

Quality of Life Associated with Radiotherapy Treatment in Women Affected by Cervical Cancer: Integrative Literature Review

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Qualidade de Vida Associada ao Tratamento com Radioterapia em Mulheres Acometidas pelo Câncer do Colo do Útero: Revisão Integrativa da Literatura

Calidad de Vida Asociada al Tratamiento con Radioterapia en Mujeres Afectadas por Cáncer de Cuello Uterino: Revisión Integrativa de la Literatura

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ABSTRACT

Introduction: Cervical cancer (CC) is among the five most common cancers in women. Initially, the treatment indicated is surgery. When the patient has risk factors associated with local recurrence, adjuvant pelvic radiotherapy is performed. Investigating the impact of treatment on the quality of life (QoL) of women with CC can help planning actions to reduce or prevent harm. **Objective:** Compile the repercussions and factors that influence the QoL of women with CC undergoing radiotherapy. **Method:** A integrative review of the literature was conducted in the MEDLINE (PubMed), LILACS and SciELO databases. The inclusion criteria were articles from the last five years, open access, written in Portuguese, English or Spanish, addressing the theme defined totally or partially. **Results:** 17 articles were selected, among which prospective longitudinal studies (n=9) predominated, followed by cross-sectional studies (n=5) and retrospective longitudinal studies (n=3). In addition, 15 different questionnaires were used, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) was more frequent, consisting of 8 studies. **Conclusion:** The QoL of women submitted to radiotherapy was influenced by socioeconomic and educational factors, marital relationships, and the modality of radiotherapy. Although the treatment methods have influenced individual factors, such as physical and emotional symptoms, they had no significant relationship with general QoL. Studies should be conducted to assess the long-term effects of radiotherapy.

Key words: Quality of Life; Uterine Cervical Neoplasms/radiotherapy; Women.

RESUMO

Introdução: O câncer do colo do útero (CCU) está entre os cinco tipos de cânceres mais frequentes em mulheres. Inicialmente, o tratamento indicado é a cirurgia. Já, quando a paciente apresenta fatores de risco associados à recidiva local, é feita a radioterapia pélvica adjuvante. Investigar o impacto do tratamento na Qualidade de Vida (QV) das mulheres com CCU pode auxiliar o planejamento de ações no sentido de reduzir ou evitar danos.

Objetivo: Compilar as repercussões e os fatores que influenciam a QV de mulheres com CCU submetidas ao tratamento radioterápico. **Método:** Foi realizada uma revisão integrativa da literatura nas bases de dados MEDLINE (PubMed), LILACS e SciELO. Os critérios de inclusão foram artigos dos últimos cinco anos, de acesso aberto, escritos em português, inglês ou espanhol e que abordassem o tema definido total ou parcialmente.

Resultados: Foram selecionados 17 artigos, entre os quais predominaram os estudos longitudinais prospectivos (n=9), seguidos dos estudos transversais (n=5) e estudos longitudinais retrospectivos (n=3). Ademais, houve a utilização de 15 diferentes questionários, sendo mais frequente o *European Organization for Research And Treatment of Cancer Quality of Life Questionnaire* (EORTC-QLQ-C30), que integrou oito estudos. **Conclusão:** A QV das mulheres submetidas à radioterapia foi influenciada por fatores socioeconômicos, educacionais, relações matrimoniais e modalidade da radioterapia. Apesar de os métodos de tratamento terem influenciado fatores individuais, como sintomas físicos e emocionais, não tiveram relação significativa com a QV geral. Estudos devem ser realizados para avaliar os efeitos da radioterapia em longo prazo.

Palavras-chave: Qualidade de Vida; Neoplasias do Colo do Útero/radioterapia; Mulheres.

