OUTCOMES FROM THE USE OF MAXIMAL ANDROGEN BLOCKADE IN PROSTATE CANCER AT HEALTH AREA WITH REFERENCE HOSPITAL TYPE 2 (1ST PART). QUALITY OF LIFE: APPLICATION OF EORTC QLQ-C30 INSTRUMENT.

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Summary.- OBJECTIVES: To analize the influence that maximal androgen blockade (MAB) exerts on quality of life in patients from the health area of Zamora diagnosed of prostate adenocarcinoma between 2000-2005.

METHODS: Basal, 12-month, 24-month and 36-month application of the health-related quality of life measurement instrument EORTC QLQ-PR25 to the population sample (n= 111), as well as a control sample (n= 100). We performed a comparative study of the outcomes between groups; between various time measurements in MAB patients; and inter-categories/ intervals of some variables in patients with hormonal deprivation therapy (third year of follow-up).

RESULTS: Cognitive and symptomatic fields were affected in patients with MAB at some specific time points. No field showed a significant constant worsening through the period of study for hormonally deprivated patients. A recovery is seen in the sociofamiliar field.

Less academic level in MAB patients represents a distinguishing factor leading to worse outcomes in the health-related quality of life parameters analyzed here.

CONCLUSIONS: There is a negative initial repercussion of MAB on quality of life, although tinged according to the different fields studied.

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Resumen.- OBJETIVOS: Analizar la influencia que ejerce sobre la calidad de vida el bloqueo androgénico completo (BAC) en los pacientes diagnosticados entre los años 2000-2005 de adenocarcinoma de próstata en el área de salud de Zamora y sometidos a dicha terapia.

MÉTODOS: Aplicación basal, al mes 12, mes 24 y mes 36, del instrumento de medición de calidad de vida relacionada con la salud EORTC QLQ-C30 a la muestra poblacional (n= 111) citada, así como a una muestra de sujetos control (n= 100). Estudio comparativo de los resultados entre ambos grupos; entre las diferentes determinaciones temporales para los pacientes con BAC; e inter-categorías/ -intervalos de determina-

das variables en pacientes con terapia de deprivación hormonal (tercer año de seguimiento).

RESULTADOS: Las esferas cognitiva y sintomática resultaron afectadas de forma temporal puntual en los pacientes con BAC. No se aprecia ninguna esfera que mantenga un deterioro significativamente constante a lo largo del periodo de estudio en los pacientes con deprivación hormonal. Se verifica recuperación en la esfera sociofamiliar. El menor nivel de estudios cursados por los pacientes en tratamiento con BAC, constituye un factor de diferenciación de cara a la obtención de peores resultados en los parámetros de calidad de vida relacionada con la salud aquí analizados.

CONCLUSIONES: Repercusión negativa inicial del BAC sobre determinados aspectos calidad de vida, aunque matizable en función de cada esfera estudiada.

Palabras clave: *Cáncer de próstata. Terapia hormonal. Calidad de Vida.*

INTRODUCTION

Prostate cancer represents one of those pathologies with most incidence at present regarding Urology, being the world´s fourth most frequent neoplasm among men (1). In USA and Western Europe it represents the second oncological cause of mortality, after lung cancer (2). Estimated incidence of prostate cancer in North America for 2007 is 218890 new cases, which represents around 29 % of overall male cancers, being the origin of approximately 9 % of all cancer-related deaths in that sex (3). In Europe, prostate cancer represents around 11 % of all male neoplasms (4), and approximately 9 % of overall male cancer-specific mortality in the European Union (5). In our country, prostate cancer is the third most frequent tumor in males and the third cause of cancer-related death (6). According to data extrapolation from the Community of Madrid for year 2000, the adjusted incidence for the spanish population would be 120.1 cases per 100000 males (7).

All mentioned data show the importance this illness represents in quantitative terms. In several nations the incidence of prostatic neoplasms has raised during the last years. This represents more signification in those populations with progressive ageing evolutive patterns in their age-sex pyramids, and an example is that one which corresponds to the province of Zamora, where our study is located.

Androgen deprivation, as far as it is concerned, is the most generalized option of paliative therapy for prostate adenocarcinoma in common practice, with its four available options (surgical castration by means of subalbugineal orquiectomy, chemical castration using gonadotrophin-releasing hormone - GnRH - analogs, antiandrogen monotherapy, or maximal blockade with analogs and antiandrogen association). The latter option is chosen with significant frequency. We therefore do not try to cure the disease in these cases, but stabilization of its course and delay of presentation of adverse effects, typical of its natural history. In this context, an increase in survival, parallel to an improvement in global quality of life these patients present - both of them points of great controversy and discussion in literature of our specialty - become paramount objetives, and they will therefore adopt priority in the study presented here.

The anual cost of maximal androgen blockade - MAB - is estimated between 8717 and 12209 american dollars (8). From a budgetary point of view, the influence of the amount of therapeutical costs wouldn´t be negligible - at least "a priori" -, specially considering the present tendency to early onset of the androgen supression. In healthcare systems like in our country, which aims to a general optimization of resources and rationalization of pharmaceutical expenses in particular, knowledge about the economic weight evolution with time on sanitary budget of the studied area regarding prescription of those mentioned drugs becomes an interesting aspect, as well as its cost/ utility relationship.

OBJECTIVES

Considering the before-mentioned aspects, the aimed objectives of this study are:

• Description of the subpopulation of patients with diagnosis of prostate adenocarcinoma, treated with MAB (flutamide or ciproterone acetate, plus gonadotrophin release hormone - GnRH - analog), who belong to the province of Zamora health area, between year 2000 and first quarter of 2005.

• Measurement - by means of application of validated psycometric instruments - of the influence on health-related quality of life - HRQoL - from the administration of that therapy to that patients.

• Assessment of the economic weight that prescription of this drug combination represents on the pharmaceutical budget of the mentioned area, with subsequent obtention of outcomes in terms of cost/ utility - through preferential ponderation rates – in the context of this neoplasm.

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Before focusing on this objectives some aspects must be specified:

HEALTH-RELATED QUALITY OF LIFE

Quality of life represents a matter of increasing importante for patients when they must participate in the election of therapy for their prostate cancer (9). Expectations and life style are significant factors at present in the context of starting a therapy which has traditionally focused on maximization of survival in terms of time. HRQoL is a concept that comprises all - positive and negative - aspects of life experience (10), including those symptoms caused by that disease, its influence on the daily functional capacity of the patient, his perception of the illness (11), as well as the own manifested behavioural answer; and its present approach is mostly based on the definition that the World Health Organization gives about the last term: " state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (12). Multidimensionality is an essential requirement for measurement instruments of HRQoL, and it means the integration of the following functional areas: physical - including daily activities and capacity for efforts -, psycological - including cognitive and affective aspects -, social – interaction with family, friends, colleagues and rest of society -, somatic - physiopatological manifestations caused by illness and/ or therapy -, and of health perception - including assessments by the patient about the influence of his health on other life aspects, like the spiritual one - (13).

There is a broad variety of available instruments for HRQoL quantification, and we consider the convenience of underlining the following ones:

EuroQol 5-D (14

Is a measurement instrument of general HRQoL, created from constitution of a multidisciplinary working group with physicians, nurses, sociologists, psycologists, philosophists and economists from Great Britain, Finland, The Netherlands, Sweden and Denmark taking part. It consists of:

• A descriptive system about the health state of the patient, comprising five dimensions - motility, self care, daily activities, pain/ discomfort, and anxiety/ depression -, each one with three possible levels of seriousness - 1= "no problems", 2= "some/ mild problems", y 3= "many problems" -, which therefore lets define a total amount of 243 different health states.

• An vertical millimetered analogical scale, 20 cm in length, with labeled end as "worst imaginable health state" and " best imaginable health state", so that the patient must draw a line from the lowest point of the scale - zero - to the point corresponding to his health state at present in his opinion.

