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USE OF VALUE-BASED HEALTHCARE METHODOLOGY TO EVALUATE A NOVEL TREATMENT PROTOCOL FOR LOCALIZED PROSTATE CANCER

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ABSTRACT

Objectives: To report toxicity and impact on health-related quality of life (HRQoL) in patients treated with a combination of high-dose-rate HDR prostate brachytherapy and prostate Stereotactic Ablative Radiotherapy (SABR) / Stereotactic Body Radiation Therapy (SBRT) for intermediate and high-risk prostate cancer in a phase II prospective trial.

Material and methods: Fifty-two men with histologically confirmed intermediate (IR), high (HR) or very-high (VHR) risk prostate adenocarcinoma were enrolled on an institutional review board-approved prospective study of combined HDR-brachytherapy (1 fraction of 15Gy) and SABR (25 Gy in 5 fractions). The patients were monitored prospectively for genitourinary (GU) and gastrointestinal (GI) toxicity according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Patient quality of life was assessed through ICHOM (International Consortium for Health Outcomes Measurement) standard sets, with Expanded Prostate Cancer Index (EPIC) and EORTC QLQ-PR25 questionnaires.

Results: 51 patients had completed treatment at the time of the current analysis with a median follow-up of 10 months, 34.6% favorable IR, 17.3% unfavorable IR, 34.6% HR and 13.5% VHR. Median age was 75 years and median baseline IPSS was 4 (0-19). Median PSA before treatment was 7.1 ng/mL (3.8-110 ng/mL) and median volume of the prostate was 33 cc (16-70 cc). No severe (i.e. G3-4) acute or late events were recorded. A majority of patients had no acute (G0) genitourinary (GU) or gastrointestinal (GI) symptoms, with cumulative incidences of 59.61% and 92.3% respectively. The maximal reported acute and late toxicity was of Grade 2 for GU events and Grade 1 for GI events. The most common acute GU symptom was dysuria whereas the most common acute GI event was proctitis. Thirty-seven patients reached a follow-up > 6 months and were eligible for chronic toxicity analysis. Among these, the cumulative incidence of late G2 GU events was 7.7%, no G2 late GI event was observed. The most common late GU symptom was nocturia. No significant decline in patient HRQoL was observed in any studied domain.

Conclusion: The combination of 15Gy HDR prostate brachytherapy and prostate SBRT (25 Gy in 5 daily fractions) is a well-tolerated scheme without severe adverse

events observed in this prospective phase II trial. Moreover, the majority of patients did not suffer from any adverse event. Patient reported outcomes confirm these results, we could not find any significant decline in any domain from baseline values.

Key words: prostate cancer, radiation therapy, brachytherapy, HRQoL, ICHOM.

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1. INTRODUCTION

1.1.PROSTATE CANCER

1.1.1. The prostate and prostate adenocarcinoma

The prostate is an internal pelvic organ located behind the pubis, in front of the rectum, immediately below the urine bladder and anterior to the seminal glands. It surrounds the first portion of the urethra (prostatic urethra). All the changes and pathological processes happening in the prostate stand in close relation with its anatomical features. McNeal described the following prostate zones: peripheral zone, central zone, transitional zone, periurethral and anterior fibromuscular zone. Most cancers occur in the peripheral zone. Adenocarcinoma is the most frequent prostate cancer (1).

1.1.2. Clinical manifestations

Clinical manifestations are commonly absent in the initial stages. As the growth is slow, symptoms tend to appear in more advanced stages. When symptomatic, prostate cancer can present with nonspecific urinary symptoms, similar to those produced by Benign Prostate Hypertrophy (BPH). Some of the most important local symptoms are urgency, dysuria, hematuria, urinary frequency, urinary incontinence, urinary retention, urinary tract obstruction or urinary urgency (2).

1.1.3. Epidemiology of prostate cancer

Prostate cancer is ranked among the top five cancers regarding incidence and mortality, with important geographical variations, being particularly common in developed countries. Globally, it is the most commonly diagnosed cancer among men, with an estimated 1.6 million cases in 2015, and it ranks fifth regarding mortality, causing an estimated 366,000 deaths in 2015 (3). Prostate cancer is the most frequent cancer diagnosis in men in Europe and in Spain. In 2015 360.000 new cases were reported in Europe, and 33.370 in Spain. Spain shows similar incidence rates as those in Europe, with an age-standardized incidence rate of 110.8 in Europe and of 103.4 in Spain in 2012 (4).

The introduction in the 1990s of Prostate Specific Antigen (PSA) testing (**figure 1**) has caused an increase in the incidence of prostate cancer, with more men being

diagnosed at earlier stages and ages, with a lead time of 10 years before symptom onset. This would cause prostate cancer to be treated in earlier stages, which could explain the reduction in mortality. Its high incidence and long survival reflect on the fact that prostate cancer has the highest 5-year prevalence among all cancers (3).

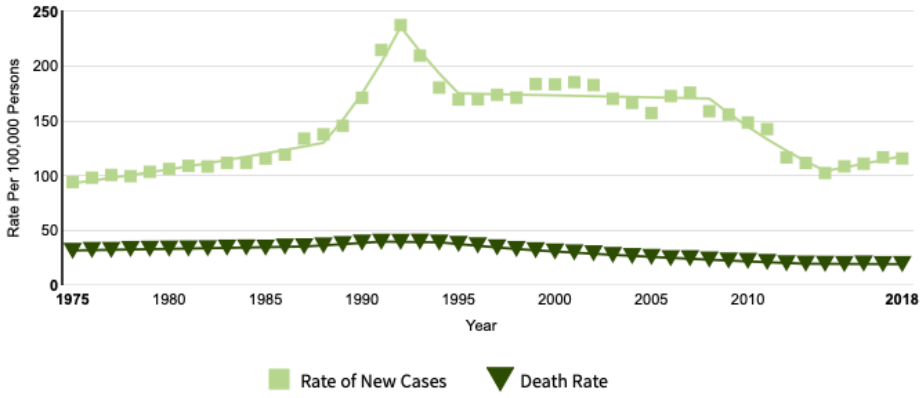

Figure 1. Changes over time in average annual age-adjusted incidence and mortality rates in the United States, 1975 to 2018. Reproduced from: Cancer Stat Facts: Prostate Cancer, Surveillance Epidemiology and End Results (SEER) Program, National Cancer Institute. Available at: https://seer.cancer.gov/statfacts/html/prost.html (Accessed on January 2021) n(5).

This increasing trend can also be observed in Spain, with great differences among regions (4). In our country, according to data from the International Agency for Research on Cancer (IARC), its standardized estimated incidence has evolved from 28.01 / 100,000 in 1993 to 70.22 / 100,000 in 2010, showing a clear ascending tendency (6). Its estimated 5-year prevalence was of 106,941 in Spain in 2018, the highest among men (7).

The evolution of prostate cancer is usually quite slow in time. Approximately 40% of men over 60 years of age present tumour foci in the prostate, yet possibly up to 95% of them will not die from this tumour (8). In Europe, in 2000-2007, the age-adjusted relative survival of cancer of prostate 5 years after diagnosis was 83.4%. The highest value was presented the countries of central and southern Europe (88.0% and 86.2%) and the lowest the countries of Eastern Europe (71.9%) (9). Spain presented a value of 84.6% (10). In 2018 prostate cancer accounted for 5,341 deaths in Spain, being the 3rd

cause of cancer death among men (7). The average age of death in Spain is 75 years (11).

Table 1. Epidemiological data for prostate cancer. Data obtained from Globocan 2020 [globocan.iarc.fr] (12).

