ADITUM International Journal of Clinical Gynaecology and Obstetrics

Open Access Research Article

Effectiveness Of A Nutritional Intervention In The Reduction Of Gastrointestinal Toxicity During Teletherapy In Women With Gynecological Tumors

Soto-Lugo J.H*, Souto-Del Bosque M.A, Vázquez Martínez C.A.

Department of Radiation oncology: Northeast Medical Center of the Mexican Social Security Institute IMSS, UMAE 25, Monterrey, Nuevo León, Mexico

Article Info

Received: March 24, 2021
Accepted: April 05, 2021
Published: April 09, 2021

***Corresponding author:** Bassim Al Bahrani, The Royal Hospital, P O Box 1331, code 111, Muscat, Oman.

Citation: Soto-Lugo J.H, Souto-Del Bosque M.A, Vázquez Martínez C.A, Effectiveness Of A Nutritional Intervention In The Reduction Of Gastrointestinal Toxicity During Teletherapy In Women With Gynecological Tumors. International J of Clinical Gynaecology and Obstetrics, 2(2); DOI: http;//doi.org/03.2021/1.1013.

Abstract

Objective: To evaluate whether nutritional intervention through a diet low in oligosaccharides, disaccharides, monosaccharides and fermentable polyols (FODMAP) reduces acute gastrointestinal toxicity by pelvic teletherapy in patients with gynecological tumors.

Material And Methods: A prospective unicentric randomized clinical trial comparing patients on a low- FODMAP diet with a standard Mexican diet designed to detect an 80% decrease in Grade 1-2 acute gastrointestinal toxicity in the normal diet group at 25% ff acute gastrointestinal toxicity Grade 1-2 in patients with low FODMAP diet.

Results: Thirteen patients were recruited per group, with a higher gastrointestinal toxicity in the normal diet group, grade 1-2 (85% vs 77%) and 3 (23% vs 0%) compared to the FODMAP diet (p 0.16). The FODMAP group had a lower symptom score at the end of treatment in the quality of life questionnaire of patients with cervical cancer (1.41 vs 1.85, p 0.01) and a lower mean deterioration in ECOG (0.61 of 0.5 vs 0.23 of 0.43 , P 0.049). 85% of the patients had an excellent attachment to the diet. No factors associated with the presence of grade 3 gastrointestinal toxicity were found.

Conclusion: The implementation of a diet low in FODMAP during treatment with pelvic teletherapy is a measure of low cost and high attachment, which decreases the deterioration of functional status and symptomatology at the end of treatment in patients with cervical cancer.

Key Words: Gynecological Tumors

Introduction

Malignant tumors of the cervix and uterine body represent in women the fourth and sixth place in incidence and the fourth and fourteenth place in cancer mortality in the world, cervical cancer in Mexico is the second most common cancer in women in incidence and mortality and uterine body cancer occupies the ninth and thirteenth place in these parameters; in addition, it is expected that these statistics will increase by 2020.[1,2]

Treatment with external radiation therapy or teletherapy is used in 60-71% of women with cervical cancer and in 38-45% of those with tumors of the uterine body at some point in the disease, [3,4,5] the main adverse effect of this therapy is gastrointestinal toxicity, presenting in mild to moderate degrees in 70% to 90% of patients and in severe degrees (III-V) in about 3%, [6] increasing its incidence and severity with commonly present factors such as concomitant use of chemotherapy, which doubles the risk of gastrointestinal toxicity grade ≥3.[7]

Women with acute gastrointestinal toxicity during pelvic teletherapy have a negative impact on abdominal symptomatology, which also affects their nutritional status and quality of life, and the prolongation or discontinuation of treatment caused by these symptoms increases the risk of obtaining suboptimal results in

disease control, survival and quality of life.[8]
Several interventions have been developed related to the modification of technical aspects of the treatment to reduce gastrointestinal toxicity by teletherapy during the last decades, however, it remains the main adverse effect in these patients and these measures can not be used in all centers due to to the technical and economic requirements involved.[9-16]
Regarding the different dietary interventions evaluated, their effectiveness has not been corroborated conclusively although they are an option of easy access and implementation, so they can be used in all care centers alone or in combination with other measures for the reduction of this toxicity.[17-20]