• A system of "preferential ponderation" or individual valuation of those different health states which are defined by the before-mentioned descriptive system. It makes an adjustment of the states defined by values "11111" y "00000", as 1 y 0, respectively, so that values corresponding to the rest of health states will adopt positive values if they are considered as better than death, or negative if worse. With this it can be got a list of coefficients, which can be used to calculate a definitive tarification value - T - through the formule $T=0.8498 - [(Vm-1) \times (0.0897)] - [(Vsc-1) \times (0.1012)] - [(Vda-1) \times (0.0551)] - [(Vpd-1) \times (0.0596)] - [(Vad-1) \times (0.0512)] - [(N3) \times (0.2119)]$, where

$Vm=$ obtained value for "motility" dimension according to the descriptive system.
$Vsc=$ obtained value for "self care" dimension according to the descriptive system.
$Vda=$ obtained value for "daily activities" dimension according to the descriptive system.
$Vpd=$ obtained value for "pain/ discomfort" dimension according to the descriptive system.
$Vad=$ obtained value for "anxiety and depression" dimension according to the descriptive system.
$N3= 1$, in case of some value equal to "3" for at least one dimension of the descriptive system. If this is not the case, $N3= 0$.

Core Quality of Life Questionnaire - QLQ-C30 -,

Developed by the European Organization for Research and Treatment of Cancer - EORTC - (15) - Figures 1a & 1b - is the most frequently used, according to the review realized by some authors (16). Its 30 items assess common domains for different varieties of tumor. The questionnaire comprises five functional scales - corresponding to physical, emotional, cognitive, of role playing, and of social relationship fields -, three symptom scales - fatigue, sickness/ vomit and pain -, and six individual items existence or not of dysnea, insomnia, appetite loss, constipation, diarrhea and financial troubles which are caused by the existence of disease. The answers to each item from the mentioned groups are quantified with a whole number which ranges from 1 to 4, the least value corresponding to a better state regarding the studied aspect. The instrument ends with two items: an scale of global health state and other one on quality of life, - both quantified with a whole number which ranges from 1 to 7, corresponding to "very bad" o "excelent" state of the patient, respectively. The items make time reference to the period of last week before the administration of the questionnaire.

Values of calculated Cronbach´s a coeffi-cients for each scale range from 0.52-0.89 - the least value corresponding to the role-playing field. Construct validity has also been confirmed. By means o analysis of covariance statistically significant differences have not been seen regarding answer dispersion in individuals when comparing questionnaire autoadministration with interview made by a doctor, based on that one (15). In spite of not inclusion of specific domains for prostate cancer, its usefulness has been demonstrated when its applied to this population of patients (17).

QLQ-PR25 module by EORTC

Figures 2A & 2B -, has been developed as specific instrument for prostate cancer, to be simultaneously used with EORTC QLQ-C30 questionnaire.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

FIGURE 1A . EORTC QLQ-C30 instrument (version 3.0).

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Its 25 items comprise scales for digestive and urinary symptoms, and sexual sphere, and three items related to presence of gynecomastia, hot flushes and swelling of inferior limbs, respectively. The obtained score for each item ranges from 0 to 4 - the largest figures corresponding to worst outcomes in terms of HRQoL, apart from three of those items included in the sexual sphere, which must be inversely interpreted -. 16 items make time reference to the period of last week before the administration of the questionnaire, while the other nine ones are referred to the last four weeks. The four final items must only be answered if

During the past week:	Not at all	A little	Quite a bit	Very much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching televisión?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties? 4	1	2	3	4

29. How would you rate your overall health during the past week?

	1	2	3	4	5	6	7	
Very poor							Excellent	

30. How would you rate your overall quality of life during the past week?

	1	2	3	4	5	6	7	
Very poor							Excellent	

FIGURE 1B. EORTC QLQ-C30 instrument (version 3.0) (continuation).

there has been sexual activity during the mentioned last four weeks.

It shows confirmed validity and reliability for patients with confined (18) as well as metastatic disease (19).

QUALITY-ADJUSTED LIFE YEARS (QALYs)

To be useful, measurement of outcomes on health improvement in an economic study context must appropriately quantify the impact that health interventions exert on all aspects of patient-valued health. These measurements should be global enough in nature to make different health interventions be comparable, having enough sensibility to show those health changes meaning significant improvements in well-being of patients as well.

Life expectancy is the broadliest used concept as measurement of health outcomes from a general point of view, but it is not suitable for detection of changes in attributes corresponding to HRQoL. QALYs are the outcome of the arithmetric product between years of net added survival and a tarification value linked to the health state - in our case it is obtained from the "preferential ponderation" system corresponding to the EuroQol 5-D instrument - (20). QALYs therefore give less value to morbility-associated years of life. In a similar way, years of life corresponding to the immediate future have more weight than those belonging to far future regarding the final outcome of QALYs calculation - "chronological discount" effect - (21).

The figure corresponding to the so-called "preferential ponderation" or "utility" usually ranges from 0 - in those cases when the heath state is considered as negative as the death itself by the individual - and 1 - in cases of health grade equivalent to the best imagineable one -. It shows (22) the preference or value which is given by the individual or society to each different posible specific levels of health - or improvement in its state -, and it can be obtained (23) with direct calculation by means of:

A). "Standard risks" technique: the patient coses between living a precise number of years with disease or taking risk of opposite options - living the period with no disease or immediate death, with varying relative probability for both of them -.

B). "Time trade off" technique: quantification of that survival time with disease that the patient is determined to sacrifice for living without it or with other better health states.

Another option to obtain preferential ponderation is through the use of rates which are previously available in literature, like that one included in the EuroQol 5-D instrument. Total preferential ponderation for a precise age results from adding the products of those partial estimated ponderations for each health state multiplied by the probability each one has to be present. Some authors (24) have proved that preferential ponderations can be influenced by duration of those states of altered health, as well as the secuenciation of their related events.

Some publications show examples of ponderated estimations in prostate cancer patients (25). Patients liken one life year with asymptomatic or stable metastatic disease to 0.92 disease-free years, whereas the values attributed to an early and late progression of disease were 0.83 and 0.42 respectively.

Use of QALYs in cost-utility analysis has some advantages so that it represents an evaluation framework of that health state improvement which is obtained through precise assistance interventions, and it can be used as a guide when budget priorities must be established, letting comparisons between assistance options that lead to different outcomes (26).

COST-UTILITY ANALYSIS

Expression of pharmacoeconomic outcomes according to the cost-utility relationship seen is part of a multidimensional analysis, so that different domains of HRQoL improvement are simultaneously been evaluated - in this case they are named as attributes -. Costs are in form of monetary units, whereas outcomes are evaluated through preferential ponderation - improvement of HRQoL-adjusted survival -, usually in form of QALYs. Other concepts that are used as well (27), although less frequently, are the disability-adjusted life years - DALYs, as measurement of those lost years of health -; and the "health year equivalent" - HYEs, as measurement of the equivalence a patient gives to a time-prolonged state of altered health in terms of full health -. As well as it happens with cost-benefit analysis, the grade of effectiveness between compared intervention options is not coincident.

The basic value for outcome report is the cost-utility ratio, defined as "cost per gained quality-adjusted life year - cost/ QALY -" or more precisely as the quantitative improvement in qualitatively-adjusted health state which is obtained from one health intervention. The so-called incremental cost-utility ratio, results from the quotient between difference of costs - incremental cost - and difference of "gained quality-adjusted life years" - incremental utility - when two different health interventions are compared.

The highest accepted threshold for cost-utility values varies between countries, and often there is not an officially accepted or recognized limit by health authorities, although they can be indirectly inferred (28).

MATERIAL AND METHODS

TYPE OF STUDY AND POPULATION BASE

Type of study

Observational, prospective, longitudinal and analytic study.

Subpopulation base of study

Those individuals who underwent prostatic biopsy procedures at the Service of Urology belonging to the Assistential Complex of Zamora from year 2000 up to the first quarter of 2005. The final figure was 852 pacients.

All patients whom ultrasound-guided transrectal prostate biopsy sampling was indicated caused for prostatic neoplasm suspiction in our outpatient consulting rooms - based on previously established clinical and/ or analitical criteria - were recruited.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Have you had to urinate frequently during the day?				
	1	2	3	4
2. Have you had to urinate frequently at night?				
3. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
4. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
5. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
6. Have you had any unintentional release (leakage) of urine?				
	1	2	3	4
7. Did you have pain when you urinated?				
	1	2	3	4
8. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
9. Have your daily activities been limited by your urinary problems?	1	2	3	4
10. Have your daily activities been limited by your bowel problems?	1	2	3	4
11. Have you had any unintentional release (leakage) of stools?	1	2	3	4
	1	2	3	4
12. Have you had blood in your stools?				
	1	2	3	4

FIGURE 2A. EORTC QLQ-PR25 instrument.