RESUMEN

Introducción: El cáncer de cuello uterino (CC) se encuentra entre los cinco cánceres más comunes en las mujeres. Inicialmente, el tratamiento indicado es la cirugía. Cuando el paciente presenta factores de riesgo asociados a recidiva local, se realiza radioterapia pélvica adjuvante. Investigar el impacto del tratamiento en la calidad de vida (CV) de las mujeres con CC puede ayudar a planificar acciones para reducir o prevenir daños. **Objetivo:** Recopilar las repercusiones y factores que influyen en la CV de las mujeres con CC sometidas a radioterapia. **Método:** Se realizó una revisión integradora de la literatura en las bases de datos MEDLINE (PubMed), LILACS y SciELO. Los criterios de inclusión fueron artículos de los últimos cinco años, de acceso abierto, escritos en portugués, inglés o español y que abordaron la temática total o parcialmente definida. **Resultados:** Se seleccionaron 17 artículos, entre los que predominaron los estudios longitudinales prospectivos (n=9), seguidos de los estudios transversales (n=5) y los estudios longitudinales retrospectivos (n=3). Además, se utilizaron 15 cuestionarios diferentes, siendo más frecuente el Cuestionario de Calidad de Vida de la Organización Europea para la Investigación y el Tratamiento del Cáncer (EORTC-QLQ-C30), que integró 8 estudios. **Conclusión:** La CV de las mujeres sometidas a radioterapia estuvo influenciada por factores socioeconómicos, educativos, relaciones maritales y el tipo de radioterapia. Aunque los métodos de tratamiento han influido en factores individuales, como los síntomas físicos y emocionales, no tienen una relación significativa con la CV general. Se deben realizar estudios más amplios para evaluar los efectos a largo plazo de la radioterapia.

Palabras clave: Calidad de Vida; Neoplasias del Cuello Uterino/radioterapia; Mujeres.

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INTRODUCTION

Cervical cancer (CC) is among the five types of cancer most frequent in women, being estimated that in 2018 only, nearly 18 million new cases and 9.6 million deaths occurred¹. Nevertheless, there are preventive and easily accessible exams as Papanicolaou ensuring the early diagnosis and more chances of cure of the patient².

The infection by the Human Papillomavirus (HPV) is the main cause for the development of cervical cancer. The 15 types of HPV with strong oncogenic potential are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. These types are considered of high risk and represent the etiology of 95% of all CC cancers. Types 16 and 18, specifically, account for nearly 90% of all the cases^{3,4}.

Social and economic factors are quite relevant as in some low and medium Human Development Index (HDI) countries, CC is one of the most incidents. In Brazil, this neoplasm is more incident in the North Region and the second most incident in the Northeast and Mid-West regions; in the South and Southeast regions, it ranks fourth and fifth^{5,1}.

The diagnosis of cancer can precede the application of certain therapeutic modalities as surgery, radiotherapy, chemotherapy, and hormone therapy, which opens a new challenging period in the life of women with CC⁶. The World Health Organization (WHO) divides the treatment of cancer in two types to support this stage: systemic – hormone therapy and chemotherapy – and locoregional – surgery and radiotherapy. The type of cancer, pathological and clinical staging, availability of proper infrastructure and skilled professionals will guide the therapeutic conduct in addition to individual characteristics as age and wish to get pregnant^{7,8}.

The treatment of CC in initial phases is surgery. Adjuvant pelvic radiotherapy is applied when the patient has risk factors associated with local relapse. Whether lymph node, parametrial or surgical margins are compromised, chemotherapy associated with radiotherapy. If is locally advanced or very bulky tumors, the association of chemotherapy with radiotherapy is recommended⁹.

Patients submitted to pelvic radiotherapy can present tissue damage, possibly with occlusion of blood vessels, thrombosis and neovascularization and atrophy and tissue contraction due to the increase of proliferation of fibroblasts. Additionally, actinic urethritis, vesicovaginal fistula, actinic cystitis and hematuria can be established as main complications of radiotherapy in the urinary tract and also in the intestine and rectum, where in the latter the most frequent is the ulcerative rectocolitis^{10,11}.

