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Quality of Life in Patients with Clinically Localized Prostate Cancer Managed with Modern Radiotherapy: Impact on Bowel Habit, Sexual Function and Urinary Symptoms

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Abstract: *Objective*: The increase in the diagnosis of tumors in early stages, associated with similar life expectations among the different treatments, create a challenge for both patients and treating doctors when choosing the best therapeutic option. The objective is to assess the impact on the quality of life in the sexual, intestinal and urinary fields in patients with localized prostate cancer who received treatment with modern radiotherapy. *Methods*: Descriptive observational study in which the validated EPIC-26 and SF-36 surveys were applied in the period between December 2015 and November 2018, in order to assess quality of life in men with localized prostate cancer before and after modern radiation therapy. *Results*: Surveys were applied to 70 individuals. In the EPIC-26 survey, relevant changes in the quality of life for urinary incontinence were found, with a previous average score of 81.75 (100 - 12.5) versus a subsequent 72.99 (100 - 0). In the SF-36 Health Questionnaire it was found that there is no significant difference in the overall quality of life, with an average score of 77 (99 - 31) and 76.63 (100 - 39.58) respectively. *Conclusion*: There is a tendency to oversize the impact of radiotherapy on the quality of life when there is a curative intent in patients with localized prostate cancer. Our study only demonstrated a clinically relevant difference in urinary incontinence, which allows us to suggest that most of the alterations in the quality of life could be secondary to natural changes in aging.

Keywords: Intensity Modulated Radiotherapy, Radiotherapy, Quality of Life, Prostate Cancer, Lower Urinary Tract Symptoms, Erectile Dysfunction, Sexual Health, Radiation Effects

1. Introduction

Prostate cancer is the second most frequent cause of cancer and the sixth leading cause of cancer-related death among men worldwide. Although little is known about its etiology, in recent years, its detection in early stages has increased mainly due to the introduction of diagnostic methods such as prostate-specific antigen (PSA), transrectal ultrasound and advances in prostate biopsy techniques. The latest statistics show that 1 in 6 men will suffer from this tumor in their life [1, 2].

Currently, there are several treatment modalities for localized cancer including radical prostatectomy, radiotherapy and active surveillance; with low specific cancer mortality rates, 3-4% and 2-10% at 10 and 15 years respectively, similar in all treatment modalities [1, 3]. The increase in the diagnosis of tumors in early stages, associated with similar life expectations among the different treatments, create a challenge for both patients and treating doctors when choosing the best therapeutic option. One of the fundamental aspects for making this decision is the impact that treatment has on the quality of life [4]

Quality of life is a primary aspect for patients with a recent diagnosis of prostate cancer. When considering various therapeutic options, patients wish to have the treatment with the best possible survival, which in turn allows them to maintain their physical and mental health while avoiding sexual, urinary and intestinal dysfunction [5] This information on the quality of life is of value not only for the patient, but also for the health agencies since the morbidities related to the treatment contribute indirectly to elevated costs and is a way of measuring quality in health services [4, 6].

In the United States, 75% of patients with localized prostate cancer are treated with radiotherapy or radical prostatectomy [3]. The role of radiotherapy for the management of prostate cancer has changed in recent decades with the development of high and low-rate brachytherapy, modulated intensity radiotherapy and image-guided radiation therapy. One of the major concerns that creates a barrier to the usage of radiotherapy among patients and doctors is the potential development of an important genitourinary and gastrointestinal toxicity that can be presented early and late in the course of treatment [4].

Sexual and intestinal dysfunction as well as urinary incontinence after cancer treatment has shown a negative impact on the quality of life in the short and medium term. In the American study on prostate cancer outcomes, in general terms, surgery showed the greatest impact on sexual and urinary function while radiation had the greatest impact on bowel function. Likewise, multimodal treatment, especially with hormonal blockade, showed a greater risk of adverse effects. This study reported the presence of sexual dysfunction in 87% of patients managed with radical prostatectomy vs 94% of those undergoing radiotherapy; urinary incontinence in 18% vs 9%; and fecal urgency in 22% vs 36% [4]. A frequent error in the interpretation of these values is that a point of comparison is not taken into account (7) [7]. Having a normal comparison group makes it possible to give greater validity to the interpretation of the results concerning quality of life, since only in this way it can be identified if the symptoms are really attributable to the treatment [4].

Although it is true that management with radiotherapy impacts the quality of life, these changes can be oversized, as patients without prostate cancer can present disturbances in the quality of life owing to natural changes related to aging.