	Number	Incidence	Prevalence (5 years)	Mortality
World	1 414 259	30.7	126.1	375 304 (7.7)
Europe	473 344	63.4	518.1	108 088 (11.1)
Spain	34 613	70.6	596.2	5798 (7.3)

***Prevalence and age-standardized incidence: per 100.000

Prostate cancer continues to rank first in incidence in the Basque Autonomous Community, representing 21.46% of cancer diagnoses among men. 20,519 new cases were reported between 2000 and 2012, with an average of 1,578 cases per year, and average age of diagnosis of 70 (13). As seen in other places, the incidence of prostate cancer has increased since the mid-90s, with an age-standardized incidence of 111.3 in 1976 and of 167.8 in 2013. In 2013, the prevalence was of 713.9. The mortality rate between 2013 and 2017 was of 35.9, being the 3rd cause of death from cancer among men (8.8% of cancer deaths). Mortality from prostate cancer has shown a declining tendency in the period 2001-2017, with an annual decrease of -1.6% (14).

As we can see in **Table 2**, age-standardized net survival decreased from 96.8% at 1 year of diagnosis up to 89.9% at the fifth year. Survival 5 years after diagnosis it was similar until 74 years of age and after this age it decreased significantly (13).

Table 2. Net survival rates at 1, 3 and 5 years in the Basque Autonomous Country 2000 – 2012. Adapted from: Gil L., Supervivencia de cáncer en la comunidad autónoma vasca. 2000-2012 (13).

	< 55 years		**55 – 64 years**		**65 – 74 years**		**≥75**		**Total***	
	(725 cases)		*(4504 cases)*		*(8813 cases)*		*(6071 cases)*		*(20113 cases)*	
YEAR	**NS%**	**CI 95%**	**NS%**	**CI 95%**	**NS%**	**CI 95%**	**NS%**	**CI 95%**	**NS%**	**CI 95%**
1	97.8	96.7-99.0	98.8	98.4-99.2	98.8	98.4-99.2	92.6	91.6-93.5	**96.8**	**96.4-97.2**
3	95.2	93.4-97.0	96.4	95.7-97.2	96.6	95.9-97.3	84.4	82.8-85.9	**92.8**	**92.1-93.4**
5	93.1	90.8-95.4	94.2	93.2-95.3	94.7	93.8-95.7	79.7	77.7-81.8	**89.9**	**89.1-90.8**

The risk factors involved in prostate are not well known, although age has proven to be the most important risk factor, prostate cancer being rare among men younger than

40, and increasingly common above 55. Other risk factors include African descent or family history (3,10).

1.1.4. Diagnostic evaluation

1.1.4.1.Screening and early detection

PSA screening is still nowadays a highly controversial issue. In the USA, PSA testing was introduced in the early 1990s for the general population, leading to a sharp increase in the diagnosis of localized prostate cancer, and a diminution of the age at the time of diagnosis. This resulted in a decrease in mortality, but also in overdiagnosis and overtreatment, raising doubts about this screening method (3,15).

In 2012, the US Preventive Services Task Force (UPSTF) issued a statement against non-selective PSA testing, adopted by the 2013 AUA guidelines. This resulted in a reduction in early detection, and in an increase in the incidence of advanced disease. A 6% increase of metastatic patients was observed, altogether with the increase of cancer-related mortality. In 2017 an updated statement by the USPSTF encouraged testing in previously informed men aged between 55 and 69 (16).

Screening is associated with an increased diagnosis of prostate cancer and detection in more localized stages, and a reduction of the risk for advanced-stage disease (10,11). It also increases the risk of overdiagnosis, defined as '*the detection by screening of a condition that would not have become clinically significant in the patient's lifetime*' (11).

Increased diagnosis can lead to over-treatment with associated side-effects, with men in early stages being treated with aggressive therapies. It needs to be taken into account that most men diagnosed with prostate cancer will die from other causes, especially older men, in whom overdiagnosis is higher (11).

The impact on the patient's overall health-related quality of life (HRQoL) is still unclear. At a population level screening has never been shown to be detrimental. The individualization of treatment is fundamental in order to decrease the risk of over-treatment (16).

Mortality rates have declined since the advent of PSA testing, which could be attributed to screening but also to the development of new treatments (10,17).

Systematic and opportunistic screening have been compared, the first one showing a higher mortality reduction as well as lower over-diagnosis rates (9). There is evidence suggesting the long-term benefit of PSA testing in the reduction of mortality The lack of survival difference seen in some studies could be explained by the fact that most men will die from other causes (18).

Two main studies have been carried on in order to examine the impact of screening: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC). The latter showed both a reduction in mortality and an increase of early detection, although the risk of overdiagnosis was also elevated (19). The absolute RR of mortality in the ERSPC study at 13 years was 1,28 per 1000 men (10).

According to the European Association of Urology (EAU), testing should be carried out in well-informed patients with a life-expectancy of 10 to 15 years. Men at high risk of cancer prostate include men >50 years or >45 years with family history or of African descent. Screening consists on a combination of PSA testing and Digital Rectal Examination (DRE), and it usually begins at 50 for the general population, and at 40-45 years for patients at high risk (11). A baseline PSA determination at 40 years has also been proposed, as PSA values above 1ng/mL at that age could increase the risk for future metastatic disease (16,19).

Interval recommendations vary in different guidelines, the optimal interval not being well known. A risk-adapted strategy based on the initial PSA level has been suggested (11).

Regular intervals of one to few years have shown a higher benefit (10), with most guidelines suggesting annual testing for those at risk and every two years for those not at risk initially (‘*initial PSA < 1 ng/mL at 40 years and a PSA < 2 ng/mL at 60 years of age and a negative family history’*) (11). Other guides suggest annual testing for those at risk, and a time period of even 8 to 10 years for those not at risk (16,20).

Life expectancy should be taken into account, with men having a life expectancy lower than 15 years being unlikely to benefit from a diagnosis (16). Screening is not recommended in individuals with a life expectancy of less than 10 years, or in men

older than 75 years with a baseline PSA ≤ 3 ng / ml, as they appear to have a very low risk of future metastatic disease (11,16).

Further examination is usually recommended with a PSA value of ≥ 4 ng/ml, and an abnormal DRE, although DRE is not recommended as a screening method (either alone or with PSA), due to its low sensitivity and specificity (11).

PSA is not specifical for cancer, and multiple causes can lead to an elevated PSA. These include BPH, acute prostatitis and some medications (such as such as 5-alpha-reductase inhibitors, NSAIDs, statins and thiazides) (30). PSA varies with age (11).

Table 3. Recommendations for screening and early detection. Source: EAU guidelines (16).

Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

1.1.4.2.Clinical diagnosis

Prostate cancer is suspected based on an abnormal DRE and high PSA levels, and definitive diagnosis relies on histological verification from the biopsy. A negative prostate biopsy cannot exclude prostate cancer (2,16).

Digital Rectal Examination (DRE)

Being mainly located in the peripheral zone, prostate cancer could be detected by DRE. An abnormal DRE indicated biopsy as it is linked to a higher-grade cancer (16). However, DRE bears a low sensitivity and sensibility, as it can only identify prostate cancer located in the posterior zone and in more advanced, voluminous stages (11).

Prostate Specific Antigen (PSA) determination

The PSA is a protein almost exclusively produced by the prostatic tissue. It can be measured in blood, and its increase can be secondary to several causes, as explained above (8). Higher levels of PSA mean a higher likelihood of prostate cancer (16).