Regardless of the several negative consequences mentioned, few studies emphasize the impact in the Quality of Live (QoL) of women submitted to cervical cancer treatment. The present study attempts to address the secondary effects of radiotherapy on the QoL, whose definition, according to WHO is “as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”¹². Investigate the impact of the treatment on the QoL of women with CC can support the planning of actions to reduce or avoid damages.

Through bibliographic review, the study tried to compile the repercussions and factors influencing the QoL of women with CC submitted to radiotherapy treatment. To evaluate these repercussions, specific questionnaires to measure the QoL were applied with the following parameters: sexual QoL, physical and psychological well-being, in addition to social, professional, and organic damages.

METHOD

Integrative review of the literature proposing to respond to the following research question: “What are the repercussions and the factors influencing the QoL of women of all age ranges affected by CC submitted to radiotherapy treatment?”. The process was developed in stages such as: choice of the database, definition of the descriptors, definition of the inclusion and exclusion criteria, data collection, titles reading, keywords and abstracts and after new exclusion, full articles reading. This last stage has also ensured the exclusion of articles whose content were not pertinent to the subject.

The database selected were: MEDLINE (PubMed), LILACS and SciELO. The descriptors were defined from the Descriptors of Sciences of Health (DeCS) and Medical Subjects Headings (MeSH) and consisted in Uterine Cervical Neoplasms, Radiotherapy and Quality of life. The three were gathered by the Boolean operator AND in all databases.

The inclusion criteria established were: (i) articles published in the last five years (2016 to 2020); (ii) open access; (iii) drafted in Portuguese, English or Spanish and (iv) addressing totally or partially the theme defined. The articles of review of literature, integrative and systematic reviews as well as those where the primary outcome was not directly associated with the study theme were excluded.

RESULTS

Upon the application of pre-determined inclusion and exclusion criteria, the exclusion of duplicate articles and

those which failed to meet the objective of the review, 17 studies remained. The flowchart of this process is shown in Figure 1.

The articles selected were evaluated according to the approach of impact on QoL each one utilized – sexual, emotional, physical, socioeconomic conditions and QoL in general. Some studies utilized questionnaires focused on one function alone as the Female Sexual Function Index (FSFI) which evaluated the sexual function only, but others adopted well consolidated questionnaires that evaluated different aspects of QoL as the European Organization for Research And Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30).

12 longitudinal studies were selected, being three retrospective and nine prospective, in addition to five cross-sectional studies. Chart 1 presents the data and main conclusions of the studies included in the review.

DISCUSSION

The evaluation of the QoL of women submitted to radiotherapy to treat CC is influenced by innumerable factors that can be related directly and/or indirectly to the treatment. They are: age, education, habits, profession, socioeconomic condition, marital status, cancer staging, and type of treatment applied are among the modifying agents of the perception of the patient about the QoL highlighted in this review.

The study of Kyei et al.¹³ hypothesized that younger women with higher education level were more aware and concerned about the side effects of the radiotherapy treatment, concluding that the physical well-being of women with CC was affected by age and education level. The affirmation was corroborated still by Singh et al.¹⁴,

whose study identified the educational level together with tobacco use and little differentiation of the tumor as an independent factor negatively affecting the general QoL.

The consequences of the professional activity of the patients in radiotherapy treatment were addressed in a cross-sectional study by Zhou et al.¹⁵ that identified correlation between professional occupation and sexual activity ever reported in the literature: survivors of cervical cancer who worked in administrative, bureaucratic or management assignments had better sexual function than the rest of the patients who worked in other positions, which can be related to the level of education and lower level of exposure to radiotherapy.

The study of Correia et al.¹⁶ utilized the abbreviated questionnaire The World Health Organization Quality of Life Assessment (WHOQOL-BREF) to assess the QoL in women who submitted to surgery, chemotherapy, or radiotherapy. It has been shown the negative relation among the worst socioeconomic conditions, diminished leisure opportunities, comorbidities, and several types of therapy, including radiotherapy. The worst physical, functional, and social results were correlated with radiotherapy as this article found.