Seeking to help in the selection of the ideal therapeutic management for patients with localized prostate cancer, this study is designed using validated questionnaires that allow an objective evaluation of the impact of modern radiotherapy on the quality of life. Likewise, in order to identify if these changes are secondary to treatment per se, the baseline state of each patient is identified prior to the initiation of radiotherapy.

The objective of this study is to assess the impact on general quality of life and on the sexual, intestinal and urinary field in patients with localized prostate cancer who received modern radiotherapy in our population.

2. Methodology

A descriptive observational study was designed for which the validated EPIC-26 and SF-36 surveys were applied in order to evaluate quality of life in men with clinically localized prostate cancer with any Gleason, prior and after management with radiotherapy, with a focus on urinary symptoms, bowel habits and sexual function. Patients with localized prostate cancer diagnosed in the last six months and who were managed with modern radiotherapy in the following year were taken.

The first surveys were applied personally to the patients during the Oncology Urology consultation before being taken to their first radiotherapy session. Surveys were repeated to the same population at least 6 months after the end of the radiotherapy management by telephone, explaining them widely to answer the questions according to their current condition.

The EPIC is a self-administered questionnaire to measure the impact of radical prostatectomy, prostate brachytherapy, external radiotherapy and hormonal therapy on the quality of life of patients with clinically localized prostate cancer. It consists of 26 items that cover 4 specific domains: urinary, intestinal, sexual and hormonal. For each domain, scores of 2 subscales (function and nuisance) and a summary score are obtained. In addition, the urinary domain has 2 additional subscales: incontinence and irritative / obstructive symptomatology.

To calculate the scores, it is first necessary to reverse the values of the response options of 20 of the items to homogenize the meaning (so that a higher value indicates better health). Secondly, a recalibration is applied to the items corresponding to each subscale based on a linear transformation so that, finally, when calculating the average, scores are obtained with a range of 0 to 100 (from worse to better quality of life).

The SF-36 is a generic questionnaire that consists of 36 items belonging to 8 health dimensions: Physical Function, Physical Role, Pain, General Health, Vitality, Social Function, Emotional Role and Mental Health. Values greater than or less than 50 mean, respectively, better or worse health status than the general population [7]. A database of the included patients was created, to record in each case the scores of the questionnaires and the answers to each of the questions. Quality of life measures were compared, and differences were evaluated using averages for each domain (intestinal, sexual, hormonal and urinary for EPIC-26).

3. Results

Surveys were applied to 70 individuals; the average age was 66 (51-79) years. The average follow-up was 22 (10-35) months. The average time in which patient surveys were applied before being taken to their first radiotherapy session was 4 months. The average time in which surveys were applied to patients after the end of radiotherapy was 10 months.

The average PSA was 10.28 (3.1-29.0) ng/ml. The most frequent stage was T1c being in 55.7% of patients, followed by T2a in 25.71% of patients and 7.14% for T2b / T2c. When the survey was applied 52.2% of the patients had not received pharmacological or surgical hormonal blockade, 75.7% of the patients received intensity-modulated radiation therapy (IMRT), while the remaining 24.2% received the volumetric modulated arc therapy (VMAT) technique; On average the total dose received was 75.8 Gy. (Table 1)

Table 1. *General characteristics of the patients n=70.*

Age	66±5.41
Follow-up in months: average (range)	22 (6-35)
Survey application time before radiotherapy in months: average (range)	4 (2-7)
Survey application time after radiotherapy in months: average (range)	10 (7-20)
TNM %(n)	
T1bN0M0	4.28 (3)
T1cN0M0	55.7 (39)
T2aN0M0	25.71 (18)
T2bN0M0	7.14 (5)
T2cN0M0	7.14 (5)
Pharmacological or surgical hormonal blockade %(n)	
Yes	47.8 (32)
No	52.2 (35)
Radiotherapy technique %(n)	
Intensity-modulated radiation therapy (IMRT)	75.7 (53)
Volumetric modulated arc therapy (VMAT)	24.2 (17)

Table 1 General characteristics of the patients. The general characteristics of the patients included in the study are described, showing the average age, the percentage for each TNM classification, for the pharmacological or surgical hormonal blockade and the radiotherapy technique applied.

Taking the 2015 Skolarus study as a reference, (Table 2), relevant changes were found only in the quality of life concerning urinary incontinence, with a previous average score of 81.75 (100 - 12.5) versus subsequent 72.7 (100-0).