Based on the lack of conclusive evidence of decreased gastrointestinal toxicity with nutritional interventions that use the modification of a single dietary element in patients treated with radiotherapy, the benefit of the diet low in fructose, olioles, disaccharides, monosaccharides and polyols (FODMAP) Is based on multiple factors influencing radiation enteropathy such as regulation of intestinal motility, lactose restriction and osmotic agents, and modification of bacterial flora [9,21,22] together with the observed improvement in abdominal symptoms of patients with inflammatory bowel disease, which has similarities to radiation-induced damage in its pathogenesis, and the high compliance reported.[23-27]
This is why it is necessary to evaluate this type of nutritional intervention in patients treated with pelvic teletherapy in order to improve tolerance to treatment and thus positively influence oncological results and patients' quality of life.

Objective

Evaluate whether nutritional intervention through a diet low in oligosaccharides, disaccharides, monosaccharides and fermentable polyols (FODMAP) decreases the acute gastrointestinal toxicity by pelvic teletherapy in patients with gynecological tumors when compared to a normal Mexican diet.

Methods

Patient selection and eligibility criteria:

Patients diagnosed with cervical cancer or endometrial cancer at the National Medical Center of the Northeast UMAE 25 of the Mexican Social Security Institute in Monterrey, IMSS, Nuevo León, considered eligible had to be between 18 and 70 years of age at the time of entry into the study, have histopathological corroboration of the diagnosis, functional status according to the scale of the Eastern Cooperative Oncology Group ECOG from 0 to 2, have adequate renal, hepatic and marrow function, absence of pregnancy or puerperium and to be candidates for Radical therapy or adjuvant therapy with teletherapy with or without concomitant chemotherapy. Patients who had received previous pelvic radiotherapy, inflammatory bowel disease, active severe comorbidity or active collagen disease, or those with distant metastases according to extension studies with chest x-ray and abdominal-pelvic tomography were excluded.
The study protocol was accepted prior to its initiation by the Local Research and Ethics Committee on Health Research and informed consent was obtained from the patient for participation in the study according to institutional guidelines.

Surgery.
Patients treated with primary surgery candidates for adjuvant treatment were treated with hysterectomy + bilateral salpingo-oophorectomy with or without lymphadenectomy.

Chemotherapy.
In the patients who were candidates for concomitant chemotherapy, cisplatin was used at a dose of 40 mg / m2 on days 1, 8, 15, 22 and 29 of radiotherapy, in case of contraindication for this drug, carboplatin was used with a dose of area under the curve Of 1.5 according to the formula of Calvert

Radiotherapy.
All patients received conformal three-dimensional radiation therapy to the pelvis, with a dose of 50 Gy in fractions of 2 Gy or 50.4 Gy in fractions of 1.8 Gy.

Diet.
The types of diets to be assigned consisted of a diet low in fructose, oligosaccharides, disaccharides, monosaccharides, olioles and polyols (FODMAP) specified by means of a food guide, the evaluation of the attachment to this diet was performed by weekly self-assessment with a Likert scale with attachment values greater than or equal to 75% of the time, 50-75% of the time, 25-50% of the time and less than 25% of the time. The other diet consisted of a normal Mexican diet according to the recommendations of Official Mexican Standard NOM-043-SSA2-2012, Basic Health Services. Promotion and education for health in alimentary matters. Criteria for guidance.

Follow-up.
At the onset of teletherapy, symptomatology, weight, functional status and quality of life were assessed by applying the European Organization for Research and Treatment Questionnaire EORTC QLQ C-30 [28,29] to all patients and specific modules For cervical cancer (CX-24) [30] or endometrium (EN-24) [31] according to the primary. Subsequently, the assessment of the degree of gastrointestinal toxicity was performed according to NCI National Cancer Institute Version 4.03 [32] scale weekly and medical and /or hospital management was granted if necessary.
At the end of treatment with teletherapy the quality of life, weight and gastrointestinal toxicity of the patients were again evaluated.

Study Design

A single-center, randomized, prospective clinical trial was performed, using tables of random assignment to patients to the low-FODMAP diet group or the Mexican Normal Diet (NOM) group.
The study was designed to detect an 80% decrease in Grade 1-2 acute gastrointestinal toxicity in the normal diet group to 25% Grade 1-2 acute gastrointestinal toxicity in patients with FODMAP diet, with an alpha value of 0.05 and A statistical power of 80%. It was planned to recruit 13 patients per group, with a total of 26 patients

Results

Characteristics of patients.