In addition, it has been shown yet that the financial difficulties due to the cost of radiotherapy and other factors influenced significantly the QoL of women submitted to adjuvant radiotherapy, as occurred too in other studies^{15,17,18}. Therefore, young patients who underwent adjuvant radiotherapy had worse global QoL in the long-term after five years. Partially, this concurs with the study of Mohanty et al.¹⁹, that revealed significant reduction of the scores of QoL after pelvic irradiation in a first moment, showing gradual and definitive improvement with time, pending the modality of radiotherapy.

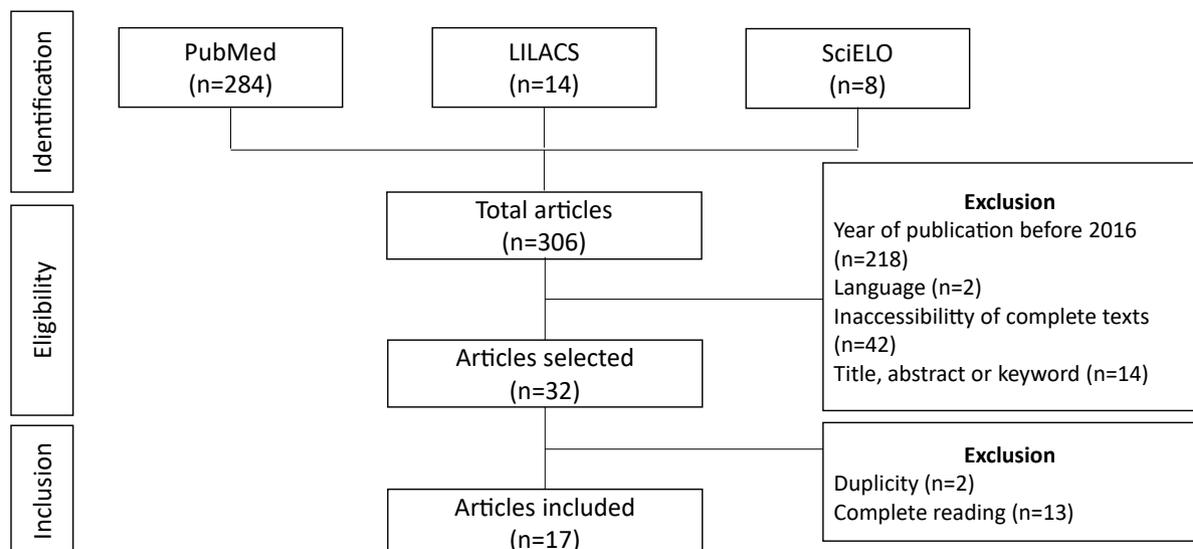


Figure 1. Flowchart of the process of selection of articles

Chart 1. Characteristics of the studies selected for the review

Author/ year	Design	Country	N	Questionnaires	Conclusions
Akbaba et al., 2018	Prospective longitudinal	Germany	83	EORTC QLQ-C30 and EORTC QLQ-CX24	The grade of acute side effects of radiochemotherapy correlated with the range of chronic symptoms. Sexual/vaginal functioning was worse in patients with larger tumors
Castaneda et al., 2019	Cross-sectional	Brazil	116	FACT-Cx	High prevalence of disability in women with CC occurred in the reproductive system. There was deterioration of QoL because of fear related to sexual life and urinary function
Cerentini et al., 2019	Prospective longitudinal	Brazil	88	EORTC QLQ-C30	No difference was detected between intervention group (vaginal dilator) and control group in relation to QoL, whose damages started to improve 3-6 months after the end of RT.
Correia et al., 2020	Cross-sectional	Brazil	46	FSFI	Women submitted to RT had more sexual symptoms than those who underwent surgery and CT
Correia et al., 2018	Prospective longitudinal	Brazil	46	WHOQOL-100	QoL was associated with clinical, socioeconomic and health conditions, connected to the type of treatment (late diagnosis reflected in the treatment with RT and CT)
Klopp et al., 2018	Prospective longitudinal	USA	278	EPIC; PRO-CTCAE; FACT-Cx and EQ-5D	IMRT resulted in lower impact in the intestinal and urinary function. Questionnaires of QoL showed that patients treated with IMRT had also less reduction of physical functioning
Kwak et al., 2017	Prospective longitudinal	Korea	136	LENT/SOMA	The results still revealed superiority of IMRT over RT. With reduced toxicity, IMRT increased the QoL of the patients and adherence to the treatment. They still suggest that with selective scaling of the dose in RT in the pelvis, IMRT is feasible and will possibly ensure better clinical results