Patients are usually referred to a urologist with PSA levels higher than 4 ng/ml. PSA can be repeated within some weeks to verify its increase (2).

Together with serum PSA levels, some other PSA-related parameters are measured. These include PSA density, PSA velocity and free/total PSA ratio (16,21). Higher values of PSA density suggest prostate cancer, whilst values lower than <0.15 ng/mL/cc are considered favorable (2,22). A higher PSA density indicates more likely a clinically significant prostate cancer (16). PSA velocity and PSA doubling time might have a prognostic role, but their diagnostic use is rather limited (16); PSA velocity that continues to rise is more likely to reflect prostate cancer (23). A lower percentage of free PSA is suggestive of cancer (16), with an f/t PSA lower than 10-15% being associated with cancer, and one higher than 25% being highly likely due to BPH (2).

Additional serum testing includes the Prostate Health Index (PHI) test, which combines f/t PSA, p2PSA and four kallikrein (4K). Prostate cancer gene 3 (PCA3) can be detected in urine (16). There is no clinical consensus regarding the clinical utility of these methods (2). The risk of prostate cancer in relation with PSA levels is exposed in **table 4** (16).

Table 4. Risk of prostate cancer in relation to low PSA levels. Source: EAU guidelines (16).

PSA level (ng/mL)	Risk of prostate cancer (%)	Risk of ISUP grade ≥ 2 prostate cancer (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

Biopsy

The decision to biopsy is taken based on multiple factors, such as the PSA levels, DRE and imaging (2,16,19). Other aspects that need to be taken into account are comorbidities and the impact on the patient's quality of life (19). PSA levels should be verified prior to biopsy (16).

Biopsy is usually carried out in patient with a life expectancy of 10 years or more and one of the following: '*PSA is elevated above the range for the patient's age cohort, or PSA has increased more than 0.75 ng/mL over one year, or there is a palpable concerning abnormality on DRE*' (2).

If prostate cancer is suspected in light of a negative biopsy, it can be repeated. Repeated biopsies can be carried out for active surveillance (24).

Regarding the biopsy technique, transrectal-ultrasound (TRUS) guided biopsy is usually chosen for the initial biopsy. There is increasing evidence that MRI-targeted biopsy shows a greater accuracy at detecting clinically significant disease than TRUS systematic biopsy (2,25,26), with studies proving the superiority of MRI-targeted biopsy for ISUP ≥2 disease (**table 5**). Compared to systematic biopsy, MRI-guided biopsy reduces detection of low-risk disease, decreasing overdiagnosis (16). Patients with a negative TRUS-guided biopsy in light of clinical suspicion of disease constitute the most accepted indication for MRI-targeted biopsy (24,27). A perineal approach is apparently associated with a lower risk of infection (2).

The Gleason grading system has classically been used to classify the primary tumour according to its anatomopathological features. The Gleason grade is based on the differentiation pattern of the sample. The Gleason score is created by combining the Gleason grades for the most prevalent histological differentiation patterns (a primary and a secondary grade) (28).

The International Society of Urological Pathology (ISUP) grading system was adopted in the 2014 ISUP consensus. It is based on the modified Gleason scores, and divides tumours into five categories. The objective of this new system is to improve the accuracy of risk stratification (28,29). The ISUP grade group classification system is displayed in **table 5** (16).

Table 5. International Society of Urological Pathology (ISUP) grade group classification system. Source: EAU guidelines (16).

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Magnetic resonance imaging (MRI)

MRI has proven to be a valuable tool both prior and following diagnosis of prostate cancer. Among the indications for MRI, we find the following: negative TRUS biopsy with clinically determined indication, prebiopsy MRI for clinically suspected disease, MRI-targeted biopsies, staging evaluation and risk stratification, selection of men for active surveillance, follow-up of men in active surveillance, and detection of local recurrence after radiotherapy (30,31). This expansion in the roles of MRI can be attributed to the standard approach offered by use of Prostate Imaging Reporting and Data System (PI-RADS) (**table 6**) (30). MRI is also a very accurate predictor of outcome (32).

A negative TRUS-guided biopsy in men with clinically determined indication for a biopsy is the most validated indication for MRI and MRI-guided biopsy (27). Men with persistently high levels of PSA and systematic negative biopsies can be diagnosed thanks to MRI (33). MRI can also serve as a guide for prostate biopsy. MRI can also identify tumours in regions not usually sampled by biopsy, such as the anterior zone (25).

MRI has proven to be a reliable tool for selecting patients for biopsy, as it offers a remarkable visualization of the lesions. The incorporation of prebiopsy MRI in the evaluation of a patient with clinically suspected prostate cancer has an improving effect on the diagnosis of clinically significant disease. It also reduces biopsy-derived side effects and minimizes the number of unnecessary biopsies. There is no current consensus on the selection for men undergoing MRI prior to initial TRUS biopsy (30).

MRI-directed prostate biopsy is more sensitive than TRUS-guided biopsy, as it increases the detection rate of clinically significant disease. This results in the reduction of diagnosis of non-significant disease (30). Prostate MRI and MRI-targeted prostate biopsy are helpful tools in the evaluation of prostate cancer risk stratification. (2,30).

According to EAU guidelines, two different diagnostic pathways exist for MRI-targeted biopsies: the combined pathway and the MRI pathway. In the latter, patients with a prebiopsy MRI undergo an MRI-targeted biopsy, and those with a negative MRI undergo no biopsy. This pathway could minimize the number of unnecessary biopsies, thus reducing the detection of low-risk disease, while maintaining the detection rate of clinically significant prostate cancer. Patients undergoing prebiopsy MRI could be selected based on their risk for prostate cancer, estimated with risk calculators. Prebiopsy must be used in selected patients with an indication for prostate biopsy, and not systematically (16).

T2-MRI imaging is the best method for staging the local extent of intermediate- and high-risk prostate cancer (16). Thanks to MRI the stage of the illness can be assessed, through the visualization of extracapsular disease or neurovascular involvement. The location and local extent can also be verified, as it is of great importance to assess the organ-confined status of the tumor when it comes to treatment decisions. As a matter of fact, an organ-confined tumor (≤T2c) can be distinguished from a locally extended one (≥T3a), which has an impact on the treatment decision (30). Tumor volume can also be measured thanks to MRI (16).

In men with very low and low-risk disease, MRI is often carried out in order to exclude the presence of high-grade disease, thus optimizing patient selection. Equally, men with localized disease treated with radiation therapy who experiment biochemical failure can have an MRI done in order to distinguish residual disease from metastasis (30).

MRI is increasingly being used for staging the local extent of prostate cancer. (7) PI-RADS was developed by The International Prostate MRI Working Group in order to standardize prostate MRI examination (34). This system assesses all focal

intraprostatic nodules seen on MRI, categorizing them into five groups based on the likelihood of cancer (**table 6**) (30).

Table 6. PI-RADS classification system. Source: UpToDate (30)

PI-RADS 1	Clinically significant cancer is highly unlikely to be present
PI-RADS 2	Clinically significant cancer is unlikely to be present
PI-RADS 3	The presence of clinically significant cancer is equivocal
PI-RADS 4	Clinically significant cancer is likely to be present
PI-RADS 5	Clinically significant cancer is highly likely to be present

MRI performed according to PI-RADS v2 criteria is highly sensitive and moderately specific for the detection of clinically significant illness (30).

Table 7. EAU guidelines for MRI in prostate cancer. Source: EAU guidelines (16).