Twenty-six patients were recruited from August to October 2016

at the National Medical Center of the Northeast who agreed to participate in the study, the characteristics of the patients assigned to each type of diet are presented in table 1.

Table 1. Patients characteristics

		FODMAP n (%)	NOM n (%)	p
Average age		46	43	0.8
Primary				1
	Cervical	10 (77)	10 (77)	
	I	1 (7)	1 (7)	
	II	5 (38)	5 (38)	
	III	4 (31)	4 (31)	
	Endometrium	3 (23)	3 (23)	0.54
	I	0 (0)	1 (7)	
	II	0 (0)	0 (0)	
	III	3 (23)	2 (15)	
ECOG				0.8
	0	2 (15)	3 (23)	
	1	8 62)	8 (62)	
	2	3 (23)	2 (15)	
Comorbid conditions				0.39
	Yes	3 (23)	5 (38)	
	No	10 (77)	8 (62)	
Previous surgery for the primary tumour				0.68
	Yes	4 (31)	5 (38)	
	No	9 (69)	8 (62)	
Concomitant chemotherapy				0.65
	Yes	9 (69)	10 (77)	
	No	4 (31)	3 (23)	
Radiotherapy dose				0.68
	50.4 Gy/28 Fx	8 (62)	9 (69)	
	50 Gy/25 fx	5 (38)	4 (31)	
Bowelbag V45 Gy >195cc				0.3
	SI	13 (100)	12 (93)	
	NO	0 (0)	1 (7)	
Rectum V 40 Gy >60%				0.14
	SI	13 (100)	11 (85)	
	NO	0 (0)	2 (15)	
Follow-up				1
	5 semanas	4 (31)	4 (31)	
	6 semanas	5 (38)	5 (38)	
	>6 semanas	4 (31)	4 (31)	

Toxicity.

The results of the maximum degree of gastrointestinal toxicity presented by the patients according to the type of diet assigned are presented in Table 2.

Table 2. Incidence of gastrointestinal toxicity according to diet. p=0.16

Toxicity	FODMAP n (%)	NOM n (%)
0	2 (15)	0 (0)
1,2	11 (85)	10 (77)
3	0 (0)	3 (23)
4	0 (0)	0 (0)

Table 3 shows the incidence according to the type and degree of toxicity presented by the patients according to the assigned diet. In both groups the most common gastrointestinal toxicity was nausea, followed by vomiting (54% vs 46%) and diarrhea (62% vs 69%), there were no gastrointestinal toxicity events grade 3 in the low-FODMAP diet group.

Table 3. Type of gastrointestinal toxicity and degree of presentation according to diet

Toxicity	Grade	FODMAP n (%)	NOM n (%)	p
Abdominal distension	0	13 (100%)	11 (86)	0.7
	1	0 (0)	0 (0)	
	2	0 (0)	1 (7)	
	3	0 (0)	1 (7)	
	4	0 (0)	0 (0)	
Pain	0	7(54)	8 (62)	0.6
	1	4(31)	2 (15)	
	2	2 (15)	2 (15)	
	3	0 (0)	1 (7)	
	4	0 (0)	0 (0)	
Nausea	0	3 (23)	2 (15)	0.83
	1	8 (62)	7 (54)	
	2	2 (15)	3 (23)	
	3	0 (0)	1 (7)	
	4	0 (0)	0 (0)	
Vomit	0	6 (46)	7 (54)	0.78
	1	4 (31)	2 (15)	
	2	3 (23)	3 (23)	
	3	0 (0)	1 (7)	
	4	0 (0)	0 (0)	
Proctitis	0	10 (77)	10 (77)	1
	1	3 (23)	3 (23)	
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
Rectal pain	0	10 (77)	10 (77)	0.87
	1	3 (23)	2 (15)	
	2	0 (0)	1 (7)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
Diarrhea	0	5 (38)	4 (31)	0.43
	1	2 (15)	4 (31)	
	2	6 (46)	3 (23)	
	3	0 (0)	2 (15)	
	4	0 (0)	0 (0)	
Constipation	0	12 (93)	12 (93)	1
	1	1 (7)	1 (7)	
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	

Attachment to the FODMAP Diet.