Kyei et al., 2020	Cross-sectional	Ghana	120	FACT-G	Patients with cancer in initial stage reported QoL scores overall higher than those with late presentation of the disease
Li et al., 2017	Prospective longitudinal	China	480	DT; HHI; FACT-Cx and JCS	Guidance about the level of hope and coping can help patients to understand the disease, reduce the psychological suffering and improve the level of hope to cope with the disease as positively as possible
Mohanty et al., 2018	Prospective longitudinal	India	64	EORTC QLQ-C30 and EORTC QLQ-CX24	Adjuvant IMRT can be associated with improvement of QoL in the long-term. The magnitude of the damage for most of the domains of QoL is lower and IMRT leads to clinically improved scores of QoL compared with 3D-CRT

to be continued

Chart 1. continuation

Author/year	Design	Country	N	Questionnaires	Conclusions
Sabulei e Maree, 2019	Cross-sectional	South Africa	153	EORTC QLQ-C30 and EORTC QLQ-CX24	CC and its treatment influenced negatively the QoL and had impacts in all the domains of life. Social functioning was the most affected, financial difficulties were problematic, especially during the treatment, urinary frequency and insomnia continued problematic and feet swelling increased with time
Shankar et al., 2020	Prospective longitudinal	India	85	LENT/SOMA	Young patients were the most affected by RT and their QoL. The advanced stage of cancer and time of follow up were directly proportional to morbidity related to sexual function
Silveira et al., 2016	Prospective longitudinal	Brazil	16	EORTC QLQ-C30	Emotional function was the most affected, suggesting that diagnosis, treatment, and side effects cause important impacts
Singh et al., 2019	Prospective longitudinal	India	90	EORTC QLQ-C30 and EORTC QLQ-CX24	Education, tobacco use, level of differentiation of the tumor, size of the tumor and cancer stage were the independent variables that mostly affected the QoL
Yang et al., 2020	Retrospective longitudinal	China	97	FSFI and EORTC QLQ-C30	Different post-operative adjuvant therapies caused significant differences in the QoL in the long-term. Financial difficulties impacted the QoL of young patients with cancer post adjuvant RT. Young patients submitted to adjuvant RT had worse global QoL after 5 years
Yavas et al., 2017	Longitudinal prospective	Turkey	100	EORTC QLQ-C30; EORTC QLQ-CX24 and HADS	There was no important adverse effect in the HRQoL in the long-term resulting from RT. Acute worsening of HRQoL during treatment improved in the long-term
Zhou et al., 2016	Cross-sectional	China	140	FACT-Cx; FACIT-Sp and FSFI	The QoL of survivors of CC was considered low. Sexual functions were harmed as well as other QoL related complications

