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ORIGINAL ARTICLE

Combined external radiotherapy and hormone therapy in patients with locally advanced prostate cancer: Predictive factors of genitourinary toxicity

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Abstract

Introduction: Radiotherapy and androgen deprivation are an established treatment option for locally advanced prostate cancer. We evaluate outcomes in efficacy and toxicity for patients treated with this combined therapy at our institution.

Methods: A retrospective study of 80 patients with locally advanced prostate cancer treated with radiotherapy combined with neo-adjuvant (2 months) and adjuvant (24 months) androgen deprivation. We studied the clinical variables and side effects. We evaluated treatment outcomes using PSA nadir and biochemical failure, and recorded acute and chronic gastrointestinal and urinary toxicity. We assessed the correlation between clinical variables and urinary toxicity by means of univariate and multivariate analyses (multiple logistic regression).

Results: The mean patient age was 68 ± 5.81 years; the initial PSA was 20.05 ± 16.27 ng/ml and the mean prostate volume 43.7 ± 27.57 cc. The clinical stage was T3a in 33% and T3b in 66%. The Gleason score was <7 in 39%, 7 in 46% and ≥8 in 15%. The mean follow-up was 44.4 months and biochemical failure was observed in 3 cases. Acute urinary toxicity was recorded in 90% of the patients (chronic in 35%) and acute gastrointestinal toxicity in 75% (late in 32%). In a univariate analysis, prostate volume and urinary symptoms were statistically correlated to acute and late urinary toxicity. Both prostate volume and urinary symptoms were independently associated with an increase in urinary toxicity in the logistic regression analysis.

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Conclusions: Hormone-radiotherapy is a valid option to treat locally advanced prostate cancer with optimal short-term outcomes, although it is not devoid of side effects. Prostate volume and urinary symptoms before treatment can predict genitourinary toxicity.

PALABRAS CLAVE
Cáncer de próstata localmente avanzado;
Radioterapia;
Hormonoterapia;
Efectos adversos;
Eficacia;
Recurrencia

Tratamiento combinado con radioterapia externa y hormonoterapia en los pacientes con cáncer de próstata localmente avanzado: factores predictivos de toxicidad genitourinaria

Resumen

Introducción: Una opción de tratamiento del cáncer de próstata localmente avanzado es la radioterapia combinada con la ablación androgénica. Revisamos los resultados de eficacia y toxicidad del tratamiento combinado en un grupo de pacientes tratados con esta terapia combinada en nuestra institución.

Material y método: Estudio retrospectivo de 80 pacientes con cáncer prostático localmente avanzado tratados con radioterapia externa y hormonoterapia neoadyuvante (dos meses) y adyuvante (24 meses). Se realiza un estudio descriptivo de las variables clínico-patológicas y de los efectos secundarios. Evaluamos la respuesta al tratamiento mediante el PSA nadir y recidiva bioquímica. Analizamos la toxicidad aguda y crónica genitourinaria, intentando establecer qué factores influyen en su aparición mediante análisis uni y multivariante (regresión logística múltiple).

Resultados: La media de edad fue 68 ± 5,81 años, el PSA inicial 20,05 ± 16,27 ng/ml y el volumen prostático medio 43,7 ± 27,57 cc. El 33% fueron estadio T3a y el 66% T3b. El Gleason fue < 7 en el 39%, 7 en el 46% y ≥ 8 en el 15%. Tras un seguimiento medio de 44,4 meses se detectó recidiva bioquímica en tres casos. La toxicidad aguda postirradiación genitourinaria apareció en el 90% (35% tardía) y gastrointestinal en el 75% (32% tardía). El análisis univariante muestra relación entre el volumen prostático y los síntomas urinarios previos con la toxicidad genitourinaria aguda y crónica. Estos se confirman como factores predictivos independientes de toxicidad genitourinaria en el análisis de regresión logística.

Conclusiones: La hormono-radioterapia es una opción válida para el tratamiento del cáncer localmente avanzado con resultados óptimos a corto plazo, aunque no está exenta de efectos secundarios. La sintomatología urinaria previa y el volumen prostático pueden predecir la toxicidad genitourinaria.

