cervix | 0.219 | 0.064 | 0.044 | 1.094 |
| Endometrium | 0.356 | 0.999 | 0.875 | 2.063 |
| Rectum | 8.000 | **<0.001*** | 4.954 | 14.342 |
| **Adherence to immunonutrition** | | | | |
| Adherent | 0.134 | **0.011*** | 1.298 | 7.566 |
| **Previous surgery** | 6.259 | 0.893 | 0.999 | 9.650 |
| **Previous chemotherapy** | 1.584 | 0.308 | 0.654 | 3.837 |
| **Dose of chemotherapy** | 1.001 | 0.254 | 0.999 | 1.003 |
| **Duration of RT** | 0.664 | 0.317 | 0.298 | 1.481 |
| **Number of fractions** | 1.145 | 0.179 | 0.940 | 1.395 |
| **Dose of RT** | 0.904 | 0.090 | 0.804 | 1.016 |
| **PG SGA category** | | | | |
| A | 0.668 | 0.999 | 0.319 | 0.831 |
| B | 1.362 | 0.462 | 0.598 | 3.103 |
| **Performance Status** | | | | |
| 1 | 1.892 | 0.568 | 0.212 | 16.915 |
| 2 | 1.892 | 0.429 | 0.390 | 9.178 |
| **End of treatment BMI** | 1.037 | 0.447 | 0.944 | 1.139 |
| **Multivariate logistic regression** | | | | |
| **Group** | | | | |
| intervention | 0.044 | **0.045*** | 0.001 | 0.373 |
| **Diagnosis** | | | | |
| Bladder | 3.709 | **0.026*** | 1.168 | 11.775 |
| Rectum | 10.010 | **0.001*** | 2.502 | 19.342 |
| **Adherence to immunonutrition** | | | | |
| Adherent | 0.663 | 0.492 | 0.390 | 0.085 |

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## DISCUSSION

In this study there were no significant differences between both groups as regards demographics, clinicopathological, and treatment data indicating homogenous patients' characteristics in both groups.

The present study included 2 groups, intervention group (1) received personal planned calculated needs in form of planned calculated diet with addition of immunonutrition formula (containing arginine, glutamine, and fish oils), and standard group (2) received planned diet only without immunonutrition, which met the same method that was used by **Chitapanarux *et al.*[22],** who randomized (non-metastatic head and neck cancer, esophageal, and cervical cancer patients candidate for CCRT either definitive treatment or adjuvant into 2 groups: group A patients who received planned diet and group B patients who received arginine, glutamine and fish oil supplements. Furthermore, our study was more specified to the patients who received pelvic irradiation for more homogeneity and reliability of the results. Our study is similar to **Ozturk *et al.*** [23] who randomized 49 patients into two groups: group 1 (25 patients) received glutamine, arginine and beta-Hydroxy beta-methylbutyric acid (HMB) mixture during RT, group 2 (24 patients) didn't use any supplements. There were no differences in demographic (age, sex) between both groups at base line, they recruited patients with histologically proven cancer indicated for pelvic RT irrespective of the primary site of diagnosis, the majority of patients received concomitant chemotherapy (87% vs 72.5% for both groups), and patients with cancer cervix received cisplatin as radiosensitizer, like our patients.

The group that used immunonutrition in the present study had higher percentage of body weight gain after treatment ($P < 0.0001$), which was observed mainly in non-obese patients (underweight & normal weight).

These results are in agreement with **Ozturk *et al.*** [23], who found significant weight gain in immunonutrition group (72% vs 37%) (P 0.03) and this could confirm the effects of immunonutrition on the nutritional status of the patients.

Immunonutrition was found to decrease the degree of toxicities caused by treatment such as oral mucositis, enteritis, oesophagitis and weight loss [5]. This was observed in our study**,** there was a significant difference in weight loss between both groups, the percentage of weight loss was lower in group 1 (p value <0.0001). This is compatible with **Ozturk *et al.*** [23] who found that immunonutrition supplements decreased weight loss, which was 62.5 % in standard diet group and 28% in immunonutrition group (p value 0.03). Also study done by **Papanikolopoulou *et al.*** [24] found that the oral glutamine administration may have a significant role in decreasing acute toxicities caused by radiation and weight loss, which is in line with our results. This could be explained by that in absence of immunonutrition supplements there were increased incidence and duration of toxicity, which decreased appetite, increased hypercatabolic state and decreased muscle mass that resulted in weight loss as reported by **Prado *et al.*** [25]**.**

Incidence of toxicity was lower in group 1 (16.7% vs 35% in group 2) (P value 0.022). This result is in line with the review of **Paccagnella *et al.*** [26] and **Papanikolopoulou *et al.*** [24]**. Paccagnella *et al.*** [26] revealed that glutamine administration during CCRT could decrease toxicities. Also some studies have showed that omega-3 fatty acids can decrease inflammatory response and decrease toxicities caused by treatment as shown by **Epstein *et al.*** [27]**.**

Although, there were no significant differences regarding grade of toxicity and type of toxicity, patients in group 2 experienced higher grades of toxicity (grade two and three) than group 1. This may be explained by the role of immunonutrition in reducing the severity of chemo-radiotherapy-related toxicity, which may be related to the inhibition of bacterial translocation, intestinal absorption, permeability changes, formation of ulcer, and the stimulation of mucosal renewal [28]**.** Furthermore, the most common toxicity was genitourinary toxicity (11.7% in group 1 vs 20% in group 2) followed by gastrointestinal (GIT) toxicity (5% vs 10% respectively). It's well known that digestive system is affected greatly by RT to the pelvic region and chemotherapy because of its constantly dividing epithelium. It's believed that glutamine is the major source of energy of GIT epithelium. **Diestel *et al.*** [29] found that glutamine improves the injury of epithelium in rats.