Captions: FSFI = Female Sexual Function Index; EORTC QLQ-C30 and EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Cx and FACT-G = Functional Assessment of Cancer Therapy; FACIT-Sp = Functional Assessment of Chronic Illness Therapy-Spiritual Well-being; EPIC = Expanded Prostate Cancer Index Composite; PRO-CTCAE = Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; DT = Distress thermometer; HHI = Herth Hope Index; JCS = Coping Style Scale; HADS = Hospital Anxiety and Depression Scale; WHOQOL-100 = Instrument for the Assessment of the Quality of Life of the World Health Organization; LENT/SOMA = Scale de Late Effects of Normal Tissue/Subjective-Objective-Management-Analytic; 3D-CRT = Three-dimensional Conformal Radiotherapy; IMRT = Intensity Modulated Radiotherapy; EQ-5D = EuroQol 5 Dimensions; RT = Radiotherapy; CT = Chemotherapy; QoL = Quality of Life; HRQoL = Health-related Quality of Life; CC = Cervical Cancer.

Still, according to Kyei et al.¹³, married women had higher mean scores than single women, the presence of the spouse was important for the emotional well-being of the patients. This data was also obtained in other studies which indicated that this support is a relevant factor for coping and treating the diseases as well as for the body image and sexual activity¹⁹⁻²¹. In patients treated with surgery combined with radiotherapy, the emotional domain was the most damaged in comparison with those

submitted to other therapeutic options – radiotherapy alone; radiotherapy and chemotherapy; radiotherapy, chemotherapy, and surgery.

Li et al.²⁰, in a study with 480 patients in accordance with the results of the studies aforementioned indicated that patients with cervical cancer, even with high morbidity of psychological suffering (68%) presented medium and high levels of hope of cure during radiotherapy. Older age, higher income, health-insurance, marital relations,

and low level of pain during treatment have also suggested higher levels of hope and, consequently, improved QoL in the sample studied.

The results of the clinical trial conducted by Sabulei and Maree¹⁸ showed that the radiotherapy treatment in association or not with chemotherapy influenced negatively all the domains of the QoL of the patients. The social domain was the most affected without significant improvement in time.

As initial is the stage of cancer, higher is the score of QoL in regard to the general QoL¹³, as also shown in other studies^{14,20}. In addition, the sexual and vaginal function was statistically and significantly worse in more advanced tumors (T3 and T4) in comparison with initial tumors (T1 and T2)²².

Klopp et al.²³ concluded in their study that among the modalities of radiotherapy treatment, the intensity-modulated radiation therapy (IMRT) caused less impact in the intestinal and urinary function during the treatment than the standard radiotherapy. Additionally, the metrics of QoL showed that the patients treated with IMRT had their physical function less impacted and minor treatment-related additional concerns in the course of radiotherapy.

Concurrently with the former study, Mohanty et al.¹⁹ inferred that IMRT may be associated with better scores of QoL in the long term. The magnitude of the damage for most of the domains of the QoL was lower and the use of IMRT resulted in statistically and clinically significant scores of QoL in comparison with tridimensional conformed adjuvant radiotherapy (3DCRT), another modality of radiotherapy.

In a prospective longitudinal study²⁴ with five women irradiated in the pelvis, the QoL was good. The score of the emotional function was the most negative, having been demonstrated that, together, diagnosis, radiotherapy treatment and side effects impact significantly the mental health of these women. In addition, the concurrent association of chemotherapy with treatment affects the physical function of the patients too. The cohort study of Akbaba et al.²² showed that although been an effective treatment, primary radiochemotherapy reduces the QoL in the long term.

Among the adverse effects caused by radiotherapy treatment in patients with CC, sexual health damages stand out. Some authors evaluated the sexual function of women post-treatment of CC through FSFI. It was found more prevalence of sexual symptoms in women submitted to radiotherapy in comparison with those treated with surgery and chemotherapy or surgery alone without adjuvant radiotherapy. Frigidity, poor lubrication, arousal, orgasm, libido, and dyspareunia were the most

common^{13,18}. Additionally, it was found that sexual disfunctions could be reversed if the woman was not submitted to post-surgery radiotherapy as long as bilateral salpingo-oophorectomy was not included in the surgical procedure.