Patient´s sample and comparative sample

From the subpopulation described above, those patients who fulfilled the following criteria where included:

• Positive pathologic confirmation for prostate adeno-carcinoma presence - focally at least in one of biopsed cylinders -.

• Start with maximal antiandrogen suppressive hormonal therapy, by means of a steroidal - ciproterone acetate - or non-esteroidal antiandrogen - bicalutamide or flu-tamide -, associated to a GnRH analog - bu-

During the past week:	Not at all	A little	Quite a bit	Very much
13. Did you have a bloated feeling in your abdomen?	1	2	3	4
14. Did you have hot flushes?	1	2	3	4
15. Have you had sore or enlarged nipples or breasts?	1	2	3	4
16. Have you had swelling in your legs or ankles?	1	2	3	4
During the last four weeks:	Not at all	A little	Quite a bit	Very much
17. Has weight loss been a problem for you?	1	2	3	4
18. Has weight gain been a problem for you?	1	2	3	4
19. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
20. To what extent were you interested in sex?	1	2	3	4
21. To what extent were you sexually active (with or without intercourse)?	1	2	3	4
Only if you have been sexually active over the last four weeks	Not at all	A little	Quite a bit	Very much
22. To what extent was sex enjoyable for you?	1	2	3	4
23. Did you have difficulty getting or maintaining an erection?	1	2	3	4
24. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
25. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

FIGURE 2B. EORTC QLQ-PR25 instrument (continuation).

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serelin, goserelin, leuprorelin or triptorelin -.

Resulting sample size was n= 111.

Patients with the following features were excluded:

• Indication of other hormone-associated kind of therapy which could be related to that diagnosed prostatic neoplasm process - radical prostatectomy, external beam radiotherapy, braquitherapy, criotherapy and/ or quimiotherapy -.

• Previous or simultaneous history of any other malign neoplasic process, irrespective of its present state.

• Request of follow-up in other hospitalary center after starting the hormonal therapy.

• Lost for clinical follow-up.

As comparative population sample (cause of scarce representation of non-treated patients with cancer) a group of patients was chosen (sample size, n= 100) - by means of probability stratified sampling, from the population of males registered at the computerized data base of outpatient consultation belonging to the Service of Admission from the Assistential Complex of Zamora -, fulfilling the following characteristics:

• Male sex.

• Similar distribution of age, academic level, and home location compared to those of the studied population sample whom prostate adenocarcinoma has been diagnosed.

• No previous or present record of urological disease.

• No record of malign neoplasic disease, irrespective of present stage.

• No mental retardation nor psychiatric record.

• Having been seen in an outpatient setting of any medical Specialty - with the exception of Urology -, without need of more follow-up regarding the studied process, before his inclusion as sampling subject, and with no evidence - by means of clinical record review - of residual comorbidities from treated processes.

VARIABLES TO BE STUDIED

General variables

Basal age. It was considered as the age of the patient at the moment of start with MAB therapy. Two groups of categories:

* A: <= 75 years old.
* B: > 75 years old.

Digital rectal examination - DRE -. The following categories were considered:

* A: mobile prostate, with smooth surface, fibro-elastic consistency.
* B: regular non-fixed prostate, with at least one area of more consistency.
* C: non-mobile prostate, with hard consistency, irregular and/ or asymmetrical surface.

PSA value at start of MAB. Groups of categories:

* A: < 20 ng/ mL.
* B: >= 20 ng/ mL.

Ultrasonography staging. The following categories were considered:

* A: no evidence of areas with abnormal ecogenicity.
* B: area with abnormal ecogenicity in peripheral zone, with no involvement of capsule or seminal vesicles (compatible with localized stage).
* C: area with abnormal ecogenicity in peripheral zone, with involvement of capsule and/ or seminal vesicles (compatible with locally advanced stage).

Positiveness of prostatic biopsy. Biopsy samples included three cylinders from each lobe. Considered categories:

* A: unilateral positiveness.
* B: bilateral positiveness.

Gleason score. Expressed as the sum of those values - 1 to 5, from largest to least histological differentiation - corresponding to both most frequent growth patterns - primary and secondary -, which are identified at the whole biopsic samples. Categories:

* A: well differentiated (from 2 to 4).
* B: moderately differentiated (from 5 to 7).
* C: poorly differentiated (from 8 to 10).

Bone scintigraphy. Defined as existence or not of radiolabel uptake images suggesting metastasis. Categories:

* A: negative.
* B: positive.

Type of MAB. Defined by the result of combinations between a steroidal - ciproterone acetate - o non steroidal - bicalutamide or flutamide - antiandrogen, and a GnRH analog - buserelin, goserelin, leuprorelin o triptorelin -. Considered categories:

* A: analog + ciproterone acetate.
* B: analog + bicalutamide.
* C: analog + flutamide.

HRQoL variables

Variables included at those different domains from EORTC HRQoL questionnaires: QLQ-C30 and QLQ-PR25.

Quality-of-life adjusted survival. Result from the application of preferential ponderation rates corresponding to the EUROQoL 5-D instrument. It is expressed in QALYs.

Pharmacoeconomic variables

Pharmaceutical expenses. Expressed in Euros.

Cost-utility ratio. Expressed in Euros/ QALY gained.

Other variables

(Applied to the subpopulation of patients whith diagnosis of prostate adenocarcinoma):

Home location. Categories:

* A: rural.
* B: urban.

Academic level of the patient. Groups of categories:

* A: None or basic.
* B: intermediate or higher.

INSTRUMENTS FOR MEASUREMENT OF HRQoL VARIABLES

Previously described, and they are:

EORTC QLQ-C30. (version 3.0).

EORTC QLQ-PR25.

Preferential ponderation rates from the EUROQoL 5-D instrument.

DATA COLLECTION. STATISTICAL ANALYSIS.

The application of HRQoL instruments, as well as that of preferential ponderation rates was done four times: basal - before starting the MAB therapy -, and another three measurements afterwards, with a 12-month gap between each one of them. Direct telephone interview with patients was used as method of data collection, its clinical investigation nature being previously explained, with obtention of their informed consent   on their recruitment for the study.

Statistical analysis of the data base outcomes was done by means of the SPSS© version 11.5 for Windows. Mann-Whitney´s test - comparison between two independent samples - was used for the assessment of those outcomes from MAB patients compared to those of patients without cancer. Mann-Whitney´s or Kruskal-Wallis´ test were used for comparison of outcomes between the different established ranks - in MAB patients - of each variable at its measurement corresponding to month 36 of follow-up, according to the number of these compared ranks if they are equal or more than two, respectively - comparison between two or k independent samples, in each case -. Finally, the comparative assessment between different measurements during follow-up - in MAB patients - by means of HRQoL instruments was done using the Wilcoxon´s signed rank test - comparison of paired data -.

OUTCOMES

BASAL DESCRIPTIVE PARAMETERS

Age distribution in patients diagnosed of prostate adenocarcinoma showed 8.11 % for the range between 60-69 years old. The percentage corresponding to the range between 70-79 years old was 57.65 %, whereas the range for >= 80 years old was 34.24 %. These percentages corresponded as well to those of the sample of individuals without cancer.

The mean age obtained for MAB patients was 77.33 years old with standard deviation - SD - equal to 5.08. Mean age for individuals without prostate cancer was 77.17 years old (SD= 6.21).

With regard to the academic level of patients, they reported to have no studies in 49.5 % of cases, in front of 47.8 % for primary, 1.8 % corresponding to those with intermediate, and 0.9 % with higher studies.

Location of patients´ home was in a rural setting in 80.2 % of cases, whereas 19.8 % was in an urban one; outcomes which correspond as well to those be-

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longing to the recruited group of individuals without cancer.

The DRE of patients with prostate adenocarcinoma showed a non-suspicious prostate in 30.6 % of cases. In 50.5 % a suspicious, mobile prostate was noticed with this exploration. In the remaining 18.9 % of patients pacientes the DRE showed a suspicious, irregular and/ or fixed prostate.

Basal PSA levels were less than 20 ng/ mL in 35.1 % of cases, whereas 64.9 % had values more or equal to 20 ng/ mL; the mean obtained value being 80.45 ng/ mL (SD= 160.01).

Images obteined by means of prostatic transrectal ultrasonography showed a gland without suspiction of malignancy in 0.9 % of cases. In 71.2 % of patients they were suggestive of a localized stage, whereas in 27.9 % being compatible with locally advanced stage.