Introduction

Prostate cancer is a major health problem.[1] It is a disease that presents itself more frequently in adulthood. In fact, approximately 70% of prostate cancers are diagnosed after the age of 65 years.[2] The incidence of prostate cancer in Spain has changed substantially in recent years, partly due to the increased life expectancy of patients and technical improvements in early diagnosis. Prostate cancer is now diagnosed in younger men and at less advanced stages.[3]

However, 27% of patients are initially diagnosed with locally advanced prostate cancer.[4] The therapeutic options at this stage include radical prostatectomy, external beam radiation therapy, hormone therapy and combination therapies. The choice of each will depend on the patient's life expectancy, his preferences, as well as the experience of the working group that must decide on the choice of treatment.

Several approaches have been implemented to improve the effectiveness of external radiotherapy. One method of radiotherapy used for prostate cancer is three-dimensional conformational radiotherapy. A minimum dosage of 76 to 81 Gy is recommended in locally advanced prostate cancers, with the usual standard dosage being 78 Gy. It is administered in split doses and gradually. Increasing the dosage improves the response and control of the disease. In fact, it has been shown that radiation dosage is an independent factor that influences biochemical progression-free survival.[5]

The use of radiation therapy is not without side effects. These patients may present genitourinary and gastrointestinal toxicity. The severity of both is usually assessed by standardized scales (RTOG / EORTC).[6] Toxicity is also classified depending on the time of evolution into acute or chronic. The most common genitourinary side effects are of an irritant nature, and in some more severe cases, hematuria may appear. The most common digestive symptoms are diarrhea and rectal bleeding.

The objectives of this study are, first, to determine the efficacy of combined treatment with radiotherapy

and hormone therapy for patients with locally advanced prostate cancer and, in addition, to evaluate both acute and chronic genitourinary and gastrointestinal toxicity. Finally, we attempt to identify factors that may predict the occurrence of genitourinary toxicity after treatment with radiotherapy.

Materials and methods

This is a retrospective study including 80 patients treated at the Hospital Clinico Universitario de Valencia in the period between 2000 and 2009. For data collection, we conducted a systematic review of medical records. We included those patients diagnosed with locally advanced prostate cancer, with stage T3a/ T3b or T4, N0 and M0 according the TNM classification of 2002, with histological confirmation.

We diagnosed locally advanced prostate cancer using DRE, PSA, transrectal ultrasound and ultrasound guided prostate biopsy with a protocolized scheme of 10 biopsies. In those cases where prior PSA was greater than 10 ng/ ml, we performed seminal vesicle biopsy. We also requested CT scan and / or pelvic MRI for local-regional staging.

Hormonal therapy was initiated at the time of diagnosis, and after two months of neoadjuvant hormonal therapy, patients began treatment with 3D-conformational radiotherapy techniques. All were given a total dosage of 76 Gy in 38 split doses. Hormonal therapy was extended to two years after completing radiotherapy. At this time the patient was followed up closely, controlling all side effects and treating them when necessary.

We carried out a descriptive study of variables such as age, pretreatment urinary symptoms (urinary frequency> 1, urgency and / or normal voiding difficulty), clinical stage, serum PSA, PSA density (PSAd), prostate volume, Gleason, PSA nadir, time from treatment to achieve the PSAn number of biochemical recurrence in accordance with *Phoenix* criteria (increasing PSA above 2 ng/ ml over PSA nadir),[7] follow-up period, mean PSA at 6 months and last PSA control.

We obtained the probability of progression curve using the Kaplan-Meier method to determine the probability of biochemical recurrence. As for toxicity data, we estimated the frequencies for acute and chronic gastrointestinal and genitourinary toxicity in accordance with the *Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer system* (RTOG-EORTC) scales.[6] It is considered acute when symptoms appear during treatment and 4 weeks after it is concluded, and chronic as of four weeks of treatment.

To analyze the possible relationship between the variables age, pretreatment urinary symptoms, prostate volume, PSA density (PSAd) and initial PSA, with the probability of both acute and chronic genitourinary toxicity, we performed the X^2 test. To find out if any of these variables can predict the occurrence of acute and chronic urinary toxicity, we carried out a multivariate logistic regression study. We stratified these variables such that we differentiated them depending on whether or not they were younger or older than 70 years, had a PSA level above or below 10 ng/ ml, a prostate volume greater or less than 20 cc, PSAd greater or less than 0.12, and the presence or absence of previous urinary tract symptoms (LUTS). We set the level of statistical significance at 0.05.