Recommendations for all patients	Strength rating
Do not use multiparametric magnetic resonance imaging (mpMRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	Strong

Recommendations in biopsy naïve patients	Strength rating
Perform mpMRI before prostate biopsy.	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low, omit biopsy based on shared decision-making with the patient.	Weak

Recommendations in patients with prior negative biopsy	Strength rating
Perform mpMRI before prostate biopsy.	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared share decision-making with the patient.	Strong

1.1.5. Initial management and risk stratification

It is of great importance to accurately assess the presence of clinically significant prostate cancer, its extent, and its risk of future progression, in order to avoid unnecessarily overtreating men at low risk (30). The initial evaluation should include DRE, PSA levels, the Gleason score, and the extent of disease in the biopsy (35).

According to these criteria, men are stratified into risk categories that will be used in the selection of treatment. Several stratification systems are used nowadays. For

example, the European Society for Medical Oncology (ESMO) divides prostate cancer into three groups: low risk (T1-T2a and Gleason score ≤ 6 and PSA ≤ 10 ng/ml), intermediate risk (T2b and Gleason score 7 and/or PSA 10 to 20 ng/mL) and high risk (≥T2c or Gleason score 8 to 10 or PSA >20 ng/mL) (36). **Table 8** shows EAU guidelines for risk stratification (16).

Table 8. EAU guidelines for risk stratification. Source: EAU guidelines (16).

Low risk	Intermediate risk	High-risk	
PSA < 10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)
and cT1-2a	or cT2b	or cT2c	cT3-4 or cN+
	Localised		**Locally advanced**

Another risk stratification system is the one defined by the National Comprehensive Cancer Network (NCCN) (35), which stratifies primary tumors into six groups (see **Annex I**).

Imaging for the assessment of distant metastases is recommended for intermediate- and high-risk disease, altogether with bone imaging. Computed Tomography (CT) can be used in order to assess for the local, regional and distant extension of prostate cancer depending on the estimate of risk (35). As mentioned above, MRI has proven to be a useful tool for the purposes of correct risk stratification and for ensuring correct diagnosis of low-grade disease. It also improves biopsy targeting (30).

Once imaging is carried out, and staging is confirmed, initial treatment decisions will be taken based on definitive clinical staging (35).

The standard staging system (see **Annex II**) is that of the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC), which analyzes the local extent of the primary tumor (T), regional lymph node involvement (N) and distant metastatic disease (M). Patients are divided into prognostic categories (see **Annex III)** based on the Gleason score and PSA levels (35). Patients undergoing radical prostatectomy are assigned a pathologic (pTNM) stage group (37).

A cancer of clinical signification can be defined as '*a lesion that is predicted to have a grade group of 2 or higher* **(table 5)** *with either a volume ≥0,5ML or extraprostatic extension*' (30,37).

1.1.6. Treatment modalities

The treatment of prostate cancer is extremely individualized, with multiple factors that need to be taken into account. These factors include the following: age, life expectancy, preferences of the patient regarding the secondary effects, comorbidities and the prognostic category (7,35).

The different treatment modalities include surgery, external beam radiotherapy (EBRT), brachytherapy (BT), chemotherapy and hormonal therapy / androgen deprivation therapy (ADT) (7).

Individuals with localized tumours can benefit from RT with or without BT, BT alone, radical prostatectomy, or active surveillance (7,35). In order to benefit from local treatment, a life expectancy of at least 10 years is a common requirement (16).

Active surveillance is typically recommended for men with very low-risk prostate cancer and a life expectancy of at least 10 years (38,39). Close follow-up with periodical PSA testing and DRE is required (35). Active surveillance aims at avoiding overtreatment, and it has a curative intention, unlike watchful waiting (**table 9**) (16). In men with low-risk disease active surveillance can also be a suitable choice, with definitive therapy offered to men in risk of progression (35,38). The treatment options consist on radiation therapy and radical prostatectomy. No difference has been remarked related to survival rates. Radiation therapy can consist on external beam radiotherapy or brachytherapy either alone (in lower-degree tumours) or combined (in higher-degree tumours) (35). ADT for 6 months is recommended in addition to radiotherapy in men with intermediate-risk disease, and in patients with high-risk disease long-term (18 to 36 months) ADT is recommended combined with radiation therapy or prostatectomy (16,35).

Table 9. Definitions of active surveillance and watchful waiting. Source: EAU guidelines (16).

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers used	DRE, PSA, mpMRI, re-biopsy	Not pre-defined, but dependent on development of symptoms of progression
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Low-risk patients	Can apply to patients with all stages

Regarding locally advanced or very high-risk disease, treatment options include radical prostatectomy and radiation therapy (consisting on RT alone or RT + BT). Addition of long-term ADT is recommended. Metastases can be treated with chemotherapy (35).

Radical prostatectomy is indicated with the objective of eradicating cancer while maintaining pelvic function whenever possible (16). The technique has evolved thanks to robotic-assisted techniques, such as Da Vinci (35).

The field of radiation therapy has experienced remarkable advances with the development of new techniques, which include external beam radiation therapy (EBRT) techniques such intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), or brachytherapy (IGRT). Combination of IMRT and volumetric arc external-beam radiotherapy (VMAT) with IGRT allows the administration of a higher dose of radiation, reducing at the same time the dose received by adjacent organs (toxicity) (7,16).

This is of great importance as high doses of radiation are needed in order to obtain an optimal biochemical control and the optimization of cancer-specific survival rate in patients with localized prostate cancer. Dose escalation allows for an increase in local disease control and decrease in biochemical failure. This can be achieved through the delivery of 74-80Gy doses, but it is brachytherapy that undoubtedly provides the best conformal dose escalation (16,40).

Brachytherapy, another suitable radiation therapy option for localized prostate cancer, delivers selective dose escalation to the dominant intraprostatic lesion (DIL), which

can be effectively identified through MRI. Brachytherapy allows a better precision together with the delivery of much higher doses into the prostate, maximizing local control, as the DIL is the region where local recurrence most frequently occurs (40). Additionally, as it delivers less dose to adjacent organs such as the urethra, bladder and rectum, BT has less side-effects, such as incontinence and impotence (41,42). Two different BT modalities are available: low-dose (LDR) BT and high-dose (HDR) BT. LDR consists on the implementation of permanent radioactive seeds, and HDR uses empty needles as a temporary source of radiation directed into the prostate (16,42).

With HDR-BT being used as a boost prior to EBRT, disease-free survival is increased, local and biochemical control is improved, and cancer-specific mortality is reduced. Moreover, the combination of HDR brachytherapy with EBRT has proven to be a safe procedure with low GI and GU toxicity (41,43). Both the American Brachytherapy Society (44) and the European brachytherapy society GEC/ESTRO (45) guidelines recommend the use of EBRT in 3 – 5 weeks after HDR – BT. Additionally, ASCO/CCO guidelines (38) recommend the use of BT as a boost previous to EBRT for all eligible patients with intermediate- and high-risk prostate cancer.

In the Radiation Oncology department of Hospital Universitario Cruces the standard treatment for intermediate- and high-risk localized prostate cancer consists on the combination of Moderate Hypofractionated External Beam Radiotherapy / VMAT (37.5 Gy in 15 fractions) and HDR (15 Gy in a single fraction) (40).

ADT is normally used in combination with radiation therapy in patients with intermediate- and high-risk disease (35). The available methods consist on antiandrogens (peripherical blockage) and LHRH agonists (central blockage). LHRH agonists are used in the form of depot injections, and can lead to a clinical flare, which can be prevented by using antiandrogens prior to LHRH. This combination is known as complete androgen blockage (CAB) (16).