Ultrasound-guided transrectal prostatic biopsy was positive for adenocarcinoma in only one lobe in 28.8 % of cases, while in 70.2 % of patients the positiveness was bilateral.

Gleason´s score ranged 2-4 in 23.4 % of cases; 5-7 in 64 % of patients; and 8-9 in the remaining 12.6 %.

Bone scintigraphy was positive in 18 % of cases.

MAB was based on combination of GnRH analog plus ciproterone acetate in 4.5 % of cases; analog plus bicalutamide in 18.8 % of patients; and analog plus flutamide in the remaining 75.7 %.

HEALTH-RELATED QUALITY OF LIFE

A. Descriptive parameters corresponding to outcomes from use of the EORTC QLQ-C30 instrument.

The value corresponding to the physical function field results from the sum of items 1 to 7 from QLQ-C30 instrument. The outcome for the emotional sphere, on the other hand, is equivalent to the addition of items 21 to 24. Cognitive sphere is based on items 20 and 25. Symptoms sphere comprises fatigue sensation, sickness/ vomit and pain - sum of QLQ-C30 items 10, 12 and 18; 14 to 15; and 9 plus 19, respectively -. Sociofamilial sphere includes the sum of items 26 and 27 from the mentioned instrument.

The complete list of mean, standard deviation and median values for each one of those mentioned HRQoL fields, as well as the total sum of QLQ-C30 instrument is shown at Tables I-IV.

B. Outcomes according to categories/ intervals of some variables (month 36 of follow-up).

The list of mean, standard deviation and median values - corresponding to the month-36 measurement in MAB patients - for the total sum of QLQ-C30 instrument according to the different categories/ intervals of "academic level" y "home location" variables is shown at Table V.

The list of mean, standard deviation and median values - corresponding to the month 36 measurement in MAB patients - for the total sum of QLQ-C30 instrument according to the different categories/ intervals of "basal age", "DRE prostatic characteristics", "basal PSA value", "prostatic morphology with transrectal ultrasonography", "uni- o bilateral positiveness of prostatic transrectal biopsy", "Gleason score", "bone scintigraphy positiveness", y "type of MAB (according to antiandrogen used)" variables is shown at Tables VI-VII.

C. Comparative assessment of outcomes from the use of QLQ-C30 instrument.

1. MAB patients vs individuals without cancer.

Significant differences were seen on emotional field at basal measurement, as well as at those corresponding to months 24 and 36, non-cancer patients resulting with worse outcomes.

The comparison corresponding to the cognitive field showed significant differences at month-12 measurement only, the group of neoplasic patients having worse outcomes.

Regarding the symptom sphere, which comprises fatigue sensation, sickness/ vomits and pain -, significant differences were obtained at measurements corresponding to months 12 and 24, patients without neoplasm resulting with better outcomes.

The comparative assessment corresponding to the sociofamilial sphere showed significant differences at month-36 measurement only, with worse outcomes for non-neoplasic individuals.

The comparison of QLQ-C30 total scores, - except for general items 29 and 30 -, show statistically significant differences at month-12 measurement only, MAB patients resulting with worse outcomes.

The complete list - for each measurement - of p values which were obtained with the comparative assessment between MAB patients and non-neoplasic individuals for each mentioned HRQoL field, as well as for the total sum of QLQ-C30 instrument is shown at Tables I-IV.

2. Inter-categories/ -intervals comparison for some variables in MAB patients (month 36 of follow-up).

Significant differences were seen regarding the total value obtained with the QLQ-C30 instrument between the subgroup of patients with primary studies or without them and those with intermediate or higher ones, more satisfactory outcomes being for the latter. No significant differences were obtained for other variables.

The complete list of p values which were obtained with the comparative assessment of different categories/ intervals corresponding to the previously mentioned variables for the total sum of QLQ-C30 instrument - at month-36 measurement, in MAB patients - is shown at Tables V-VII.

3. Inter-measurement comparisons (MAB patients).

Comparison between those different measurents in MAB patients showed significant differences on physical function between basal values and those corresponding to month 12, as well as between the latter and those belonging to month 24. Difference between month-36 and basal values resulted statistically significant too.

Regarding the emotional sphere, significant differences were confirmed between basal values and those corresponding to month 12, as well as between the former and those belonging to month 36. Significant outcomes for the cognitive sphere coincide with those reported for the emotional sphere.

Comparisons between values of different measurements for the symptom sphere showed statistically significant differences between the basal score and that of month 12, as well as between the latter and that of month 24. The difference between the basal score and that of month 36 was significant as well.

Significant differences were seen on sociofamilial field only when basal and month-12 measurements were compared.

TABLE I. MAIN DESCRIPTIVE STATISTICS CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER. OUTCOMES FROM A COMPARATIVE STATISTICAL STUDY BETWEEN MAB PATIENTS AND INDIVIDUALS WITHOUT PROSTATIC NEOPLASM. BASAL MEASUREMENT.

	MAB patients		Non-neoplasm individuals		p**
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	
PHYSICAL SPHERE	8,58 (2,06)	8	8,62 (2,94)	8	0,514
EMOTIONAL SPHERE	4,41 (0,74)	4	5,08 (1,8)	4	**0,007**
COGNITIVE SPHERE	2,61 (0,91)	2	2,48 (0,88)	2	0,226
SYMPTOM SPHERE	8,76 (2,06)	8	8,52 (2,34)	8	0,215
SOCIOFAMILIAL SPHERE	2,22 (0,51)	2	2,22 (0,79)	2	0,197
TOTAL QLQ-C30* SCORE	33,7 (5,81)	32	34,36 (8,14)	31	0,919

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test.
Statistical significance if p< 0,05 (bold-typed); (blue cells= worse outcomes in non-neoplasm individuals).

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With regard to the value of the sum of the total score from QLQ-C30 instrument – except for general items 29 and 30, as previously reported -, it shows significant differences between basal and month-12 outcomes, as well as between the latter and that of month 24. The difference between basal and month-36 values was significant as well.

The complete list of p values which were obtained with the inter-measurement comparative assessment for each mentioned HRQoL field, as well as for the total sum of the QLQ-C30 isntrument is shown at Tables VIII-XI.

DISCUSSION

According to data from year 2002 (29), Spain has, for the whole population, a life expectancy of 79.9 years, clearly superior to the European Union´s - EU - mean which reaches 78.3 years. Spain is the EU´s country with highest life expectancy, after Italy and Sweden. If outcomes are broken down according to sex, in our country, life expectancy in males is 76.5 years for males, while it is 83 for females. If we besides consider a synthetic fertility rate of 1.346 children/ woman, according to data from the National Statistics Institute corresponding to year 2005, it can be inferred that elder population take progressively more importance in a national level (30).

As far as Zamora´s heath area is concerned, it has traditionally considered to be composed of aged population. According to figures published by the Junta of Castilla and León for year 2005, 30.72 % of males in the province are 60 year old or older. Population variation between years 2004-2005 maintains the negative trend seen in previous years, reaching a figure of -0.24 %, and the provincial synthetic fertility rate is 0.924 children/ woman, with a decrease from 1.972 during the last 30 years. All mentioned data must be set in a context of rural population predominance – 59.03 % of males -, with 88.9 % of them distributed among municipalities ranging 101-2000 inhabitants (31).

Above-mentioned data explain the raising influence that elder population exerts on assistance demand, specially with regard to those diseases like prostate cancer, typical of elder decades of life, which have potential influence on HRQoL

TABLE II. MAIN DESCRIPTIVE STATISTICS CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER. OUTCOMES FROM A COMPARATIVE STATISTICAL STUDY BETWEEN MAB PATIENTS AND INDIVIDUALS WITHOUT PROSTATIC NEOPLASM. MEASUREMENT AT MONTH 12 OF FOLLOW-UP.

	MAB patients		Non-neoplasm individuals		p**
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	9,41 (3,06)	8	8,78 (3,26)	8	0,096
EMOTIONAL SPHERE	4,79 (1,45)	4	5,11 (1,8)	4	0,281
COGNITIVE SPHERE	2,84 (1,05)	2	2,47 (0,78)	2	**0,006**
SYMPTOM SPHERE	9,73 (3)	9	8,54 (2,33)	8	**< 0,001**
SOCIOFAMILIAL SPHERE	2,25 (0,61)	2	2,23 (0,79)	2	0,253
TOTAL QLQ-C30* SCORE	36,8 (8,28)	34	34,58 (8,28)	32	**0,015**

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test.
Statistical significance if p< 0,05 (bold-typed); (red cells= worse outcomes in MAB patients).

