

Dietary Counseling Outcomes in Locally Advanced Unresectable or Metastatic Cancer Patients Undergoing Chemotherapy

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Background: Cancer-related malnutrition led to poor outcomes of treatment, decreased functional status, decreased quality of life, and delay treatment.

Objective: To examine the effects of dietary counseling for regular foods consumption on nutritional outcomes in patients with cancer undergoing chemotherapy.

Material and Method: A prospective randomized study was performed on locally advanced unresectable or metastatic cancer patients undergoing chemotherapy at Department of Medicine, Chiang Mai University, between December 2013 and July 2014. Fifty patients were randomly assigned to dietary counseling group and routine care group. The dietary counseling was performed by a dietitian before starting chemotherapy. Outcomes were evaluated at the end of three to four cycles and six to eight cycles of chemotherapy or after two months if the chemotherapy was stopped earlier.

Results: The dietary counseling group significantly increased percent change of body weight 2.29 (± 6.20) vs. -1.70 (± 6.23) percent in the routine care group, $p = 0.03$ and increased BMI 2.27 (± 6.09) vs. -1.53 (± 5.92) percent, $p = 0.03$ at the end of three to four cycles of chemotherapy, but there was no significant change at the next two months. Furthermore, PG-SGA score was lower in the dietary counseling group (6.67 (± 1.99) vs. 10.04 (± 3.73), $p < 0.001$, and quality of life was significant increased in dietary counseling group at the end of three to four cycles of chemotherapy and at the next two months (score 39.40 (± 10.61) vs 46.16 (± 7.55), $p = 0.01$). Absolute lymphocyte count, serum albumin, energy intake, number of patients who delayed chemotherapy, cause of delay chemotherapy, and number of total cycles did not differ between the groups.

Conclusion: Dietary counseling have significantly improved body weight, BMI, PG-SGA scores, and quality of life scores in patients with locally advanced unresectable or metastatic cancer undergoing chemotherapy compared with routine care. We should be concerned about screening for malnutrition in all cancer patients and we should provide nutritional counseling.

Keywords: Dietary counseling, Malnutrition, Cancer, Chemotherapy

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Cancer-related malnutrition is quite important. Malnutrition and weight loss lead to poor treatment outcomes, increased complications, decreased quality of life (QoL), and disruptive treatment⁽¹⁻⁴⁾. Furthermore, malnutrition can proceed to cancer cachexia, a specific form of malnutrition characterized by loss of lean body mass, muscle wasting, impaired immune, and poor physical and mental function⁽⁵⁾. On the other hand, early nutrition intervention for cancer patients can improve the nutritional status, not only helping the patients to maintain body weight, but also better tolerate to treatment, and improve QoL⁽⁶⁻⁹⁾.

There were many studies showing outcomes of dietary counseling in cancer patients. Ravasco et al^(10,11) compared between dietary counseling for regular diet, supplementary diet, and control group in head and neck cancers and colorectal cancer undergoing radiotherapy, and found that patients who received nutritional intervention were significantly improved of Patient Generated-Subjective Global Assessment (PG-SGA) score⁽¹²⁾, body mass index (BMI), body weight, and QoL during radiotherapy. Furthermore, dietary counseling for regular foods can maintain the outcomes for three months.

Meta-analysis study of Baldwin et al showed that nutritional interventions such as dietary counseling, oral nutrition supplements, and combination of dietary counseling and oral supplements in cancer patients receiving intensive treatments or palliative cares could

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improve calories intake and QoL, but it does not improve survival rate⁽¹³⁾.

The International Guidelines on the nutritional management of patients with cancer from the European Society for Clinical Nutrition and Metabolism (ESPEN), the American Dietetic Association (ADA), the American Society for Parenteral and Enteral Nutrition (ASPEN), and the Dietitians Association of Australia recommend that nutritional intervention be started in malnourished patients or those in whom difficulties with eating are anticipated⁽¹⁴⁻¹⁸⁾. In the United Kingdom (UK), the National Institute for Health and Clinical Excellence (NICE) recommends that health care professionals consider oral nutritional support to improve nutritional intake for people who can swallow safely and who are malnourished or at risk of malnutrition⁽¹⁹⁾.