Table 1 Clinical characteristics of the patients

Variable	Mean (DE)
Age (years)	68 (5.81)
Prostate volume (cc)	43.66 (27.57)
Initial PSA (ng/ ml)	20.05 (16.27)
PSA 6 months (ng/ ml)	0.29 (0.86)
PSA nadir (ng/ ml)	0.14 (0.38)
PSA nadir period (months)	6.4 (6.68)

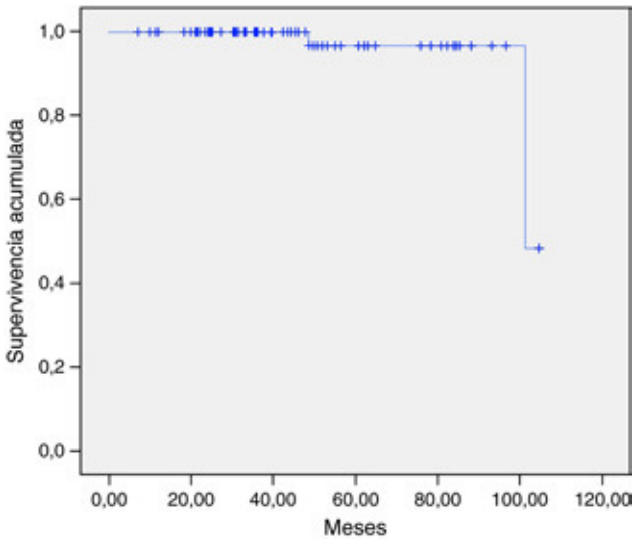

Figure 1 Biochemical recurrence-free survival. Kaplan-Meier Curve.

Results

The clinical characteristics of patients are listed in table 1. As regards staging, 33% were T3a, 66% were T3b and only one patient was stage T4. In the group of patients with stage T3b, we performed diagnosis by means of seminal biopsy and imaging. In 70%of the cases the result of the biopsy and the suspected involvement of seminal imaging techniques coincided. In 8% seminal biopsy was

Table 2 Frequency of acute genitourinary toxicity (GUT) and acute gastrointestinal toxicity (GIT)

	Acute GUT N (%)	Acute GIT N (%)
No changes	7 (8.8)	18 (22.5)
Grade 1	31 (38.8)	30 (37.5)
Grade 2	35 (43.8)	22 (27.5)
Grade 3	6 (7.5)	8 (10)
Grade 4	0 (0)	0 (0)

Table 3 Frequency of chronic genitourinary toxicity (GUT) and chronic gastrointestinal toxicity (GIT)

	Chronic GUT N (%)	Chronic GIT N (%)
No changes	33 (41.3)	35 (43.8)
Grade 1	22 (27.5)	15 (18.8)
Grade 2	5 (6.3)	10 (12.5)
Grade 3	1 (1.3)	1 (1.3)
Grade 4	0 (0)	0 (0)

positive, while staging was less in accordance with imaging techniques, and finally, in the remaining 22%, we performed diagnosis by means of imaging techniques. Mean PSA nadir was 0.14 (± 0.38) ng/ml was obtained in all cases during follow-up after starting treatment with radiotherapy as well as androgen deprivation. Gleason score was <7 in 39%, 7 in 46% and ≥ 8 in 15%.

As medical history related to gastrointestinal disorders, 4%had an episode of diverticulitis prior to treatment, and 21% hemorrhoids. Regarding previous urological diseases, three patients (3.75%) were operated on for benign prostatic hyperplasia by means of transurethral resection. Mean follow up was 44.36 (7.26 to 104.79) months. During follow-up, biochemical recurrence only occurred in 3 cases (3.75%) (fig. 1).

As regards data on acute toxicity (table 2), predominant genitourinary toxicity was mild (grade 1 and 2) and included the appearance of urinary frequency, urgency, pain or bladder spasms, which were solved with analgesia without requiring other specific treatments in the milder cases. In cases in which the symptoms were more pronounced, it was necessary to administer alpha-blockers or anticholinergics, depending on the prevalence of obstructive or irritant symptoms. Grade 3 toxicity in patients with hematuria was treated conservatively. Bowel disorder was the most common symptom in acute gastrointestinal toxicity (37.5%), which we resolved with conservative measures, such as treatment with fiber and enemas in cases of constipation and with loperamide in cases of diarrhea. A small percentage of patients (8%) presented rectal bleeding, which subsided without any treatment.