TABLE III. MAIN DESCRIPTIVE STATISTICS CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER. OUTCOMES FROM A COMPARATIVE STATISTICAL STUDY BETWEEN MAB PATIENTS AND INDIVIDUALS WITHOUT PROSTATIC NEOPLASM. MEASUREMENT AT MONTH 24 OF FOLLOW-UP.

	MAB patients		Non-neoplasm individuals		p**
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	9,36 (2,87)	8	8,99 (3,50)	8	0,172
EMOTIONAL SPHERE	4,73 (1,50)	4	5,24 (1,65)	5	**0,004**
COGNITIVE SPHERE	2,88 (1,21)	2	2,56 (0,82)	2	0,113
SYMPTOM SPHERE	9,72 (3,19)	9	8,83 (2,47)	8	**0,033**
SOCIOFAMILIAL SPHERE	2,15 (0,41)	2	2,32 (0,87)	2	0,423
TOTAL QLQ-C30* SCORE	36,80 (8,61)	35	35,50 (8,86)	32	0,209

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test.
Statistical significance if p< 0,05 (bold-typed); (blue cells= worse outcomes in non-neoplasm individuals, red cells= worse outcomes in MAB patients).

TABLE IV. MAIN DESCRIPTIVE STATISTICS CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER. OUTCOMES FROM A COMPARATIVE STATISTICAL STUDY BETWEEN MAB PATIENTS AND INDIVIDUALS WITHOUT PROSTATIC NEOPLASM. MEASUREMENT AT MONTH 36 OF FOLLOW-UP.
(SD)= STANDARD DEVIATION.

	MAB patients		Non-neoplasm individuals		p**
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	8,87 (2,54)	8	9,52 (4,11)	8	0,735
EMOTIONAL SPHERE	4,66 (1,46)	4	5,48 (2,04)	5	**< 0,001**
COGNITIVE SPHERE	2,72 (1,04)	2	2,60 (0,86)	2	0,565
SYMPTOM SPHERE	9,17 (2,69)	8	9,17 (3,19)	8	0,431
SOCIOFAMILIAL SPHERE	2,12 (0,42)	2	2,44 (1,01)	2	**0,016**
TOTAL QLQ-C30* SCORE	35,20 (7,29)	34	37,00 (10,98)	33	0,73

(SD)= STANDARD DEVIATION.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test.
Statistical significance if p< 0,05 (bold-typed); (cells= worse outcomes in non-neoplasm individuals).

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PHYSICAL ACTIVITY SPHERE

There are several physiological effects of hormone therapy on patient´s physical field, and at scientific literature reports on generic features as reduction of subjective energy levels can be seen (32), toghether with other more specific ones as decrease of muscle mass index (33).

When sensation of energy loss is intended to be explained, the link between androgen production and erythropoietic cativity must be mentioned. Hormone deprivation affects in a negative fashion the normal production of erythrocytes due to alteration of the process of their precursors maturation, which leads to low hemoglobin levels, and therefore decrease of the capacity of oxygen transportation to the

TABLE V. MAIN DESCRIPTIVE STATISTICS AND OUTCOMES FROM A COMPARATIVE STUDY BETWEEN DIFFERENT CATEGORIES/ INTERVALS CORRESPONDING TO "ACADEMIC LEVEL" AND "HOME LOCATION" VARIABLES FOR THE TOTAL SCORES FROM QLQ-C30 INSTRUMENT - AT MONTH-36 MEASUREMENT, IN MAB PATIENTS -.

	TOTAL QLQ-C30* SCORE month 36		
	Mean (SD)	Median	P**
Academic level			**0,018**
No one/ basic	35,45 (7,30)	34	
Intermediate/ higher	28,33 (0,58)	28	
Home location			0,241
Rural	35,57 (7,31)	35	
Urban	34,05 (7,26)	32	

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test. Statistical significance if p< 0,05 (bold-typed); (red cells= worse outcomes if no one/ basic academic level).

tissues, as well as symptoms of anemia like fatigue and diminished vitality (32). These manifestations are present in an estimated 13-30 % of patients.

Effects of androgen blockade on body composition are pottentially significant as well. The absence of anabolic effect of testosterone is the basic explanation for this phenomenon, and some authors (34) deepen in that sense when they describe the existence of mutations that affect the normal androgen action at the level of skeletal muscle receptors. Physiological age-related secondary sarcopenia (35), would represent just one of several factors leading to loss of body lean mass. Total body mass is also reduced with hormone blockade (33). Data reported by some authors suggest that upper limbs are affected earlier - after 3-12 months of hormone therapy -, while strength and resistance of lower limbs keep yet preserved after that period (36).

Bone mineral density is reduced by androgen deprivation too. Measurement of this parameter shows annual decreases of 2-8 % at vertebral column and 1.8-6.5 % at hips of patients with that therapy cause of prostate cancer (37). The cease of protective effect from peripheral conversion of testosterone into estrogens (32) causes a predominant osteoclastic activity in those patients at bone level, while the percentage of pathological fractures gets worse if a vitamin D deficit coexists. Some authors suggest that bicalutamide monotherapy would entail a lesser loss of bone density in stage-M0 prostate cancer patients (38). Differences have been reported as well about loss of that density between intermittent - 2-4 % - compared to continuous blockade - 10 % -, after two years of therapy (39).

In spite of a negative influence of androgen blockade on capacities for physical activity, some reports (40) emphasize on the importance of exercise as one of the less possibilities of contributions to improve cancer-related fatigue. In the same sense it has been reported that resistance training can improve the physical function in those individuals (41), with a good muscle condition being preserved at the same time. 19.4 % of males under androgen deprivation that survive at least five years will suffer of pathological fractures; and in thsi respect it has been insisted on the importance of weightlifting physical exercise as a preventive method against their presentation (37).

Some authors have published special training programs for patients under androgen blockade, with 12-week duration - three times per week -, and initial intensities ranging 50-60 % of one repetition maximum - RM, or highest weight an individual can lift

in one single attempt -, progressing to 70-90 % of one RM afterwards (42). With this kind of exercises the mentioned authors report outcome improvement when fatigue - FACT-F - and HRQoL scales - FACT-P - are applied; without changes in body weight or patient´s body mass index seen. Programs with initial intensities of 50 % RM - 30 minutes, 2-3 times per week prove to be effective to reduce anemia-induced fatigue (43), and home sessions freely patient-regulated being uneffective. In any case, surpassing of an 80 % RM limit is not suitable, since an increase of serum testosterone levels have been seen from that percentage.

Benefits that exercise offers are not limited to an improvement in fatigue, vigor and physical functional capacity, but they positively influence against presentation of sickness as well as depression and anxiety (41). Use of questionnaires to assess the aspects of exercise-related behaviour showed that an improvement of joining and participation in programs is associated to higher levels of patient´s understanding about the importance of links between exercise and quality of life, emphasizing as well the relevance that esternal supports have at the start of training programs.

TABLE VI. MAIN DESCRIPTIVE STATISTICS AND OUTCOMES FROM A COMPARATIVE STUDY BETWEEN DIFFERENT CATE-GORIES/ INTERVALS CORRESPONDING TO "BASAL AGE", "PROSTATIC CHARACTERISTICS ON DRE", "BASAL PSA VALUE" AND "PROSTATIC MORPHOLOGY ON TRANSRECTAL ULTRASONOGRAPHY" VARIABLES FOR THE TOTAL SCORES FROM QLQ-C30 INSTRU-MENT - AT MONTH-36 MEASUREMENT, IN MAB PATIENTS -.

	TOTAL QLQ-C30* SCORE month 36		
	Mean (SD)	Median	P**
Basal age (years)			0,057
<= 75	34,41 (8,88)	31	
> 75	35,67 (6,27)	35	
DRE			0,55
Non-suspicious	33,48 (5,00)	32	
Suspicious, mobile	35,81 (7,30)	34	
Suspicious, irregular and/ or fixed	36,50 (10,38)	34	
Basal PSA value (ng/ ml)			0,12
< 20	34,06 (6,87)	32	
>=20	35,89 (7,50)	35	
Prostatic morphology (transrectal ultrasonography)			0,488
Normal	29,00 (-)	29	
Localized stage	35,77 (7,84)	34,5	
Locally advanced stage	33,82 (5,23)	32,5	

(SD)= standard deviation.
* *Except for general items 29 and 30.*
** *p value obtained by means of Mann-Whitney´s test (or Kruskal-Wallis´ if the variable consists of more than two different categories/ intervals).*
Statistical significance if p< 0,05.