Currently, Department of Medicine, Chiang Mai University has many cancer patients who received chemotherapy, but their nutritional status had not been routinely evaluated. Nutritional counseling is performed by physicians and nurses as routine care but has limitation of time and knowledge. The physicians and nurses have not received any counseling from a dietitian. Therefore, we studied the outcomes of nutritional counseling by the dietitian compared with the routine care.

Material and Method

Study design

A prospective randomized study was performed on the patients undergoing chemotherapy at Department of Medicine, Chiang Mai University, between December 2013 and July 2014. The inclusion criteria were age at least 18 years, locally advanced unresectable or metastatic cancer patients undergoing first line chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, anorexia or eating less before being treated with chemotherapy, oral intake more than 50% compared to usual eating. Patients who had dysphagia, bowel obstruction, and diabetes were excluded. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University. All patients provided written informed consent.

Nutritional intervention

The dietary counseling group was individualized and intensive dietary counseling by a dietitian focusing on maintaining and improving the patient's energy and protein intake. The counseling

was performed before starting the first cycle of chemotherapy, which was based on ESPEN guideline⁽¹⁴⁾. The patient's energy requirement was estimated at 30 to 35 kcal per kg per day. The protein requirement was normally estimated at 0.8 g to a maximum of 1.2 g per kg per day. This group involved the prescription regular food which was adjusted to the individual's usual diet, allowed supplement diet if required.

The routine care group had received dietary counseling for general dietary recommendations by a physician and a nurse as a routine care before starting the first cycle of chemotherapy, but no counseling by the dietitian.

Statistical analysis

Sample size was calculated based on Ravasco et al data^(10,11) that at least 25 patients for each group to get a p -value <0.05 and 90% power. Fifty patients were randomized 1:1 stratified by cancer types (lung cancer or cholangiocarcinoma) with Randomization Allocation Program.

The primary end point was the mean percent change of body weight at the end of four cycles of chemotherapy (12 weeks). We allowed to evaluate after the end of three cycles of chemotherapy (9 weeks) for some patients in whom chemotherapy were stopped due to progression of disease. Secondary end points included mean percent change of BMI, PG-SGA score⁽¹²⁾, QoL score, serum albumin, and total lymphocyte count at the end of three to four cycles of chemotherapy (9 to 12 weeks) and after two months of follow-up if chemotherapy was stopped at three or four cycles or at the end of six to eight cycles of chemotherapy (18 to 24 weeks), number of patients, and causes of delayed treatment. The demographic data were presented as means, median, range, and percentage. For comparison between the groups, Mann-Whitney U test, and independent student t-test were used for continuous variables, while Chi-square or Fisher's exact test were used for categorical variables. The level of statistical significance was set at p -value <0.05 , using SPSS software version 16.0.

Results

Between December 2013 and July 2014, 50 patients diagnosed of locally advanced unresectable or metastatic cancer and fulfilling the inclusion criteria were enrolled in the present study. After enrollment, 50 patients had received three to four cycles of chemotherapy were eligible for the analysis