Radical prostatectomy and EBRT (combined with 6 months of ADT) were compared in a study. After a follow-up of 10 years, no difference was observed between radiotherapy and surgery regarding outcomes (46). Side effects for radical prostatectomy include incontinence and erectile disfunction. Some risks linked to surgery itself are deep venous thrombosis (DVP), infection, ileus, or organ injury (16).

Side effects for radiotherapy typically include gastrointestinal and urinary adverse effects, such as dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis (47). There is a higher incidence of acute toxicity, as most side-effects resolve over time (16). Prostatectomy has shown worse incontinence than any other option over five years, and worse sexual dysfunction than EBRT with ADT (48).

There is a current trend to shorten radiation therapy treatment times. Following this research line, in June 2019 a prospective phase II clinical trial investigating a novel radiation schedule for patients with intermediate and high-risk prostate cancer was set up in our radiation oncology department. This novel approach, consisting of the combination of single fraction 15Gy HDR and Stereotactic Ablative Radiotherapy (SABR) / Stereotactic Body Radiation Therapy (SBRT) (25Gy in 5 fractions), shortens the overall treatment time to 5 days. These two treatments differ in the number of fractions of radiotherapy, which is allowed by the implementation of SABR/SBRT, thus trying to be more efficient in the management of Localized Prostate Cancer and ameliorating the quality of life of patients (7).

1.2.VALUE-BASED HEALTHCARE

1.2.1. Definition of VBHC

Value is the result of dividing the outcomes experienced by the patient by the cost to achieve them (49,50). Value-based healthcare (VBHC) aims at delivering the best outcomes possible at the lowest cost, in order to increase the quality of healthcare and curb inefficiencies (49).

Outcomes are the results derived from treatment that patients really care about. These are not lab results or technical details (50). Outcomes include disease control (clinical outcomes), complications of treatment and quality of life. The latter is closely related to patient-reported outcomes (PROMS), which in the case of prostate cancer include include urinary incontinence, urinary obstruction, bowel irritation and sexual dysfunction (49,50). VHBC focuses on clinical outcomes, patient-reported outcomes (PROMS) and patient-reported experience (PREM) (51).

Nowadays, health care systems are focus their efforts into clinical indicators or reputation, but outcomes are systematically ignored (50). Outcome measures are inconsistently reported, which impairs population comparisons. Systematic outcome measurements through standardized tests can lead to improvement in health systems (51).

1.2.2. ICHOM (International Consortium for Health Outcomes Measurement)

ICHOM was founded in 2012 by Professor Michael Porter of Harvard Business School, Martin Ingvar of the Karolinska Institute and the Boston Consulting Group. As defined by the organisation, '*ICHOM's mission is to unlock the potential of value-based health care by defining global Standard Sets of outcome measures that really matter to patients (PROMs) for the most relevant medical conditions and by driving adoption and reporting of these measures worldwide'* (50).

ICHOM methodology was implemented in 2017 in Cruces University Hospital for all patients undergoing definitive treatment for prostate cancer. ICHOM methodology, through the implementation of standardized tests, enables the evaluation and comparison of different treatment modalities assessing PROMS and clinical outcomes (49,51).

1.3. GENERAL OVERVIEW OF THE PROYECT

The current standard of care for intermediate and high-risk disease localized prostate cancer in the Radiation Oncology department consists on the combination of HDR brachytherapy and moderate hypofractionated EBRT (dose of 37.5Gy in 15 fractions). In June 2019, a prospective phase II clinical trial investigating a novel radiation schedule for these patients was set up.

This novel approach, consisting of the combination of HDR and SABR, shortens the overall treatment time from 21 days to 5 days. By these means, cost per patient is decreased. The purpose is to show that cancer control is maintained or even increased, and that the quality of life of patients is improved. Thus, by improving outcomes and minimizing costs, the value of this treatment would be superior.

BT-HDR and SABR are nowadays considered to be the best radiation techniques for localized prostate cancer in terms of conformality and precision. Moreover, the combination of brachytherapy and external radiotherapy has proven to be the treatment with most optimal local and biochemical disease control. In the phase II study, the best technique for brachytherapy (HDR-BT) and the best external radiation technique (SABR) were combined.

In this study VHBC-ICHOM methodology will be used in order to evaluate this novel treatment protocol. The tolerance, toxicity, quality of life, costs and clinical outcomes of both protocols will be analysed according to the ICHOM Standardized Set for Localized Prostate Cancer. These standardized, impartial tests enable the comparison of treatment at a global level, with outcomes that are meaningful to patients being measured.

Data from the patients undergoing this novel treatment schedule will be recorded in a database and analyzed. The prospective implementation of ICHOM methodology will allow us to evaluate the toxicity, functionality and survival results of this treatment. In a longer term a comparison will be held between this treatment protocol and the standard protocol in order to see which one holds better results. If the results of our phase II trial are positive, a randomized phase III trial will be set up involving more patients and different hospitals.

2. HYPOTHESIS AND OBJECTIVES

2.1. HYPOTHESIS

The hypothesis of this study is that the combined treatment of HDR and SABR is a safe and well-tolerated treatment, with and incidence and prevalence of secondary effects similar to those produced by the standard treatment of HDR and hypofractionated RTE (37.5 Gy in 15 fractions) (7).

2.2. OBJECTIVES

- This study is based on a phase II prospective clinical trial investigating a novel radiation schedule for patients with intermediate- and high-risk prostate cancer. The main objective of the clinical trial is to assess the safety of this new

treatment by measuring parameters linked to toxicity, tolerance and quality of life (20).

- To use VBHC-ICHOM methodology to decide whether a novel treatment can substitute the standard of care in our department

3. MATERIAL AND METHODS

3.1. DESCRIPTION OF THE SAMPLE

54 patients have been treated according to an institutional review board-approved prospective study of combined HDR-brachytherapy and SABR. Eligibility criteria are exposed in **table 10**. Patients were free to remove themselves from the study at any time. Treatment would be suspended in the light of adverse criteria that justified it.

Table 10. Patient eligibility criteria.

Inclusion criteria	Exclusion criteria
Histological confirmation of prostate adenocarcinoma Intermediate*- or high**-risk prostate cancer Life expectancy of ≥ 10 years Eastern Cooperative Oncology Group (ECOG) functional state of 0-2 The subject has been informed and given sufficient time and opportunity to consider his participation and has provided his written informed consent. The subject is willing and able to meet all study requirements.	Contraindication for interstitial prostate brachytherapy Clinical stage of T3 or T4 in which the distance of extracapsular extension doesn't allow for an optimal dosimetric cover through brachytherapy. Similarly, those patients with a T3b clinical stage and a tumoral infiltration of the seminal vesicles of more than 2 cm will be excluded. Prostate volume in MRI of ≥70 IPSS >17 PSA > 50 ng/mL Patients on antiplatelet or anticoagulant treatment in whom treatment can NOT be safely stopped for a minimum of 7 days. Patients not apt for general or epidural anaesthesia. Any unstable medical or psychiatric process or substance abuse that, the opinion of the researcher, could affect the patient's ability to complete the study or prevent his participation.

*Intermediate-risk prostate cancer criteria: ≤T2c / Gleason = 7 and iPSA ≤20ng/ml / Gleason ≤6 and iPSA between 10 and 20 ng/ml.

**High-risk cancer criteria: T3a-b / Gleason score 8-10 / PSA >20 ng/ml.

In the Radiation Oncology department in Cruces University Hospital, several treatments are available for patients with intermediate- and high-risk prostate cancer.