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Physiological sarcopenia is also improved by means of resistance training with 80 % RM intensities three times per week (35), achieving increases of strength and muscle mass - through optimization of activation and coordination of motor units and neural codification -. Differences between patient´s ages were not decisive in order to achievement of those values.

The outcomes from our study regarding the physical field of HRQoL show a negative effect of MAB that significantly extended through the first 24 months. A trend towards stability can be seen afterwards. As yet reported, individual´s effort to maintain his daily activities, and the possibility of being complemented with programmed exercises, is a key aspect. It becomes easier in those populations that get used to a non-sedentary proffession - this is the case of societies, like the one studied here, with important involvements on the primary sector of economy -.

The absence of significant differences - in none of the sequential measurements - seen between patients with MAB and non-cancer individuals must be emphasized. The influence of basically age-related loss of physical condition, is therefore in no way negligible.

TABLE VII. MAIN DESCRIPTIVE STATISTICS AND OUTCOMES FROM A COMPARATIVE STUDY BETWEEN DIFFERENT CATE-GORIES/ INTERVALS CORRESPONDING TO "UNI- OR BILATERAL POSITIVENESS OF PROSTATIC TRANSRECTAL BIOPSY", "GLEASON SCORE", "BONE SCINTIGRAPHY POSITIVENESS", AND "TYPE OF MAB ACCORDING TO ANTIANDROGEN USED" VARIABLES FOR THE TOTAL SCORES FROM QLQ-C30 INSTRUMENT - AT MONTH-36 MEASUREMENT, IN MAB PATIENTS -.

	TOTAL QLQ-C30* SCORE month 36		
	Mean (SD)	Median	P**
Transrectal biopsy positiveness			0,385
Unilateral	35,11 (9,01)	31,5	
Bilateral	35,26 (6,43)	35	
Gleason score			0,591
Well differentiated	37,50 (9,99)	34	
Moderately differentiated	34,65 (6,45)	33,5	
Poorly differentiated	33,89 (4,86)	35	
Bone scintigraphy			0,071
Negative	34,96 (7,65)	32	
Positive	36,57 (4,94)	35	
Type of MAB (according to antiandrogen used)			0,254
Analog + ciproterone acetate	36,33 (7,51)	36	
Analog + bicalutamide	32,83 (5,58)	31,5	
Analog + flutamide	35,79 (7,63)	35	

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Mann-Whitney´s test (or Kruskal-Wallis´ if the variable consists of more than two different categories/ intervals).
Statistical significance if p< 0,05.

EMOTIONAL SPHERE

The communication of a prostate cancer diagnosis to a patient entails his adoption of mechanisms to confront a potentially deadly disease. If an androgen deprivation therapy is added, he must face up the risk to suffer alterations in other spheres of his integrity as well, like sexuality and masculinity feeling. Age ranks affected by this disease generally correspond to advanced decades of life, especially in those cases when patient´s survival is prolonged due to the therapy, with addition of its complications in a context of those ones just related to age worsening and situations linked to the latter - loss of general health and energy, retirement, loss of beloved people, etc -.

Urologists trend to underestimate the psycological comorbidity of patients with prostate cancer, often without contributing, therefore, the possibility of an interdisciplinar solution (44). On the other hand, it has been demonstrated an inversely proportional connection between patient´s age and their predisposition to transmit the presence of emotional disorders to the doctor, and to undergo psychiatric assessment and/ or therapy as well (45). Thus, in the series of

neoplasic patients from the latter report 32.6 % of anxiety and 15.2 % of depression disorders were seen, while from the total amount, 40 % of patients loss or refused psychiatric consultation.

Another aspect to be considered about the emotional sphere is the increasing importance given to the patient´s involvement on therapy decision-making, circumstance in front of which not all individuals initially feel comfortable. However, at one report (46) it has been studied the role played by information acquisition in order to modify anxiety and depression levels in prostate ccancer patients with recently started therapy, and after the first six weeks lower scores were obtained when anxiety was measured by means of the Spielberger State-Trait Anxiety Inventory instrument in those patients whom the possibility of discussion as well as questions to their specialist were provided in addition to simple written information. Significant differences on measurement outcomes of depression symptoms were not seen.

Between 25-47 % of cancer-diagnosed patients present psychiatric disorders (44). Reactive anxiety is the entity by which the derivation of most consultations is originated, and this manifestation

TABLE VIII. OUTCOMES FROM A COMPARATIVE STUDY BETWEEN BASAL AND MONTH-12 MEASUREMENTS IN MAB PATIENTS FOR VALUES CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER.

| | COMPARATIVE STUDY BETWEEN MEASUREMENTS (MAB PATIENTS) | | | | p** |
| | Basal | | Month 12 | | |
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	8,58 (2,06)	8	9,41 (3,06)	8	**< 0,001**
EMOTIONAL SPHERE	4,41 (0,74)	4	4,79 (1,45)	4	**< 0,001**
COGNITIVE SPHERE	2,61 (0,91)	2	2,84 (1,05)	2	**< 0,001**
SYMPTOM SPHERE	8,76 (2,06)	8	9,73 (3)	9	**< 0,001**
SOCIOFAMILIAL SPHERE	2,22 (0,51)	2	2,25 (0,61)	2	**0,046**
TOTAL QLQ-C30* SCORE	33,7 (5,81)	32	36,8 (8,28)	34	**< 0,001**

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Wilcoxon´s signed rank test.
Statistical significance if p< 0,05 (bold-typed); (red cells= worsening).

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presents not only at the moment of verification of the neoplasic process, but from the very moment of request of diagnostic tests or during the time-gap waiting for their outcomes (47). In this respect, some authors have reported increases in psicological stress together with raising serum cortisol levels in patients who have undergone prostate neoplasm screening - highest levels seen two weeks after biopsy in those patients whom it was indicated -. The decrease in serum testosterone concentration seen in stress situations could be linked to a down-regulation at a Leydig cell level caused by the mentioned increase in glucocorticoid levels (48). Sleep disturbances are also present, although with a greater delay comparing those mentioned before (49).

Post-traumatic stress disorder - PTSD – has also been described in patinets diagnosed of prostate cancer (50), and it can be manifested in form of dreaming re-experiencies about the traumatic event, remembering thougths and "flash-backs". Limited social support, previous history of psicological trauma, or pre-existent psychiatric disorders are factors predisposing for PTSD to be present. Therapies focusing on cognitive and behavioural spheres, as well as support groups can make the control of this disorder to be easier.

Anxiety entails a dead weight consuming part of patient´s fighting efforts against their disease, and it can even be transferred to the couple relationship field since it negatively affects on affective life (51). These authors have pointed at lack of acceptance, changes in self-perception and regret from previous therapy decisions as factors promoting that problem.

Depression disorders present even a 20 % incidence in patients with diagnosis of neoplastic disease. Factors related to the latter as clinical stage, its clinical course, type of therapy undergone, and presence or not of associated pain, significantly influence on presentation of symptoms compatible with depression (52). from a physiopathological point of view, it has be demonstrated a correlation between decrease of serum testorterone levels and depression episodes (53), together with presence of raised urinary cortisol levels, in the context of a down-regulation as that mentioned before at the reactive anxiety section. Similar phenomena are seen with PTSD, which can lead to depression (54).

It is necessary, however, a distinction between sadness usually secondary to the communication of disease diagnosis and real depression manifestatio-

TABLE IX. OUTCOMES FROM A COMPARATIVE STUDY BETWEEN MONTH-12 AND MONTH-24 MEASUREMENTS IN MAB PATIENTS FOR VALUES CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER.