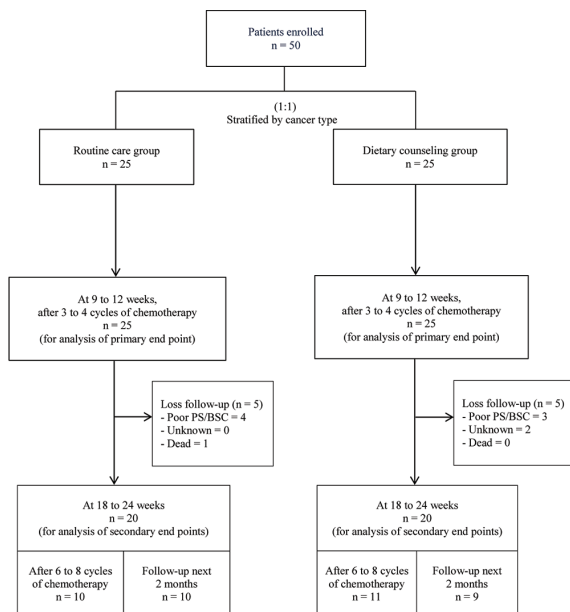


Fig. 1 Diagram showing patient registration, treatment arm assignments, and exclusion.

as primary end point (Fig. 1). Ten patients were excluded from the study before completely receiving six to eight cycles of chemotherapy or following-up after two months due to disease progression, poor

performance status, or referral to other hospital for palliative care.

The two groups were well balanced for baseline patient characteristics and baseline nutritional status as showed in Table 1 and 2 respectively. For baseline patient characteristics (Table1), most patients were male, had universal coverage insurance, lung cancer, stage IV, used carboplatin/paclitaxel regimen and had ECOG performance status = 1. Half of the patients had significant weight loss, more than 10% in six months, which was not significantly different between the groups. Mostly patient had poorer nutritional status measured by PG-SGA scores (high scores mean poor nutritional status) and low energy intake per day.

Nutritional assessments

Body weight

At the end of three to four cycles of chemotherapy, mean body weight in the dietary counseling group was 50.89 (± 7.31) kg, which was higher than the 46.04 (± 11.24) kg of the routine care group. There was significantly higher mean percentage change of body weight in the dietary counseling group, which was 2.29 (± 6.20) percent vs. -1.70 (± 6.23) percent in the routine care group, $p = 0.03$ (Fig. 2). At the follow-up, two months later, there was higher

Table 1. Baseline patient characteristics

Characteristic	Routine care group (n = 25)	Diet counseling group (n = 25)	p-value
Gender, n (%)			0.23
Male	14 (56)	19 (76)	
Age, mean (range)	62.7 (48 to 72)	61.3 (45 to 81)	0.55
Insurance, n (%)			0.57
Government	3 (12)	1 (4)	
Universal coverage	19 (76)	22 (88)	
Social security coverage	3 (12)	2 (8)	
Cancer type, n (%)			1.000
Lung	18 (72)	17 (68)	
Cholangiocarcinoma	7 (28)	8 (32)	
Cancer stage, n (%)			1.000
Stage III	2 (8)	1 (4)	
Stage IV	23 (92)	24 (96)	
Chemotherapy regimen, n (%)			0.62
Carboplatin/paclitaxel	16 (64)	13 (52)	
Cisplatin/gemcitabine (low dose)	7 (28)	8 (32)	
Cisplatin or carboplatin/etoposide	2 (8)	4 (16)	
ECOG performance status, n (%)			1.000
1	24 (96)	24 (96)	
2	1 (4)	1 (4)	

ECOG = Eastern Cooperative Oncology Group

Table 2. Baseline nutritional status

Nutritional assessments	Routine care group (n = 25)	Diet counseling group (n = 25)	p-value
Percent of weight loss in 6 months before treatment, n (%)			1.00
<10%	12 (48)	12 (48)	
≥10%	13 (52)	13 (52)	
Body weight, mean (range)	46.5 (28.9 to 72.0)	49.9 (36.8 to 65.0)	0.27
BMI (kg/m ²), n (%)			0.06
<18.5 (underweight)	15 (60)	9 (36)	
18.5 to 24.9 (normal)	10 (40)	16 (64)	
Mean (range)	18.4 (13.5 to 24.0)	19.3 (13.8 to 24.6)	0.28
PG-SGA score, mean (range)	14.9 (10 to 18)	14.4 (9 to 18)	0.48
QoL score, median (range)	41 (11 to 49)	40 (18 to 50)	0.78
Serum albumin (g/dL), mean (range)	3.6 (2.3 to 4.7)	3.5 (2.5 to 4.1)	0.45
Total lymphocyte count (cell/mm ³), mean (range)	2,236.9 (1,043 to 3,814)	1,981.0 (955 to 3,960)	0.21
Energy intake (kcal/day), mean (range)	1,510.24 (655 to 2,470)	1,414.68 (455 to 2,420)	0.48