Table 2. *Values of minimally significant differences by domain of the EPIC - 26 survey.*

EPIC-26 domain	Minimally significant differences
Urinary incontinence	6-9
Urinary symptoms	5-7
Intestinal function	4-6
Sexual function	10-12
Hormonal symptoms	4-6

Table 2 Recommended values of minimally significant differences by domain of EPIC-26 (urinary, intestinal, sexual and hormonal) extracted from the article by Skolarus et al. ([9])

Regarding the other domains, it was not possible to demonstrate an impact on the quality of life or for the rest of the urinary, intestinal, hormonal or sexual symptoms. With average scores prior to radiotherapy of 72.35 (100 - 0), 85.92 (100 - 0), 85.19 (100 - 20), 48 (100 - 0) vs posterior of 71 (100 - 0), 85.11 (100 - 0), 84.60 (100 - 20), 43.16 (100 - 0) respectively. (Figure 1)

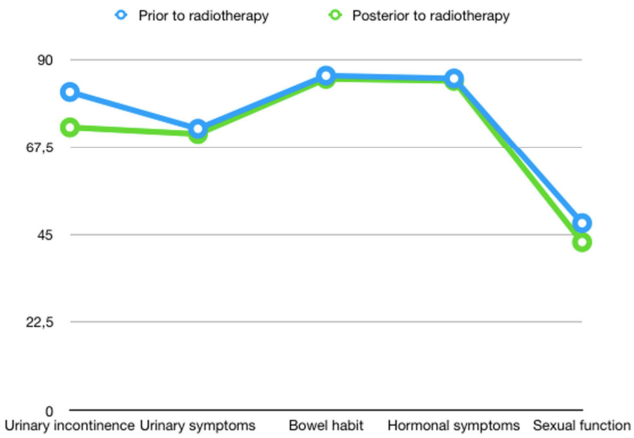

Figure 1. *Comparison of quality of life by domain according to EPIC-26.*

Figure 1. The comparison of the average score for each domain of the EPIC-26 survey (urinary incontinence, urinary symptoms, bowel function, sexual function and hormonal symptoms) is observed before and after radiotherapy management in patients with localized prostate cancer.

In the SF-36 Health Questionnaire it was found that there is no significant difference in the quality of life before and after the management with radiotherapy, with an average score of 77 before (99 - 31) and after of 76.63 (100 - 39.58).

4. Discussion

The concept of quality of life is subjective, however, in oncology cohorts, specific tools have been developed and validated. These questionnaires evaluate common issues that afflict men after the diagnosis and treatment of prostate cancer and generate scores that reflect their impact on quality of life [8].

In recent years, quality of life has been established as an important aspect when determining the best treatment for localized prostate cancer, which is why recent studies such as COMPACTERS identified quality of life as a result that should be measured in all clinical trials [9]. The most used scales for this measurement are EPIC, UCLA-PCI and EORTC QLQ-C30 [8].

In a systematic review based on the latest available evidence they describe that the choice of primary treatment for localized prostate cancer has different impacts on the specific quality of life for cancer in a period of up to 6 years after treatment. The men who received management with active surveillance presented a good quality of life in general, with comparable or better results than those of the patients who received radical management. Patients who received surgical management had a more pronounced negative impact on urinary and sexual function when compared to active surveillance and radiotherapy; while radiotherapy had a more pronounced negative impact on bowel function when compared to active surveillance and radical prostatectomy. Additionally, in patients with low-risk disease it was reported that radiotherapy in its brachytherapy modality has a negative impact on urinary function at one year of follow-up, however

it does not show significant differences in cancer-specific quality of life at 5 years after treatment [8].

When reviewing the literature, we found several changes in the evaluation of the impact on quality of life, being in general terms, the most frequent assessed: alterations in sexual function and incontinence in those patients taken to radical prostatectomy, and gastrointestinal and urinary in those managed with radiotherapy after a follow-up at 5-15 years (ProtecT, Prostate Cancer Outcomes Study) [10, 11].

This variation could be explained by the usage of different measurement tools. Studies that report changes in urinary function after radical prostatectomy use the UCLA-PCI tool, which focuses primarily on urinary incontinence, while studies that report irritative / obstructive symptoms use the EPIC tool, which addresses these symptoms and provides a more complete evaluation of the quality of urinary life [8, 12].