In this study, there was low incidence of hematological toxicity (fever, neutropenia, and anemia) in group 1 when compared to group 2 although the difference wasn't significant (p=0.154). These results are in line with **Chitapanarux *et al.*** [22]**,** who found that supplementation with immunonutrition formula during radiotherapy decreased incidence of severe hematologic toxicities (5%) in group 1 versus (23%) in the other group with significant P value (0.03). The decreased incidence of hematological toxicity in both studies in patients receiving immunonutrition could be explained that arginine in the formula stimulates the cytotoxicity of natural killer cell and also increases T-cell proliferation which stimulates host immunity against hazardous side effects caused by tumor itself or the active treatment [30].

In this study, there was significant decrease of time to recovery from toxicity in group 1 (P=0.001), which could be explained by lower incidence of high grade toxicity in this group, and so rapid recovery of patients from toxicity. Thus, as incidence of toxicity decreased, treatment interruption decreased in immunonutrition group with significant p value (0.022). Our results are in line with **Alsubaie *et al.*** [31] who found that oral glutamine (which is a protein component of immune nutrition formula) decreased treatment interruption in head and neck cancer patients.

There was a decrease in incidence of hospital admission in immunonutrition group. This is in line with **Chitapanarux *et al.*** [22] who found that immunonutrition supplements during radiotherapy could decrease rate of hospital admission. This finding is also consistent with **Paccagnella *et al.*'s** [26] review, which demonstrated that dietary supplementation with branched amino acids and glutamine might minimize the duration of hospitalization and toxicities from cancer therapy.

No significant difference in overall treatment time between both groups in our study and this is compatible with **Chitapanarux *et al.*** [22]**.**

Obese patients showed decrease in post-treatment weight in both group, although p value was not significant, ((P value 0.086, 0.229 respectively). This may be explained by the use of successful dietary regimen in both groups as we didn't use actual body weight for calculation of patient caloric needs and used adjusted body weight for obesity, which is beneficial for the patients as obesity is considered as a risk factor for toxicity. Obese patients have a high risk of increased chemotherapy and radiotherapy related toxicity [32].

Although, there was no significant difference between both groups as regards response (P value 0.213), patients in group 1 achieved higher complete response (CR) rates than group 2 (51.7% vs 39.6% respectively), and lower progressive disease (3.4 % vs 9.4% respectively). This may be explained by positive effects of immunonutrition such as stimulated immunity, decrease of the incidence and degree of toxicity, prevention of weight loss (all these factors could improve food intake of the patients and so maintained the nutritional status and improved the tolerance to treatment) , and reduction of treatment gap so increased response to anti-cancer treatment. This is consistent with current evidence, which had confirmed that immunonutrition can control inflammatory and immunological response in cancer patients, reducing

initial toxicity and improving treatment outcomes [33]. But, evaluating this conclusion requires more trials with a large number of patients and long-term follow-up.

In this study by univariate and multivariate analysis, it was found that group 1 associated with lower toxicity (odds ratio: 0.692, P value 0.024, odds ratio 0.044, P value 0.045 respectively), which is consistent with **Chitapanarux *et al.*** [22] who found that immunonutrition group was associated with lower hematological toxicity, by univariate and multivariate analysis (Odds ratio 1 compared to 6.18 in the other group, P value 0.02, and odds ratio 6.08 vs 1 p value 0.03 respectively).

It is important to document that in this study and other studies conducted by **Ozturk *et al.*** [23], and **Chitapanarux *et al.*** [22], there were no reported toxicities related to oral immunonutrition formula administration.

The mixture that was used by **Ozturk *et al.*** [23] during pelvic RT contains 7.4 gr glutamine, 7.4 gr arginine which is compatible with the formula used in our study. In addition, **Ozturk *et al.*** [23] formula contained 1.3 gr HMB an active metabolite of leucine amino acid, which stimulates muscle growth that was absent in our formula, but our formula contained EPA/fish oil, which is effective in reducing systemic inflammation, inducing weight gain and increasing dietary intake as reported by **Pappalardo *et al.*** [34]. This may raise a question about the most effective dose and the best composition of immunonutrition formula.

**Study Limitations:** like unacceptable taste of the formula so accepted flavor was added to the formula like chocolates, and during the period of diarrhea the formula was added to large amount of water to decrease osmolarity of the formula and decrease incidence of diarrhea.

## CONCLUSION

Arginine, glutamine, fish oil containing immunonutrition formula administration could reduce the incidence of radiotherapy-related toxicities, incidence and duration of hospital admission, treatment gap, and prevent weight loss in patients with pelvic malignancies. These results revealed that immunonutrition may have promising protective effect on chemo-radiation related toxicity.

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