Only those patients eligible for the treatment consisting on a combination of EBRT for 3-4 weeks with HDR BT were included in the clinical trial.

3.2. DESCRIPTION OF THE PROCEDURE

Patients diagnosed from localized intermediate- or high-risk prostate cancer were sent to Radiation Oncology. The following exams had already been carried out (if not, they were carried out by the Radiation Oncology department): TRUS guided biopsy, CT, MRI, blood analysis including PSA. MRI was used as a confirming tool for the local extension and localization of the tumour. Patient eligibility was based on the MRI results evaluated by two specialists in uroradiology and according to the aforementioned inclusion and exclusion criteria.

Selected patients were evaluated at a baseline visit, after which a preoperatory evaluation, and were then treated with HDR BT. Once this was done, SABR treatment was planned through CT. Between 2 and 4 weeks after HDR BT the 5 fractions of SABR were applied in a period of 1 week.

3.3. TREATMENT

3.3.1 High-dose-radiation Brachytherapy

As mentioned above, brachytherapy allows for a better precision and the delivery of much higher doses into the prostate, while having less side-effects. Patients in this study were treated with HDR BT in a single fraction of 15 Gy, as a ‘boost’ prior to SABR. This was allowed through the implementation of needles right into the prostate.

Under general or epidural anaesthesia, the patient was placed in dorsal lithotomy position dorsal. The urethra was identified by inserting a three-way Foley catheter that allows visualization on ultrasound. A TRUS of the prostate was then performed. Using the TRUS, a set of continuous images was acquired using the longitudinal mode for 3D reconstruction of the prostate in order to plan the BT-HDR 15Gy.

The pre-implantation Clinical Target Volume (CTV) was outlined on this set of images: the entire prostate, and the adjacent organs at risk (OR) (urethra and rectum). In patients with a visible intraprostatic dominant nodule, this Gross Tumour Volume GTV could be transferred from the planification study (MRI).

Once the different volumes, the target volume and the ORs had been identified a virtual treatment plan was carried out, in which the number of needles, the arrangement and the depth of these were defined. The placement of the needles was chosen based on the volume and prostate morphology.

The insertion of the stainless-steel needles was carried out in real time under the guidance of the TRUS image. Once all the needles were correctly inserted and the tips identified in 3D on ultrasound, a second set of continuous ultrasound images of the prostate was obtained. The prostate was contoured, and the path of the needles identified.

The real corrected position of the needles was used for optimization. A Radiophysicist generated an optimized plan satisfactory in terms of dosimetric coverage. All plans were approved by both the Oncologist radiotherapist in charge and the Radiophysicist.

The homogeneity parameters used for dose optimization aim for prostate V100 >98%, V125 of <60%, V150 of <35%, and V200 <8%, where Vn is the fractional volume of the organ that receives n% of the prescribed dose; maximum point dose inside the urethral volume (urethral Dmax) <115%; and the dose to 1 cc of rectal wall (RD1 cc) was limited to <70% of the prescribed dose. A deviation of up to 2% from these constraints was considered acceptable.

In order to assure the correct performance of the procedure and subsequent treatment, the patient remained under general anesthesia in the dorsal lithotomy position in the operating room until the treatment plan was ready.

Once the needles had been introduced and the experimental treatment optimized, the transfer tubes were connected to each needle and treatment was administered according to the permanence times determined in the optimized plan. The treatment is completed in approximately 15 to 30 minutes.

Upon completion of treatment, 3 gold fiducial markers were inserted into the prostate transperineally, and the Foley catheter and all needles were removed. The patient was transferred to the Post-Anesthesia Care Unit (UCSI). The patients were discharged according to the protocol once an adequate recovery from anesthesia and spontaneous urination were achieved. Those patients not achieving a spontaneous urination in the

UCSI, could be discharged with a urinary catheter that would be removed the next morning.

In case the patient was not apt for treatment, it would be considered as a screening failure, and exclusive EBRT would be administered, either 60Gy in 20 fractions or 70Gy in 28 fractions.

3.3.2 Stereotactic Ablation Radiation Therapy

SABR is a novel radiation technique that allows the administration of elevated doses of radiation in few fractions. Through the use of lineal accelerators dosimetric values similar to those obtained by brachytherapy can be achieved. The implementation of this technique is allowed by important advances in the field of radiation oncology, such as Intensity-Modulation Radiation Techniques (IMRT) and Image-guided Radiation Techniques (IGRT). More adjusted treatment volumes can be defined, thus reducing the dose administered to surrounding healthy tissues. Total treatment time is significantly reduced.

Once the BT HDR treatment was finished, the EBRT treatment was planned according to the standard in the Radiation Oncology department, based on CT simulation with slices of 1 millimeter. The CTV was be the prostate exclusively in patients with intermediate favorable risk, and the prostate + seminal vesicles in patients with intermediate-unfavorable risk or high-risk disease. The OR to be contoured were the rectum, the vesicle, the penile bulb and the femoral heads.

The coverage limits and the limiting doses to the OR were:

PTV coverage: minimum dose 95% of the prescribed dose, maximum dose 107% of the prescribed dose. At least 95% of the PTV should receive 95% of the prescribed dose and not more than 1% of the PTV should receive 107% of the prescribed dose.

Rectum: V22 <20%, V19.3 <35%, V16 <50%. Bladder: V19.3 <35%

The PTV is the CTV plus a 5mm margin in all directions except posteriorly where it will be of 2 mm. The treatment was administered through a linear accelerator (LINAC) equipped with multilayer, with mega-voltage energy (6 MV), VMAT technique, with Cone-Beam CT performed prior to each treatment and fusion of fiducial, realization

of intra-fraction image control by “Auto Beam Hold” (system that allows the monitoring of prostate movement during treatment establishing tolerance limits and allowing irradiation to be stopped if these are exceeded limits) with fractions of 5 Gy.

The patients were instructed on how to have a full but comfortable bladder and an empty rectum for each treatment.

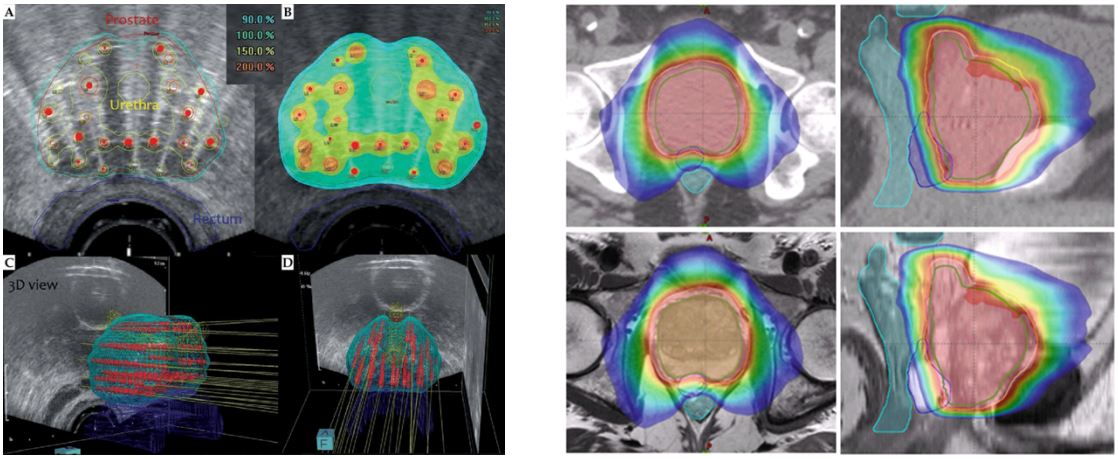

Figure 2. CT simulation for HDR brachytherapy and SABR.