It was considered an excellent dietary attachment when a dietary follow-up score was obtained using the Likert scale above 75% in 50% or more of the evaluated weeks, if this percentage was 50-75%, it was considered regular and below 50% was considered detachment. In Table 4, the data of the attachment to the low diet

in FODMAP are reported.

The excellent attachment to this diet did not have a significant association for the prevention of the development of gastrointestinal toxicity in any degree, with an odds ratio of 0.93 (95% CI 0.93-11.77, p 0.96).

Tabla 4. Attachment to low-FODMAP diet	
Cumplimiento	n (%)
Excelent	11 (85)
Regular	2(15)
Detachment	0 (0)

Weight loss and functional status.
Table 5 reports the weight loss during treatment and the decrease in ECOG functional status at the end of treatment, reporting a greater deterioration of functional status in the patients assigned to the NOM diet group compared to the low FODMAP diet.

Table 5. Average decrease of weight and ECOG at the end of teletherapy			
	FODMAP	NOM	p
Average decrease of weight	2.43 kg (SD 2.33)	3.12 kg (SD 3.17)	0.48
ECOG final	1.3 (SD 0.63)	1.3 (SD 0.63)	1
ECOG decrease	0.23 (SD 0.43)	0.61 (SD 0.5)	0.049

Quality of life.

The averages of the initial and final scores obtained in the EORTC QLQ C-30 general quality of life test and the EN-24 endometrial cancer specificity did not differ significantly, however, in the specific test for cervical cancer, a significant difference with a lower presence of symptoms in the final questionnaire of the patients assigned to the FODMAP diet. The results are presented in Table 6

Table 6. Mean of initial and final quality of life scores and changes in scores									
		INITIAL			FINAL			CHANGE	
		FODMAP	NOM	p	FODMAP	NOM	p	FODMAP	NOM
QLQC-30	Global quality of life	4.9	4.9	0.95	5.03	4.92	0.84	0.13	0.02
	Physical	1.58	1.64	0.76	1.58	1.76	0.17	0	0.12
	Role	2	1.69	0.35	1.88	1.69	0.51	-0.12	0
	Emotional	1.86	2.09	0.47	1.57	1.53	0.86	-0.29	-0.56
	Social	1.92	1.57	0.34	1.8	2	0.58	-0.12	0.43
	Fatigue	2.15	1.99	0.6	2.4	2.09	0.22	0.25	0.1
	Nausea/ vomit	1.8	1.6	0.9	2	1.7	0.8	0.2	0.0 6
	Pain	1.96	1.96	1	1.92	1.61	0.31	-0.04	-0.35
	Dysnea	1.46	1.46	1	1.38	1.54	0.45	-0.08	0.08
	Insomnium	1.92	1.85	0.94	1.85	1.69	0.64	-0.07	-0.16
	Appetite loss	2.15	1.46	0.69	2.15	2.23	0.83	0	0.77
	Constipation	2	2.15	0.72	1.46	1.54	0.74	-0.54	-0.61
	Diarrhea	1.08	1.15	0.55	2.15	2.31	0.59	1.07	1.16
	Financial difficulties	2.46	1.92	0.18	2.54	1.92	0.09	0.08	0
CX-24	Body image	1.39	1.63	0.46	1.73	1.76	0.94	0.34	0.13
	Sexual activity	1.2	1.5	0.38	1.1	1	0.33	-0.1	-0.5
	Symptoms	1.89	1.67	0.49	1.41	1.85	0.01	-0.48	0.18
	Lymphedema	1.1	1.1	1	1	1	1	-0.1	-0.1
	Neuropathy	1.6	1.5	0.79	1.5	1.4	0.77	-0.1	-0.1
	Menopause	1.9	1.6	0.4	1.7	1.3	0.14	-0.2	-0.3
	Sexual preocupation	1.5	1.9	0.34	2.4	2.3	0.88	0.9	0.4
EN-24	Sexual interest	2.33	1.33	0.1	1.33	1	0.37	-1	-0.33
	Sexual activity	2	1.33	0.37	1	1	1	-1	-0.33
	Lymphedema	1.33	1.67	0.55	1.33	1.33	1	0	-0.34
	Urologic symptoms	1.41	1.66	0.6	1.5	2.25	0.25	0.09	0.59
	Gastrointestinal symptoms	1.13	1.13	1	1.2	1.46	0.2	0.07	0.33
	Body image	1.33	1.67	0.67	1	1.33	0.37	-0.33	-0.34
	Pain back/pelvis	1	1.33	0.37	1.33	1	0.37	0.33	-0.33
	Numbness	1.33	1.67	0.51	1.33	1.33	1	0	-0.34
	Muscular pain	1	1.33	0.67	1.33	1	0.67	0.33	-0.33
	Hair loss	2	3	0.51	1	2	0.37	-1	-1
	Taste changes	2	2	1	1	1.33	0.37	-1	-0.67

Factors influencing gastrointestinal toxicity.