However, as previously mentioned, one of the main factors in the interpretation of the impact of the different treatment modalities on the quality of life is that there is no follow-up in time or control groups that allow establishing the symptomatology baseline of these patients and this is what we seek to determine with the present study. Our results demonstrate a low rate of disturbances in the quality of life, in first place, due to the advances in the radiotherapy modalities that allow the isolation of adjacent organs and thus reduce the risk of adverse effects [8], and secondly because it establishes, as stated in our hypothesis, that the vast majority of patients, prior to the start of radiotherapy already have a significant alterations in sexual, gastrointestinal and urinary functionality.

Since only a small proportion of patients with early-stage prostate cancer progress to metastatic disease and die of cancer within 10 to 15 years [13], it is essential to understand the long-term impact of treatment on specific quality of life of the illness. A systematic review revealed an important knowledge gap based on evidence, since they could only identify a non-randomized comparative study that reported quality of life results at a follow-up of more than 10 years [11]. Data from the Prostate Cancer Outcomes Study [12] showed that there were no significant differences in the adjusted probabilities of urinary incontinence, bowel dysfunction or erectile dysfunction between radical prostatectomy and external radiotherapy at 15 years of patient follow-up [11]. This study provided two other important observations: first, at the end of the follow-up, the prevalence of erectile dysfunction was very high (80%) in both treatment groups and, secondly, the patients had a significant decrease in sexual and urinary function during follow-up [8].

In a study conducted in a Colombian center of high complexity, the data of patients taken to radical prostatectomy for 10 years were reviewed, the UCLA-PCI questionnaire was applied, finding that in the domain of urinary function 57% of patients reported having total control of the urine, 53% never had an involuntary leakage of urine, 82% did not require the use of protectors and 62% had urine dripping less than 1 time per week. In the domain of sexual function, 69.3% rated their ability to have an erection as poor or very poor, 25% regular and 7% good or very good. For 20% the erection was enough to achieve intercourse. And for 52% it implied a problem in his life. The impact on the quality of life showed that 91.8% of the patients considered that their health is generally very good or excellent and 70% did not have any type of physical limitation [14]. However, these results are not comparable with the results of the present study since different surveys were used to obtain data.

In the study published by Litwin et al in 1995 they reported that there were no differences between the treatment groups when comparing the overall quality of life. However, significant differences were observed between the treatment groups specifically in the sexual, urinary and intestinal domains. Similar findings were found when cancer patients were compared to men of similar age without prostate cancer. It was found that men without prostate cancer, although they did not have full potency or continence, had better results than prostate cancer patients treated with surgery or radiation [15].

Our results yielded similar findings to those reported by Litwin in 1999, with baseline alterations prior to radiotherapy mainly in the sexual field, and to a lesser extent in gastrointestinal and urinary symptoms [16].

Perhaps the main contribution of our study is to achieve the follow-up of patients over time, which allowed us to have an objective point of comparison when interpreting the results. Additionally, the use of validated questionnaires facilitates the comparison of our results with others published in the literature.

One issue in the interpretation of our results was to find the clinical relevant cut-off point, which is why we rely on the study of Skolarus, which used a cohort of more than 1000 patients to establish clinical relevant cut-off points extrapolated to the rest of the population [16].

It is important to keep in mind that this study is only based on patients who received radiotherapy as a first line of management with curative intent; in those with adjuvant and salvage radiotherapy we would expect to find a greater impact on the quality of life.

Although our results do not show much difference in urinary, sexual and gastrointestinal symptoms in patients treated with radiotherapy, it is important to remember that the decision of one treatment over another should be taken based on many other variables and this is only one more tool for decision making.

It is necessary to carry out more studies that include larger populations, with larger periods of follow-up, and inclusion of patients' comorbidities, which can also alter the interpretation of the results.

5. Conclusion

Radiotherapy is one of the options used for localized prostate cancer, being one of the most used therapies in the USA. One of the major concerns related to its usage are the urinary and gastrointestinal toxicity and its impact on the

quality of life of these patients.

Based on the findings of our study and according to previously reported articles, there is a tendency to oversize the impact of radiotherapy on the quality of life when there is a curative intent in patients with localized prostate cancer related to gastrointestinal, urinary an erectile symptoms. Our study only demonstrated a clinically relevant difference in urinary incontinence, which allows us to suggest that most of the alterations in the quality of life could be secondary to natural changes in aging.

Declarations

Ethics Approval and Consent to Participate

This study was conducted with the subjects' understanding and consent. Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no competing interests.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

IV, JC: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

AA, VR: Data analysis, Manuscript writing/editing

RS, JG: Protocol/project development, Data collection or management.

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