BMI = body mass index; PG-SGA = Patient Generated-Subjective Global Assessment; QoL = quality of life

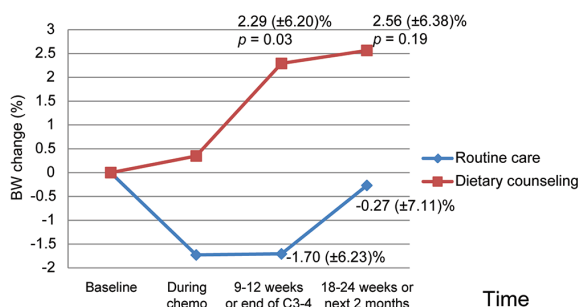


Fig. 2 Percent change in mean body weight at the end of chemotherapy and the follow-up next 2 months, mean (±SD).

mean percentage change of body weight in the dietary counseling group, which was 2.56 (±6.38) percent vs. -0.27 (±7.11) percent in the routine care group, but it was not significant different, $p = 0.19$.

Body mass index (BMI)

At the end of three to four cycles of chemotherapy, mean BMI in the dietary counseling group was 19.70 (±2.72) kg/m², which was higher than the routine care group with the BMI of 18.17 (±2.97) kg/m². There was significantly higher mean percent change of BMI in the dietary counseling group, which was 2.27 (±6.09) percent vs. -1.53 (±5.92) percent in the routine care group, $p = 0.03$. At the follow-up two months later, there was higher mean percentage change of BMI in the dietary counseling group of 2.55 (±6.44) percent vs. 0.09 (±6.88) percent in the routine care group, but it was not significant different, $p = 0.25$.

Patient generated-subjective global assessment (PG-SGA) score⁽¹²⁾

There was significant lower PG-SGA score (better nutritional status) in the dietary counseling group than that in the routine care at the end of three to four cycles of chemotherapy and at the follow-up two months later (Table 3).

Quality of life score

The QoL score was evaluated by the Thai-Modified Function Living Index Cancer Questionnaire Version 2 (T-FLIC 2)⁽²⁰⁾, higher score means better QoL (maximum score = 66). At the end of three to four cycles of chemotherapy, there was significantly higher QoL score in the dietary counseling group than that in the routine care group, 46.16 (±7.55) vs. 39.40 (±10.61), $p = 0.01$ (Table 3). At the follow-up, two months later, the QoL score was higher in the dietary counseling group 46.45 (±7.34) vs. 41.10 (±11.21) in the routine care group, $p = 0.08$, but it was not significantly different.

Serum albumin and total lymphocyte count

There was no difference in serum albumin and total lymphocyte count between the two groups (Table 3).

Energy intake

There was higher energy intake in the dietary counseling group than the routine care group at the follow-up two months later, 1847.19 (±442.60) vs. 1615.45 (±313.10) kcal/day, but it was not significantly different, $p = 0.06$ (Table 3).