No factors that had a significant influence on the presentation of grade 3 gastrointestinal toxicity were observed in the univariate analysis. Table 7.

Tabla 7. Univariate analysis of grade 3 gastrointestinal toxicity predictive factors		
	Odds ratio (IC 95%)	p
Cervical cancer	2.18 (.17-27)	0.54
Endometrial	.45 (.03-5.78)	0.54
Stage 1	.83 (.03-19.97)	0.91
Stage 2	.77 (.06-9.88)	0.84
Stage 3	2.8 (.222-35.28)	0.42
Low-FODMAP diet	0.11 (.0052-2.39)	0.16
NOM diet	9 (.41-194)	0.16
ECOG 0	.48 (.02-10)	0.64
ECOG 1	.26 (.02-3.4)	0.3
ECOG 2	13.33 (.9-196)	0.05
Comorbid conditions	1.41 (.1-18.5)	0.79
Chemotherapy	0.7 (.05-9.2)	0.79
Bowelbag V45>195cc	.46(.01-13)	0.65
Rectum V40>60%	.09 (.004-2.07)	0.13
Surgery	.93 (.07-11)	0.96
RT dose 50.4 Gy	4.51 (0.21-99.2)	0.33
RT dose 50 Gy	0.21 (.10-4.7)	0.33

Discussion

The incidence of gastrointestinal toxicity in patients treated with pelvic teletherapy has been previously reported in values ranging from 70% to 90% in grades 1 and 2 and in 3% to 9% grade 3 and 4, in our study We observed an incidence of toxicity grade 1 and 2 similar, with 77% and 85% according to the assigned diet group FODMAP or NOM respectively; on the other hand, the incidence of grade 3 gastrointestinal toxicity was higher than that reported in the literature, with all events of this grade in the NOM diet group, corresponding to 11% of the total patients and 23% of the patients assigned to This diet group. Likewise, the type of toxicities presented by the patients corresponds to what was observed in other studies, the main toxicities being nausea, vomiting and diarrhea, all of which are higher in the NOM diet group.

The higher incidence of gastrointestinal toxicity in the NOM diet group was accompanied by a greater average weight loss in these patients (2.43 kg vs 3.12 kg) and a greater average deterioration in functional status according to ECOG at the end of treatment (0.61 DE 0.5 vs 0.23 of 0.43). This difference was statistically significant (p 0.049). Cervical cancer patients who were assigned to this group had a higher symptom at the end of treatment according to the CX-24 specific quality of life questionnaire (1.41 vs 1.85, p 0.01).

For this reason, although a statistically significant decrease in gastrointestinal toxicity with the FODMAP diet was not achieved, the severity of FODMAP was lower in this group of patients and it was accompanied by superiority in some aspects of patients' quality of life With cervical cancer and less weight loss during treatment.

On the other hand, the high rate of excellent attachment to the FODMAP diet (85%) places it as a tool that can be performed alone or in conjunction with other measures carried out to decrease gastrointestinal toxicity, which, in addition, requiring resources or specific infrastructure can be implemented in any center.