Still based in the FSFI scores, Zhou et al.¹⁵ identified that 70% of the study patients had sexual dysfunction after the oncologic treatment (radiotherapy, chemotherapy, and hysterectomy). Psychologic and cognitive issues are strong modifiers of the experience and sexual QoL of the patients, most of all, concerns about the recurrence of cancer (63.8%) and fear of pain and bleeding because of sexual intercourse (31.9%). These results were also found in the study of Correia et al.²⁵, which was an additional motive for women to avoid sexual intercourse after CC treatment.

Additionally, the study of Castaneda et al.²⁶ concluded that disabilities related to the structures of the reproductive system were more prevalent in women, followed by problems in the functions of energy and impulse. In addition, it appeared that there were fear related to the sexual life and urinary disorders. In the present study, radiotherapy was not utilized alone but combined with chemotherapy.

One of the disabilities associated with females' genital tract detected in the present study was the feeling of vaginal narrowing and shortening. In addition, vaginal stenosis after the treatment is also a common complaint²⁶. Similarly, Cerentini et al.²⁷ attempted to evaluate the benefit of vaginal dilators during radiotherapy treatment in the vaginal canal because of cervical cancer. There was no difference in the QoL of women who utilized dilators compared with the control group.

A prospective study conducted by Shankar et al.²⁸ concluded that the combination of radiotherapy with surgery increased the disfunction and sexual dissatisfaction, mainly in younger women. The most common complaints in descending order were dyspareunia, worsening of the sexual quality of life and less interest in sex. The study suggested that in the future, the emphasis should be given to the obligation of disclosing the risk of sexual and general alterations after radiotherapy and the necessity of elaborating more comprehensive scales addressing physical and psychological disruptions²⁸.

Once the adverse effects of radiotherapy treatment are identified and their impact on how the patients evaluated the QoL during the treatment, it is possible to analyze the changes in the assessment of QoL by the patients after the treatment. In the clinical trial of Yavas et al.²⁹ the QoL of the patients with gynecological cancer was reviewed immediately before the radiotherapy, post-radiotherapy and during 24 months of follow-up post-radiotherapy.

No significant adverse effect from radiotherapy over the general QoL of the patients in the long-term was encountered. It was noticed that the scores of sexual activity and sexual pleasure deteriorated post-radiotherapy, however, in the 24th month of follow-up, both scores improved significantly.

The study of Singh et al.¹⁴ concluded there was improvement of the functional scale related to the general QoL six months after the radiotherapy treatment associated or not with chemotherapy in comparison with the period prior to the beginning of the treatment (baseline). Physical and emotional functions stood out. However, these improvements occurred most of all because of less concern with cancer diagnosis. Also, unsatisfactory sexual pleasure and significant sexual dysfunction were detected. These data corroborate the study of Yavas et al.²⁹, that showed reduction of the levels of anxiety and depression along the time. These authors¹⁷, however, found that the physical and emotional functions of women submitted to adjuvant radiotherapy did not improve with time.

CONCLUSION

The treatment of CC with radiotherapy is associated with high prevalence of sexual dysfunctions, especially in younger women. The combination of radiotherapy with chemotherapy caused more physical symptoms and with surgery, more emotional impact. Nevertheless, the forms of treatment did not present statistically significant relation with general QoL.

The positive impact in the QoL was found in women with higher family income, and education, married and less pain during treatment. In counterpart, the factors related to worse socioeconomic conditions, poor leisure activities, comorbidities and single marital status negatively impacted the QoL of these women.

In the long-term, the studies diverged in relation to improvement of physical and emotional functions. It is suggested more studies to better understand the effects of radiotherapy along the time.

CONTRIBUTIONS

Louyse Jerônimo de Moraes, João Lucas Pordeus de Menezes, Aluísio José de Oliveira Monteiro Neto, Maria Gabriela Porfírio Pereira, and Yasmin Dantas Pereira contributed for the study conception and/or design, collection, analysis and interpretation of the data, wording and critical review. Veriana Márcia da Nóbrega contributed for the wording and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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