Table 3. Nutritional outcomes at the end of 3 to 4 cycles of chemotherapy and the follow-up next 2 months

	Routine care group	Diet counseling group	<i>p</i> -value
PG-SGA score, mean (\pm SD)			
End of chemotherapy (n = 25)	10.04 (\pm 3.73)	6.67 (\pm 1.99)	<0.001
Next 2 months (n = 20)	7.75 (\pm 2.79)	5.65 (\pm 1.35)	<0.01
QoL score, mean (\pm SD)			
End of chemotherapy (n = 25)	39.40 (\pm 10.61)	46.16 (\pm 7.55)	0.01
Next 2 months (n = 20)	41.10 (\pm 11.21)	46.45 (\pm 7.34)	0.08
Serum Albumin, mean (\pm SD)			
End of chemotherapy (n = 25)	3.94 (\pm 0.54)	4.05 (\pm 3.85)	0.89
Next 2 months (n = 20)	4.12 (\pm 0.39)	4.09 (\pm 0.42)	0.82
Total lymphocyte count, mean (\pm SD)			
End of chemotherapy (n = 25)	1,872.76 (\pm 1,517.20)	1,896.80 (\pm 756.55)	0.89
Next 2 months (n = 20)	1,873.45 (\pm 660.75)	2,110.60 (\pm 1,007.12)	0.38
Energy intake change, mean (\pm SD)			
End of chemotherapy (n = 25)	1,640.92 (\pm 343.12)	1,832.00 (\pm 671.75)	0.21
Next 2 months (n = 20)	1,615.45 (\pm 313.10)	1,847.19 (\pm 442.60)	0.06

Table 4. The number of total chemotherapy cycles and response of treatment

	Routine care group (n = 25)	Diet counseling group (n = 25)	<i>p</i> -value
The number of total cycles, n (%)			
Completed 3 to 4 cycles	15 (60)	14 (56)	0.428
>4 cycles	10 (40)	11 (44)	0.736
Median (range)	4 (3 to 8)	4 (3 to 8)	
Response of treatment, n (%)			0.860
Progression of disease	3 (12)	4 (16)	
Stable of disease	10 (40)	8 (32)	
Partial response	12 (48)	13 (52)	

Effects to treatment

There was higher number of patients who delayed chemotherapy in the routine care group, 12 (48%) vs. 9 (36%) in the dietary counseling group, but with no significant difference $p = 0.57$. For the causes of delay, neutropenia was higher in the routine care group, 12 (48%) vs. 8 (32%) in the dietary counseling group, but with no significant difference, $p = 0.39$. Furthermore, infection, the number of total chemotherapy cycles and response of treatment were not different between the two groups (Table 4).

Discussion

The present study demonstrated the beneficial effect of the dietary counseling on weight change, BMI, nutritional status, and QoL for patients with locally advanced unresectable or metastatic cancer undergoing chemotherapy as compared with the routine care.

For baseline characteristics in the present study, it was well balanced between two groups, since most of patients had malnutrition that required the dietary intervention. The dietary counseling group had

significantly increased in body weight and BMI at the end of three to four cycles of chemotherapy and could maintain body weight after completion of chemotherapy. However, there was no significant difference in the following two months because 20% of each group was lost to follow-up (n = 20 per each group). In contrast, the routine care group decreased in body weight and BMI during the time of chemotherapy. Furthermore, the dietary counseling group could significantly improve PG-SGA scores and QoL scores at the end of three to four cycles of chemotherapy and maintained it at the two months follow-up. The energy intake was higher in the dietary counseling group at the two-month follow-up but it was not significantly different because some patients were lost follow-up. Furthermore, we evaluated energy intake by food record form that was recorded by individual patient, which might be incomplete. However, we tried to correct this problem by using three days food record instead of one day.

Previous randomized control studies of the dietary counseling on nutritional status and QoL in

malnourished patients with cancer had similar results. A randomized study performed by van den Berg et al demonstrated that individual dietary counseling on regular foods for head and neck cancer patients undergoing radiotherapy can decrease unintended weight loss and malnutrition⁽²¹⁾. Another study by Isenring et al demonstrated that the intensive nutritional counseling and nutritional supplement if required for gastrointestinal, head and neck cancer patients receiving adjuvant or neoadjuvant radiotherapy can improve mean body weight change, PG-SGA score and QoL score compared with the routine care after started radiotherapy 12 weeks⁽²²⁾.