	COMPARATIVE STUDY BETWEEN MEASUREMENTS (MAB PATIENTS)				p**
	Month 12		Month 24		
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	9,41 (3,06)	8	9,36 (2,87)	8	**< 0,001**
EMOTIONAL SPHERE	4,79 (1,45)	4	4,73 (1,50)	4	0,794
COGNITIVE SPHERE	2,84 (1,05)	2	2,88 (1,21)	2	0,334
SYMPTOM SPHERE	9,73 (3)	9	9,72 (3,19)	9	**< 0,001**
SOCIOFAMILIAL SPHERE	2,25 (0,61)	2	2,15 (0,41)	2	0,317
TOTAL QLQ-C30* SCORE	36,8 (8,28)	34	36,80 (8,61)	35	**< 0,001**

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Wilcoxon´s signed rank test.
Statistical significance if p< 0,05 (bold-typed); (blue cells= improvement, red cells= worsening).

ns, such as failure feeling, separation from the rest of society, penalization feeling, suicide ideas, lack of satisfaction, hesitation and crying (55). Risk factors for development of depression disorders are varied, but some of them must be emphasized as social isolation, recent loss of relatives and/ or friends, trend to pessimism, economic troubles, emotional lability, alcoholism, previous suicide ideas, poor control of disease-related pain, and consciousness about its metastatic stage. Considering that even 55 % of prostate cancer patients suffer from some kind of pain (56), the proposal of analgesics plus antidepressants seems suitable in many cases (57).

Some reports show improvement of depression and anxiety symptoms in patients with intermittent compared to continous androgen blockade (58).

The discovery in our study of significantly worse outcomes on emotional field of HRQoL at month-12 measurement compared to the basal one in MAB patients, can be understood in a context of influence that a new situation like the start of a mixed oral-parenteral therapy exerts on patients, together with those effects that the latter perceive to a greater or lesser extent regarding the rest of spheres and fields

of his quality of life. The stability of outcomes at later months can be linked to a combination of habituation to the new therapy need and patient´s adaptation to the own general situation noticed by himself.

Presence of significant differences seen in our study between MAB group and non-cancer individuals let demonstrate poor outcomes for the latter. This offers a certain paradoxical component regarding what is a priori expected; However, considering the information filter usually applied to the neoplasic individual with regard to his "prostatic problem", the lack of unfavorable outcomes for cancer patients can be understood, to which potential external influences on this HRQoL sphere can be added in non-neoplasic patients, non yet identified.

COGNITIVE SPHERE

Individual´s cognitive capacity is influenced by several factors, including education and developmental setting, as well as cultural base, experience and hereditary components. The physiological role played by sex hormones in this respect is controversial. Differences on spacial cognitive aspect between

TABLE X. OUTCOMES FROM A COMPARATIVE STUDY BETWEEN MONTH-24 AND MONTH-36 MEASUREMENTS IN MAB PATIENTS FOR VALUES CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER.

| | COMPARATIVE STUDY BETWEEN MEASUREMENTS (MAB PATIENTS) | | | | p** |
| | Month 24 | | Month 36 | | |
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	9,36 (2,87)	8	8,87 (2,54)	8	0,157
EMOTIONAL SPHERE	4,73 (1,50)	4	4,66 (1,46)	4	0,317
COGNITIVE SPHERE	2,88 (1,21)	2	2,72 (1,04)	2	0,317
SYMPTOM SPHERE	9,72 (3,19)	9	9,17 (2,69)	8	0,157
SOCIOFAMILIAL SPHERE	2,15 (0,41)	2	2,12 (0,42)	2	0,317
TOTAL QLQ-C30* SCORE	36,80 (8,61)	35	35,20 (7,29)	34	0,132

(SD)= standard deviation.
 * Except for general items 29 and 30.
 ** p value obtained by means of Wilcoxon´s signed rank test.
 Statistical significance if p< 0,05.

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both genders have been reported, males standing out with mental organization, and some authors find a positive association between testosterone levels and outcomes from tests measuring those capacities (59), although other reports show negative relations between them (60). In any case, there seems to exist a link between ultradian rythms of gonadotropin/androgen secretion and spacial cognitive capacities (61).

Literature reports information demonstrating that GnRH analogs can negatively influence on patient´s cognitive functions such as memory and attention. Other manifestations less frequently described are delirium, ataxia, and states of altered consciousness, with a reversible nature seen after the administration supression of those involved drugs (62).

Some studies have also demonstrated direct links between testosterone shortage and reduction of cognitive capacity (63), while it can be seen as well that replacement therapies with testosterone in hipogonadism-affected patients lead to an increase of visual-spacial orientation (64) by means of their activating effect on definite brain areas; although some authors have not found significant effects with

the mentioned therapy regarding the cognitive sphere (65).

In a randomized study with 65 patients diagnosed of advanced prostate cancer (66), memory, attention, carrying-out function, intelligence quotient, state of mind and their general health were assessed, previously distributed into four subgroups - treated with an esteroideal antiandrogen, with two different types of GnRH analogs, and with no therapy -. Basal outcomes and values after six months of follow-up were obtained. In the control group, stabilization or some improvement of final outcomes compared to the initial ones was seen, specially outstanding with regard to measurement of verbal memory, while these outcomes - according to the Auditory Verbal Learning Test - were worse at six months of follow-up in the goserelin-treated group. In leuprorelin-treated patients a lesser capacity for visual memory and attenion, as well as worse carrying-out function were observed compared to basal values. 24 out of 50 patients with active therapy showed a decrease in at least one of those fields of cognitive function evaluated, and seven individuals in two or more of them. Correlation between changes of cognitive capacity and states of mind was not observed, according to outcomes of

TABLE XI. OUTCOMES FROM A COMPARATIVE STUDY BETWEEN BASAL AND MONTH-36 MEASUREMENTS IN MAB PATIENTS FOR VALUES CORRESPONDING TO DIFFERENT HRQOL SPHERES FROM QLQ-C30 INSTRUMENT, AS WELL AS THOSE REFERRED TO TOTAL SCORES FROM THE LATTER.

| | COMPARATIVE STUDY BETWEEN MEASUREMENTS (MAB PATIENTS) | | | | p** |
| | Basal | | Month 12 | | |
	Mean (SD)	Median	Mean (SD)	Median	
PHYSICAL SPHERE	8,58 (2,06)	8	8,87 (2,54)	8	< 0,001
EMOTIONAL SPHERE	4,41 (0,74)	4	4,66 (1,46)	4	0,006
COGNITIVE SPHERE	2,61 (0,91)	2	2,72 (1,04)	2	0,001
SYMPTOM SPHERE	8,76 (2,06)	8	9,17 (2,69)	8	< 0,001
SOCIOFAMILIAL SPHERE	2,22 (0,51)	2	2,12 (0,42)	2	0,157
TOTAL QLQ-C30* SCORE	33,7 (5,81)	32	35,20 (7,29)	34	< 0,001

(SD)= standard deviation.
* Except for general items 29 and 30.
** p value obtained by means of Wilcoxon´s signed rank test.
Statistical significance if p< 0,05 (bold-typed); (red cells= worsening).

Depression Anxiety Stress Scales. After one year of follow-up, differences regarding mnemonic capacity between patients treated with different GnRH analogs were not significant (67).

Outcomes from published studies suggest that affectation of cognitive function is not only limited to memory or other specific aspects, but rather related to global processing of complex information. In any case, these alterations are not usually the cause for the need of therapy interrruption (68).

Tolerance to MAB in terms of cognitive function seems to improve with intermittent hormone blockade (69).

The presence of significant differences between basal and month-12 measurements -unfavorables for the latter - in MAB patients with regard to the cognitive sphere of HRQoL, can be placed upon the negative initial effect, as mentioned before, that therapy can exert on it. Outcome stabilization afterwards, as well as the presence of significant differences only at month 12 of follow-up between patients with and without neoplasm from our study, relativizes the impact of the androgen deprivation seen on the assessed field.

SOCIOFAMILIAL SPHERE

Prostate cancer patients need, as well as those affected of any other potentially significant disease, support from his closest circle - relatives, friends, etc. -, and in relation with that one, published studies have focused on the situation and role played by his partner as provider of emotional support, encouraging and entertainment. However, she often represents a higher psychological stress than that of patient´s, which increases as the neoplasm progresses, with no clear differences of gender when emotional stress is referred, o really verified cause of being witness of a pathological process, often manifested as anticipated anxiety (50). Some studies report the preference of partners for early-detection strategies and/ or those which can offer an increase in survival even at the expense of a potential reduction in quality of life, although inter-individual variability is significant when collaborating in therapy decisions (70).