With regard to chronic toxicity (table 3), a significant percentage of patients reported no genitourinary symptoms (41%) and 30%had grade 1 toxicity (mostly irritant symptoms not requiring treatment). The same occurred with chronic gastrointestinal toxicity, in which 43.5% of patients were asymptomatic. The most common symptom in the remaining patients was diarrhea, treated with dietary regimen and loperamide. Following RTOG scales, none of the patients in the study had grade 4 gastrointestinal or genitourinary symptoms associated with massive hematuria and rectal bleeding that require transfusion and in some cases surgery.

Table 4 Association between clinical variables and acute genitourinary toxicity

	No changes N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	p* value
Urological symptoms					
Yes	7 (8.7)	26 (32.5)	28 (35)	5 (6.2)	0.016
No	1 (1.2)	5 (6.2)	8 (10)	1 (1.2)	
Prostate volume					
< 20 cc	5 (6.2)	8 (10)	7 (8,7)	0	0.034
> 20 cc	3 (3.7)	23 (28.7)	29 (36.2)	6 (7.5)	

*X^2 Test.

Table 5 Association between clinical variables and chronic genitourinary toxicity

	No changes N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	p* value
Age					
< 70 to	25 (31.2)	13 (16.2)	2 (2.5	0	0.021
> 70 to	8 (10)	10 (12.5)	3 (3.7)	1 (1.2)	
Urological symptoms					
Yes	14 (17.5)	2 (2.5)	1 (1.2)	0	0.019
No	19 (23.7)	21 (26.2)	4 (5)	1 (1.2)	
Prostate volume					
< 20 cc	15 (18.7)	0	0	0	0.001
> 20 cc	18 (22.5)	23 (28.7)	5 (6.2)	1 (1.2)	

* X^2 Test.

The univariate analysis shows a statistically significant relationship with the occurrence of acute genitourinary toxicity and prostate volume above 20 cc (p=0.034), and the presence of urinary symptoms prior to radiotherapy (p=0.016). The appearance of chronic genitourinary toxicity is associated with age above 70 years (p=0.021), with a prostate volume greater than 20 cc (p=0.019) and urological symptoms (p=0.001) (table 4 y 5 .) In the logistic regression analysis, prostate volume exceeding 20 cc (OR=10.93 with p=0.023) and previous urinary tract symptoms (OR: 2.93 and p=0.019) appear as independent predictive variables of acute genitourinary toxicity. For chronic genitourinary toxicity volume exceeding 20 cc (OR: 12.93 and p=0.00) and age over 70 years (OR=10.41 with p=0.047) were independent predictive factors.

Discussion

The use of radiotherapy associated with neoadjuvant and adjuvant hormonal therapy has been the subject of numerous studies. The first experience to show the benefit of combination therapy in a prospective randomized trial was that of Bolla et al.[8] Their results found a higher overall survival rate at 5 years in the combination therapy group compared to that of radiotherapy alone (79% vs. 62%). Moreover, the proportion of patients free of disease at 5 years was higher in the combination therapy group (85%vs. 48%, p=0.001).

After this study, others confirmed the results,[9-14] giving evidence of the usefulness of combination therapy. Widmark et al.[14] compared a group treated with hormone therapy alone versus hormone therapy plus radiation therapy and concluded that there is a decrease in cancer-specific mortality at 10 years in the combination therapy group versus hormone therapy alone (11.9%versus 23.9%).

On account of these results, efforts have been aimed at identifying the hormonal treatment regimen that confers better control of the disease. In a subsequent study, Bolla et al. compared overall survival in the combination therapy with radiotherapy and hormone therapy with a similar 6-month regimen compared to another at 3 years.[15] The results at 5 years favor prolonged treatment (cancer-specific mortality 4.7%in the short regimen versus 3.2%in the prolonged regimen, P=0.002). Other studies have found similar results,[16-18] thus advocating long-term hormonal therapy after radiotherapy. A recent study by Horwitz et al.[19] provides more specific information about the groups that benefit from long-term hormonal treatment. According to this study, after a 10-year follow up, the increase in survival for combination therapy is only significant in the group of patients with Gleason score 8-10, suggesting that it should be a treatment regimen for high-risk patients. Notwithstanding, the duration of hormone therapy is still being studied, therefore today, despite being accepted, there is no standardized regimen for prolonged therapy.