Furthermore, the randomized controlled study by Ravasco et al demonstrated that individual dietary counseling for patients with colon cancer undergoing radiotherapy could improve energy intake, BMI, PG-SGA score, and QoL score by the end of chemotherapy and maintained for three months after the treatment⁽¹¹⁾. These were similar with the results of the present study.

Total lymphocyte count and serum albumin were not significant difference between the two groups, which was similar to Um et al⁽²³⁾ study. It showed that intensive nutritional counseling improved PG-SGA scores and nutritional symptoms during and after radiotherapy in Korean cancer patients, but no significant difference in total lymphocyte count and serum albumin⁽²³⁾.

For effect to treatment in the present study, the routine group seemed to have higher number of patients who delayed chemotherapy, but it was not significantly different. For the response of treatment and the number of total chemotherapy cycles, there were no difference between groups. This is the same as the results of Ovesen et al⁽²⁴⁾, which was done on NSCLC, breast, and ovarian cancer patients who received chemotherapy. There was no significant difference between groups in response rate after three and five months of chemotherapy⁽²⁴⁾.

Conclusion

The dietary counseling significantly improved body weight, BMI, PG-SGA scores, and QoL scores in patients with locally advanced unresectable or metastatic cancer undergoing chemotherapy compared with the routine care. We should be concern about screening for malnutrition status in all cancer patients before starting chemotherapy and have early nutritional therapy if needed.

Limitations

The present study had small sample sizes as we calculated to detect a difference in body weight change, but not detect difference in other aspects. The lack of adequate information was one of the factor that resulted from the difficulty to follow-up in some patients after complete chemotherapy of three to four cycles over two months. Type of cancers were lung cancer and cholangiocarcinoma. The patients with lung cancer mostly presented with chronic cough and dyspnea. The patients with cholangiocarcinoma had abdominal distension, early satiety, and eating problems. Those might decrease the amounts of food consumed and thus, did not meet the energy needs. Another limitation of the present study was that the evaluation of energy by the food record form for individual patients was not complete in dietary details. Further study with large sample size is warranted.

What is already known on this topic?

The early nutritional intervention for cancer patients can improve the nutritional status, maintain body weight, better tolerate treatment, and improve the quality of life.

What this study adds?

This study demonstrates that dietary counseling by a dietitian can improve nutritional outcomes such as body weight, BMI, PG-SGA scores, and quality of life scores in patients with locally advanced unresectable or metastatic cancer undergoing chemotherapy. This was accomplished by providing a single dietary counseling session before starting the first cycle of chemotherapy. Therefore, we should be concerned about screening for malnutrition status in all cancer patients before starting chemotherapy and have early nutritional therapy if needed.

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Potential conflicts of interest

None.

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ผลของการให้คำแนะนำด้านโภชนาการในผู้ป่วยมะเร็งระยะลุกลามที่ผ่าตัดไม่ได้หรือระยะแพร่กระจาย ที่ได้รับการรักษาด้วยยาเคมีบำบัด

นภาพรพรณ สุภรณาส, บุษยามาศ ชีวสกุลยง, สุภรณพร บวรณพิต

ภูมิหลัง: ภาวะทุพโภชนาการในโรคมะเร็ง ทำให้ได้รับผลการรักษาที่แย่ง คุณภาพชีวิตลดลง ความสามารถในการทำงานลดลง และมีการเลื่อนการรักษาออกไปมากขึ้น

วัตถุประสงค์: เพื่อศึกษาผลของการให้คำแนะนำด้านการรับประทานอาหารจากนักโภชนาการ ในผู้ป่วยมะเร็งที่ได้รับการรักษาด้วยยาเคมีบำบัด