3.3.3. Hormonal treatment

Additionally, androgen deprivation therapy was administered according to risk stratification: </= 6 months for IR and > 12 months and <24 months for HR and VHR. This included antiandrogens (peripherical blockage) and LHRH agonists (central blockage).

3.4. FOLLOW-UP

A baseline visit was scheduled before the treatment, aiming at knowing the basal situation of the patient. 48 hours after the BT-HDR, patients were monitored for tolerance, symptoms derived from the treatment and the presence of acute urinary retention. At the end of the combined treatment (last day of SABR), the patients were

evaluated for gastrointestinal and genitourinary tolerance, and follow-up visits were scheduled at 1, 3, 6, 12 months and every 6 months thereafter.

The patients were monitored prospectively for toxicity and Health-Related Quality of Life (HRQoL). Acute tolerance was described in terms of the incidence of episodes of acute urinary retention in the first 48 h after the procedure and changes in the International Prostatic Symptoms Score (IPSS) from baseline. Acute toxicity was assessed in terms of the incidence and severity of genitourinary (GU) and gastrointestinal (GI) adverse events from 48 h until 3 months after the procedure. Toxicity occurring after the third month was considered chronic.

Both toxicity and HRQoL were measured at baseline, 1, 3, 6, 12 months and from then on every year. The IPSS was also completed by the patients at baseline and at each visit. PSA was quantified at each follow-up visit.

3.5. MEASUREMENT

The impact in the patients' quality of life was evaluated in genitourinary, gastrointestinal, sexual and hormonal grounds. These outcomes were measured using the ICHOM standard test for localized cancer. This standard test assesses for parameters: acute complications, patient-reported health status, survival and disease control, and costs. These sets include initial conditions and risk factors to enable meaningful case-mix adjustment globally.

Acute and chronic toxicity derived from treatment was monitored using the Common Terminology Criteria for Adverse Events (CTCAE) scale, version 5.0 (52). HRQoL was assessed by measuring patient-reported outcomes, which included urinary incontinence, frequency, obstruction and irritation, bowel irritation, sexual dysfunction and vitality. Expanded Prostate Cancer Index Composite (EPIC) (53) and EORTC QLQ-PR25 (54) questionnaires were completed by patients in order to assess PROMS.

Survival and disease control parameters included overall survival, metastasis, cause-specific survival and biochemical recurrence. PSA was monitored in order to assess them.

Biochemical failure was defined using the nadir plus 2ng/mL definition, and cDFS event was defined as clinical evidence of disease by any clinical, pathological or radiological method.

During treatment, patients were clinically evaluated weekly and at 1 and 3 months thereafter. Follow-up visits with PSA measurement were scheduled 3-6-monthly during the first year and 6-monthly thereafter".

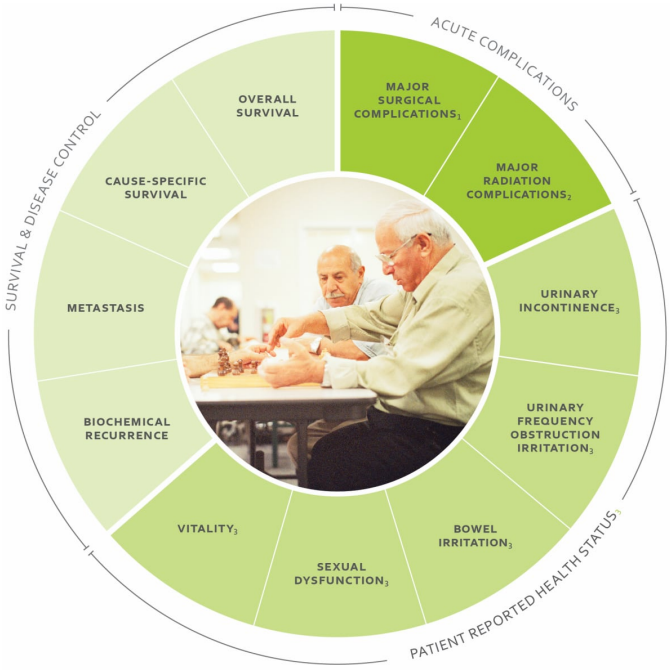

Figure 3. ICHOM Standard Set for Localized Prostate Cancer. The parameters analyzed through this standard set include: survival and disease control, acute complications, and patient reported health status. Reproduced from: ICHOM Connect (55).

3.6. STATISTICS

A clinically significant decrement was considered an EPIC score decrease greater than one-half of the standard deviation (SD) of the baseline value for each domain. The protocol was approved by the Institutional Review Board of the hospital. Descriptive statistics were calculated (medians and ranges) to summarize the clinical and pathological characteristics of the patients. Complete data were available for all

parameters included. All analyses were conducted using IBM SPSS Statistics. p-Value <0.05 was considered statistically significant.

4. RESULTS

4.1.DESCRIPTION OF THE SAMPLE

At the time of the current analysis 51 consecutive patients with intermediate/high-risk localized prostate cancer have completed the treatment, with a median follow – up of 10 months. The median age was of 75 years (range 30-79), the median baseline IPSS 4 (0-19). Median PSA before treatment was 7.1 ng/mL (3.8-110 ng/mL) and median volume of the prostate was 33 cc (16-70 cc). 34.6% of the patients had favourable intermediate-risk disease, 17.3% had unfavourable IR, 34.6% high-risk and 13.5% very high-risk.

Short-term ADT was administered to 21.2% of patients whereas 42% received long-term ADT, the rest of the patients did not receive hormonal therapy.

Table 11. Clinical and tumor characteristics.

Characteristics	Category	N	Percentage (%)
Clinical stage	T1c	25	48.07
	T2a	7	13.46
	T2b	3	5.77
	T2c	9	17.3
	T3a	3	5.77
	Missing	5	9.61
MRI stage	Tx	2	3.87
	T1a	11	21.15
	T1b	4	7.7
	T1c	10	19.23
	T2a	19	36,54
	T2b	1	1.92
	Missing	5	9.61
ISUP score	1	10	19.23
	2	24	46.15
	3	8	15.38
	4	8	15.38
	5	2	3.85
Risk group (MRI)	Intermediate favorable	18	34.6
	Intermediate unfavorable	9	17.3
	High	18	34.6
	Very high	7	13.5

	Median	*Range*
Age (years)	72	30 – 79
PSA (ng/mL)	12.63	3.8 – 110
IPSS score	5	0 – 19
Volume in MRI (cc)	37.31	16 – 70
Volume in TRUS (cc)	32.97	14 – 73

4.2.TOXICITY

48 hours after administration of brachytherapy acute tolerance was measured. Four patients suffered from acute retention, 22 patients had hematuria, and 23 patients had other toxicities, which consisted mostly on dysuria.

Toxicity was measured at the end of the combined treatment; Twenty patients had GU toxicity at this moment, mostly dysuria and nocturia. Only 2 patients developed GI toxicity, consisting on proctitis.

Regarding toxicity at follow-up visits, no severe (i.e. G3-4) acute or chronic events were recorded. The maximal reported acute and late toxicity was of Grade 2 for GU events and Grade 1 for GI events. The proportion of patients reported to have toxicity at each visit is listed in **Table 12**, and the acute and chronic GU and GI toxicity results are listed in **Table 13** and **Table 14**.