In the case of our study, patients received a two-month neoadjuvant hormone therapy regimen and an extended two-year regimen after radiotherapy. Combination therapy has achieved good results in terms of biochemical progression-free time, which data is consistent with that found in literature. However, the fact that we have such a low rate of biochemical recurrence may be due to the short follow-up period in the case of prostate cancer. We hope that after 10 years of follow-up the rates are higher, which is why it is necessary to carry out a longer-term analysis.

To assess the effectiveness of treatment in our study, we analyzed PSA nadir and PSA evolution. Several studies have suggested a statistically significant association between a given value of PSA nadir after radical radiotherapy and biochemical failure-free survival. Many of these studies agree on the results and indicate that a PSA nadir ≤ 1 ng/ml would be a valid cutoff value, which would behave as an independent predictor of biochemical failure-free survival, along with other recognized prognostic factors, such as pre-treatment PSA, stage and Gleason score.[20]

As regards the technique used in radiotherapy, 3D-CRT techniques allow administering a higher dosage of radiation with better preservation of healthy tissue than conventional radiation therapy. All the patients in the study were irradiated with this technique using a dose schedule, with a total dosage of 76 Gy divided into 38 split doses. The beneficial effects of the dose schedule were shown in a randomized trial, which compared the use of 64-70 compared to 78 Gy, noting a significant increase in disease-free survival, which especially benefited those with a pretreatment PSA above 10 ng/ml.[21]

Despite finding a benefit in terms of treatment efficacy in our series, the rate of toxicity is high and similar to those obtained in numerous relevant studies.[22] In 2005, the results of a multicenter study that analyzed acute and chronic gastrointestinal and genitourinary radiation in accordance with radiation dosage were published.[23] After 31 months of follow-up genitourinary toxicity rates for dosages of 78 Gy were 46% grade 0/1, 40% grade 2 and 13% grade 3, with figures slightly higher than ours. As regards acute gastrointestinal toxicity, its rate was 47% grade and 24% grade 3.[23] These values are close to those of our experience, except for the fact that our patients had a higher rate of grade 3 acute gastrointestinal toxicity (10%). As in our series, there was no evidence of serious acute gastrointestinal or genitourinary toxicity. Grade 2 or higher chronic gastrointestinal toxicity was 29.7% and genitourinary toxicity was 28.5%, the most common symptom being nocturia.[23] In our case, the figures are also very close to 30%for mild chronic toxicity (table 3). These results lead to the conclusion that, although we are using techniques that aim at minimizing toxicity, the side effects of treatment remain high.

In view of these rates of morbidity, the possibility of obtaining factors capable of predicting toxicity is raised, to try to prevent it as far as possible. In our study we consider age, prostate volume, initial PSA, stage and pretreatment urinary symptoms as possible variables that may potentially modify genitourinary toxicity.

In the study by Peeters et al.,[23] the total dosage received and prior urinary symptoms are shown as independent variables associated with genitourinary toxicity. In our case, all patients received the same total dosage and therefore it cannot be associated as a causal factor. In other more recent studies,[24] clinical and dosimetric factors predictive of toxicity are evaluated. In the study by Arcangeli et

al.,[25] the IPSS prior to treatment is evaluated as a clinical factor. It appears in the multivariate analysis as the only factor associated with increased urinary symptoms after radiotherapy. Our results also show an association between lower urinary tract symptoms prior to treatment and subsequent toxicity. Moreover, prostate volume above 20 cc is added to this for acute toxicity and age over 70 years for chronic toxicity. This data suggests that toxicity can be minimized by individualizing treatment in accordance with the characteristics of each patient. A more detailed prospective study that differentiates genitourinary toxicity risk groups would be interesting.

In summary, despite the limitations of a small series and retrospective analysis, our study shows that treatment of locally advanced prostate cancer with external radiotherapy and hormone therapy is effective in the short term, with good local control and biochemical progression rates. The use of high doses of radiation is associated with a high rate of side effects. Both prostate volume and the presence urinary symptoms prior to treatment are associated with acute and chronic genitourinary toxicity.

Conflict of interest

The authors declare that they have no conflict of interest.

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