วัสดุและวิธีการ: เป็นการศึกษาแบบสุ่มไปข้างหน้า ในผู้ป่วยมะเร็งระยะลุกลามที่ไม่สามารถผ่าตัดได้ หรือ ระยะแพร่กระจาย ซึ่งได้รับยาเคมีบำบัดที่หน่วยมะเร็งวิทยา ภาควิชาอายุรศาสตร์ มหาวิทยาลัยเชียงใหม่ ตั้งแต่เดือนธันวาคม พ.ศ. 2556 ถึง กรกฎาคม พ.ศ. 2557 มีจำนวนผู้ป่วยทั้งหมด 50 ราย ถูกสุ่มแบ่งเป็น กลุ่มที่ได้รับคำแนะนำด้านการรับประทานอาหารจากนักโภชนาการก่อนได้รับยาเคมีบำบัด และกลุ่มที่ได้รับการดูแลตามปกติ โดยประเมินผลหลังจากได้ยาเคมีบำบัด 3-4 ครั้ง และ 6-8 ครั้ง หรือติดตามไปอีก 2 เดือน หากหยุดยาเคมีบำบัดไปก่อน

ผลการศึกษา: กลุ่มที่ได้รับคำแนะนำด้านการรับประทานอาหารจากนักโภชนาการ มีการเพิ่มขึ้นของน้ำหนักตัวร้อยละ $2.29 (\pm 6.20)$ เทียบกับกลุ่มที่ได้รับการดูแลตามปกติที่น้ำหนักลดลงร้อยละ $1.70 (\pm 6.23)$, $p = 0.03$ และมีดัชนีมวลกาย (*body mass index*) เพิ่มขึ้นร้อยละ $2.27 (\pm 6.09)$ เทียบกับกลุ่มที่ได้รับการดูแลตามปกติที่ลดลงร้อยละ $1.53 (\pm 5.92)$, $p = 0.03$ ในช่วงหลังได้ยาเคมีบำบัด 3-4 ครั้ง และสามารถคงน้ำหนักให้เท่าเดิมได้หลังจากติดตามผลไป 2 เดือน แต่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ นอกจากนี้กลุ่มที่ได้รับคำแนะนำด้านการรับประทานอาหารจากนักโภชนาการมีค่าเฉลี่ย PG-SGA score ลดลงเหลือ $6.67 (\pm 1.99)$ เทียบกับกลุ่มที่ได้รับการดูแลตามปกติที่มีค่า $10.04 (\pm 3.73)$, $p < 0.001$ และค่าคะแนนคุณภาพชีวิตดีขึ้นอย่างมีนัยสำคัญทางสถิติ $39.40 (\pm 10.61)$ เทียบกับ $46.16 (\pm 7.55)$, $p = 0.01$ ในช่วงหลังได้ยาเคมีบำบัด 3-4 ครั้ง และหลังจากติดตามผลไป 2 เดือน ส่วนค่า *absolute lymphocyte count*, *serum albumin* พลังงานที่ได้รับในแต่ละวัน จำนวนผู้ป่วยที่ถูกเลื่อนการรับยาเคมีบำบัด สาเหตุของการเลื่อนยาเคมีบำบัด และจำนวนครั้งของยาเคมีบำบัดที่ได้รับ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุป: การให้คำแนะนำด้านการรับประทานอาหารจากนักโภชนาการ สามารถช่วยทำให้น้ำหนักตัว ดัชนีมวลกาย PG-SGA score และคุณภาพชีวิตของผู้ป่วยมะเร็งระยะลุกลามที่ผ่าตัดไม่ได้หรือระยะแพร่กระจาย ที่ได้รับการรักษาด้วยยาเคมีบำบัดดีขึ้น เมื่อเทียบกับการดูแลตามปกติ ดังนั้นจึงควรให้ความสำคัญในการคัดกรองภาวะทุพโภชนาการในผู้ป่วยมะเร็งทุกราย และรีบให้การรักษาด้านโภชนาการตั้งแต่เริ่มแรก