The rest of social supports are positively linked to psychological well-being, because it reinforces self-esteem, often favoring the obtention of help and advice (44). The feeling of being accompanied and entertained is also a relief of the burden patients hold cause of their neoplasm. The collaboration of others on the instrumental and/ or financial aspects

entails the promotion of stability feelings. It is, however, necessary the establishment of fluent channels of interpersonal communication, avoiding reluctant or isolating attitudes, which are especially verified in disfunctional familial environments, for which a competent psycosocial help is essential (46). Prostatic neoplasm patient´s problems of social adaptation are more obvious, in any case, in advanced disease, where the component of pain, fatigue or micturition disturbances is manifested in a more significant fashion (44).

All mentioned sociofamilial supports turn into health benefits that can fisiologically explained by those positive influences exerted on immune and neuroendocrine systems (71).

In the study presented here, the presence of significant inter-temporal differences in sociofamilial sphere scores at basal and month-12 measurements only, at the same time relativized by a lack of statistical significance between cancer patinets and non-neoplasic individuals at these time points, as well as at month 24, would show a limited influence of hormone-deprivation therapy on the field of patient´s relationships with family and society. On the other hand, significant differences seen at month 36 favoring MAB patients compared to non-cancer individuals could be linked to a higher easiness that patient´s closest environment would provide to him in order to a better interaction with regard to familial and social interpersonal relationships.

FATIGUE, SICKNESS/ VOMITS AND PAIN

Fatigue sensation with hormone therapy of prostate cancer is related to those effects that androgen deprivation exerts on superior functions of the brain, body composition and erythropoyesis. Several cross-sectional HRQoL studies (72) (73) including assessment of MAB patient´s fatigue or energy level, have shown a link between androgen blockade and presentation of higher severity in those manifestations.

A prospective study (74), by means of application of the Fatigue Severity Scale - FSS -, has obtained 14 % of fatigue prevalence in hormone blockade patients, as well as an increase of scores obtained after three months. This raise of fatigue levels are not accompanied, however, with decrease of functional habilities. In the same form, outcomes from Southwest Oncology Group´s INT-0105 study showed a higher degree of fatigue in the MAB group, compared to the orquiectomy-only one, although the physical function sphere was not significantly altered (75). Aerobic

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exercise programs (76) as well as administration of psychoestimulant drugs like metilfenidate (77) can be effective when reduction of fatigue intensity is intended in patients with advanced prostate cancer.

Incidence of sickness and/ or vomits can be up to 22 % of cases (78), with local toxicity of flutamide as one of potentially responsible factors. In the same form, as it happens with specifically intestinal symptoms, they are presented more frequently in MAB patients (79).

Importance given by patients to the problem of cancer symptom manifestations is significant. The fear they feel is directcly related with the aprehension to suffer severe pain, and so, up to 69 % of neoplasic patients refer that it could even make them consider suicide ideas, so that 57 % of them think that cancer-related death may be painful (80).

Somatic-type pain is the most frequently presented in prostate cancer patients, generally caused by bone metastasis. It is usually characterized by being located, varying between intermittent and constant, and being described as sharp pain or "cramp-like" type. This is related to sensitiation of myelin and non-myelinated fibers localized at periostium, as consequence of prostaglandine and osteoclast activator factors production during processes of reabsortion and deposit of neoformed bone (81).

The most frequent locations for bone metastasis are the vertebral bodies, initially asymptomatic, specially if there is no difficulty on structural stability. Pain generally begins when a great bone destruction initially leads to microfractures which can evolve to pathological fractures and/ or associated neurological compression disorders (82).

By use of McGill Pain Questionnaire, Beck Depression Inventory and State-Trait Anxiety Inventory it has been shown that up to 43 % of prostate cancer patients refer pain at any time of the process, being the subgroup with higher probability of association with depression - up to 20 % of cases - or anxiety. Patients with pain manifestations correlate with more advanced stages of disease (56).

In a population study with prostate cancer patients made by application of EuroQoL and Brief Pain Inventory instruments, 42 % of them perceived some degree of pain during the previous week while 26 % scored their quality of life at 50 % or less according to the analogical scale. Availability of medical attendance and lesser elapsed time from the moment of prostate cancer diagnosis were predictive factors in order to obtain better pain scores. The latter fac-

tor, together with age, low medical attendance and/ or paliative care availability resulted to be decisive factors leading to worse quality of life (83). Doctor´s and/ or patient´s negative attitudes with regard to use of specific analgesic drugs - like opioids - entails a handicap against good symptom control (84). When quality of life during the last year before death is assessed in the same population mentioned above it was seen that 29 % of deceased individuals referred their worst pain degree during the last week of life. Mean score for the total of patients who died cause of prostate cancer was 54 in a pain scale (85).

From a descriptive model applied to Swedish population it has been calculated that an optimal therapy which could reduce to zero the pain manifestations of porstate cancer during the whole disease process would entail to add a mean of 0,85 QALYs for each patient with that neoplasm (86).

In a Southwest Oncology Group´s randomized study of advanced prostate cancer comparing the effect on pain of docetaxel-estramustine versus mitoxantrone-prednisone combinations it has been seen by use of Present Pain Intensity scale from McGill Pain Questionaire- Short Form a similar degree of pain paliation between both therapies, although a significant difference in mean survival is shown favoring the former - 17.5 versus 15.6 - (87).

Improvements in up to 81 % of cases have been reported alter external-beam radiotherapy administration to bone metastasis, with complete responses in 23 % of patients (88).

With administration of Strontium-89 favorable responses up to 63 % have been published regarding pain (89). Outcomes from a phase-II double-blind randomized study comparing the analgesic effectiveness of strontium-89 opposite quimiotherapy combination of 5-fluorouracil, epirrubicin, and mitomicin C in patients diagnosed of hormone-resistant metastatic prostate cancer with persistent bone pain show significant reduction in intensity and presentation of symptoms after three weeks of follow-up (90).

In a clinical trial comparing zoledronic acid versus placebo in metastatic prostate cancer, applying the Brief Pain Inventory instrument bone pain was assessed at basal, three and six weeks of therapy, and every six weeks afterwards up to 60 weeks. In the group of bisphosphonate-treated patients is obtained a 33 % probability of favorable response, compared to 25 % for those who received placebo (91).

With administration of intravenous clodronate, by means of application of the Visual Pain Scale

and Karnofsky´s Index, it has been seen pain relief in 91.4 % of hormone-resistant advanced prostate cancer patients, persisting for a mean of 6.3 months.

Administration of vitamin D has allowed reports of score improvements in bone pain manifestations up to 25 % of cases, and 37 % of patients showed higher muscle strength, although a decrease of analgesic doses required was not simultaneously evidenced (92).

Managemento of neoplasic-related pain although presents the possibility of being approached from a psycological perspective. Application of supporting psycotherapy techniques allow patients to receive the help they need for a correct adaptation to a pain crisis, favoring incresing self-control as well as reduction in lack of hope and helplessness feelings they can potentially suffer. Some techniques are mainly cognitive, focusing on perception and perception and thoughts processes, while other ones are essentially behavioral, directed to modulate those attitudes patients present when they confront the neoplasic pain (93).

The introduction of the concept of patient´s dosing self-control for opioids has entailed the opening of a channel to individualize the analgesic administration by use of intravenous perfusion pumps.

If we focus on the study presented here, the unfavorable evolution of HRQoL outcomes for the symptom association of asthenia, sickness/ vomits and pain objetived up to month 24 in MAB patients is in keeping with that previously documented. It is reinforced the influence exerted by adverse effects as well as pain component of the neoplasic disease on males affected. On the other hand, the lack of significant differences between outcomes at months 24 and 36 of follow-up, as well as with the comparation between cancer- and non-cancer individuals at the latter measurement may be due to adoption of measures like those ones described before - sometimes unnecessarily delayed - in order to symptom control.

CONCLUSSIONS

Cognitive and symptom spheres, although they don´t represent aspects of maintained differentiation, they show significant differences at specific time points between MAB patients and non-cancer individuals, to the detriment of the former.

There is not any sphere or field which maintains a constant significant worsening during the period studied in MAB patients, Although at initial stages it is seen - in higher or lesser degree - for all aspects studied, including the assessment of subjective perception of general health state as well as quality of life. Improvement in sociofamilial sphere is verified.

Lesser academic level of MAB patients entails a distinguishing factor in order to obtain worse outcomes of HRQoL parameters assessed here.

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