In conclusion, the implementation of a diet low in FODMAP during the treatment with pelvic teletherapy is a measure of low cost and high attachment, which decreases the deterioration of functional status and symptomatology at the end of treatment in patients with cervical cancer; A long-term follow-up of patients is required to assess their impact on chronic toxicity and to conduct a study in a larger number of patients designed to decrease severe toxicity during teletherapy (grade 3-4) to establish their role in this scenario.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al.: Globocan 2012 v1.0, Cancer Incidence and Mortality Worldwide. Lyon, France: International Agency for Research on Cancer, 2013. IARC CancerBase No. 11. Accesado 4 abril, 2016.
2. Perfil epidemiologico de los tumores malignos en Mexico, SSA, 2011
3. Barton M, Review of optimal radiotherapy utilization rates, Ingham Institute for Applied Medical Research, Australia, 2013, 6: 61-88, 26: 464-513
4. Delaney G, Estimation of an optimal radiotherapy utilization rate for gynecologic carcinoma: part I--malignancies of the cervix, ovary, vagina and vulva.Cancer. 2004;101(4):671.
5. Delaney G, Estimation of an optimal radiotherapy utilization rate for gynecologic carcinoma: part II--carcinoma of the endometrium. Cancer. 2004;101(4):682.
6. Nout RA, Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. The Lancet. 2010;375: 816–823
7. Andreyev HJN, Does acute gastrointestinal toxicity during radical pelvic radiotherapy predict late gastrointestinal toxicity? A study using the IBDQ and a Vaizey score, more sensitive measures of radiotherapy-induced toxicity than the RTOG or LENT SOM scales, Abstracts for the NCRI Cancer Conferences. 2008. Accesado 12 de abril 2016
8. Andreyev HJN, Gastrointestinal Problems after Pelvic Radiotherapy: the Past, the Present and the Future, Clinical Oncology. 2007. 19: 790 e 799
9. Sher, ME and J Bauer, Radiation-induced enteropathy. Am J Gastroenterol. 1990. 85:121–128.
10. Letschert JG, The volume effect in radiation-related late small bowel complications: results of a clinical study of the EORTC Radiotherapy Cooperative Group in patients treated for rectal carcinoma. Radiother Oncol. 1994;32(2):116.
11. Louidice TA, Effects of abdominal surgery on the development of radiation enteropathy, Gastroenterol. 1977;73:1093.
12. A Radiation Therapy Oncology Group Consensus Panel Atlas, Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. e353 e e362, 2012
13. Hymel R, Jones GC, Simone CB2nd, et al: Whole pelvic

intensity-modulated radiotherapy for gynecological malignancies: A review of the literature. Crit Rev Oncol Hematol 2015; 94(3):371-379.

14. Wiesendanger-Wittmer EM, Systematic review of the role of a belly board device in radiotherapy delivery in patients with pelvic malignancies, Radiotherapy and Oncology 102 (2012) 325–334
15. DeLuca FR, Ragins H. Construction of an omental envelope as a method of excluding the small intestine from the field of postoperative irradiation to the pelvis. Surg Gynecol Obstet. Apr/1985. 160(4):365-6.
16. Zimmerer T, Z Gastroenterol. 2008 May;46(5):441-8, Z Gastroenterol. 2008 May;46(5):441-8
17. Henson CC, Nutritional interventions for reducing gastrointestinal toxicity in adults undergoing radical pelvic radiotherapy (Review) Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD009896.
18. Stacey R, Radiation-induced small bowel disease: latest developments and clinical guidance, Ther Adv Chronic Dis, 2013. 0(0) 1 –15
19. Wedlake LJ, Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy, Aliment Pharmacol Ther 2013; 37: 1046 – 1056
20. Wedlake L.J, Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: an observational study. Eur J Cancer 2008; 44: 2212–7.
21. Wedlake L, Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: An observational study.Eur J Cancer. 2008;44(15):2212.
22. Gibson PR, Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach Journal of Gastroenterology and Hepatology 25 (2010) 252–258
23. Staudacher H.M., Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome J Hum Nutr Diet. 2011. 24, pp. 487–495
24. Khan MA, Low-FODMAP diet for irritable bowel syndrome: is it ready for prime time?, Dig Dis Sci. 2015; 60: 1169-77
25. Halmos EP, Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2015;64: 93-100
26. Gearry RB, Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease — a pilot study. Journal of Crohn's and Colitis (2009) 3, 8 – 14
27. Prince AC, Fermentable Carbohydrate Restriction (Low FODMAP Diet) in Clinical Practice Improves Functional Gastrointestinal Symptoms in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016;0:1 – 8
28. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer,Brussels 2001.
29. Aaronson NK, The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993; 85: 365-376
30. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Cervical Cancer Module: EORTC QLQ-CX24. Cancer 14:1812-1822, 2006.
31. Greimel E, Nordin A, Lanceley A, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24) Eur. J Cancer (2010)
32. U.S. Department of Health and Human Services, Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 14,2010