A majority of patients had no acute (G0) GU or GI symptoms, with cumulative incidences of 59.61% and 92.3% respectively. 15 patients had acute G2 GU toxicity (28.85%), and 5 had acute G1 GU toxicity (9.62%). Only 2 patients (3.85%) had G1 GI symptoms, and none had G2 GI symptoms. The most common acute GU symptom was dysuria whereas the most common acute GI event was proctitis.

Thirty-seven patients reached a follow-up ≥ 6 months and were eligible for chronic toxicity analysis. Among these, only 4 patients had late G2 GU toxicity (7.7%), and 13 had late G1 GU toxicity (25%). No late G2 GI event was observed, and only 2 patients had G1 chronic GI symptoms. The most common late GU symptom was nocturia.

Table 12. Toxicity results at each follow-up visit.

		Grade 0	*Grade 1* *N (%)*	*Grade 2* *N (%)*	*Lost*
Genitourinary	1 month	32 (61.53%)	13 (25%)	5 (9.62%)	2 (3.85%)
	3 months	20 (38.46%)	10 (19.23%)	2 (3.85%)	20 (38.46%)
	6 months	20 (38.46%)	12 (23.07%)	3 (5.77%)	17 (32.7%)
	12 months	10 (19.23%)	6 (11.54%)	3 (5.77%)	33 (63.46%)
Gastrointestinal	1 month	48 (92.3%)	2 (3.85%)	0	2 (3.85%)
	3 months	31 (59.61%)	1 (1.92%)	0	20 (38.46%)
	6 months	34 (65.38%)	1 (1.92%)	0	17 (32.7%)
	12 months	18 (34.61%)	1 (1.92%)	0	33 (63.46%)

Table 13. Acute and chronic genitourinary toxicity results.

	Acute (at 1 and 3 months)	Chronic (6 and 12 months)
0	31 (59.61%)	20 (38.46%)
1	5 (9.62%)	13 (25%)
2	15 (28.85%)	4 (7.7%)
Missing	1 (1.92%)	15 (28.85%)

Table 14. Acute and chronic gastrointestinal toxicity results.

	Acute (at 1 and 3 months)	Chronic
0	48 (92.3%)	35 (67.3%)
1	2 (3.85%)	2 (3.85%)
2	0	0
Missing	1 (1.92%)	14 (28.85%)

4.3.HEALTH-RELATED QUALITY OF LIFE

In terms of HRQoL, no significant decline in patient QoL was observed in any studied domain. Mean values in the EPIC questionnaires for all the studied domains are displayed in **Table 15**.

Table 15. Mean and standard deviation in the EPIC-26 questionnaire for each EPIC domain in each visit.

	Urinary incontinence		Urinary irritation		Bowel irritation		Vitality		Sexual disfunction	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	94.11	10.17	89.11	11.89	96.66	3.96	83.05	13.95	25.5	12.04
1 month	86.04	22.64	84.04	20.95	91.47	12.16	85.45	17.45	28.2	16.33
6 months	95.58	8.29	96.05	6.14	96.03	6.90	92.14	10.55	32.88	26.33
12 months	98.7	2.89	99.00	3.16	100.0	0.0	93.0	10.59	35.66	28.53

A non-statistically significant decline between months 1 and 3 was observed in the following EPIC domains: urinary incontinence (p = 0.129), urinary irritative (p = 0.091), and bowel irritative (p = 0.141). Mean values for all domains returned to baseline by month 12, as shown in **Figure 4**.

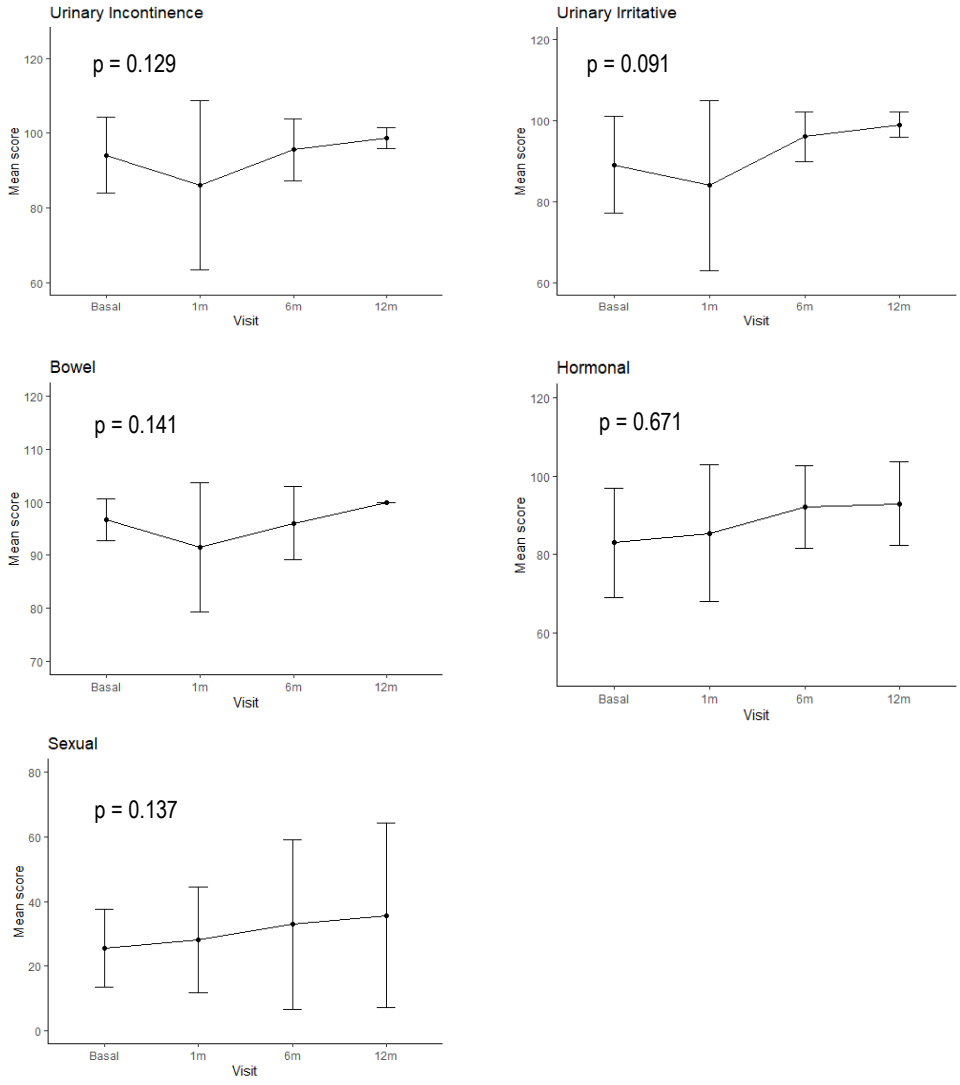

Figure 4. Health-related quality of life in all EPIC domains. Health-related quality of life was recorded using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. EPIC domains: urinary incontinence, urinary irritative/obstructive, bowel, sexual and hormonal.

4.4.SURVIVAL AND DISEASE CONTROL

In terms of survival and disease control, all patients presented a decline of PSA over time. As shown in **Figure 2**, the median PSA values at 1, 3, 6 and 12 months were 1.38 ng/mL (range 0.0 – 5.58 ng/mL), 0.74 ng/mL (range 0.01 – 8.13 ng/mL), 0.66 ng/mL (range 0.01 – 5.81ng/mL) and 0.37 ng/mL (range 0.01 – 1.91ng/mL).

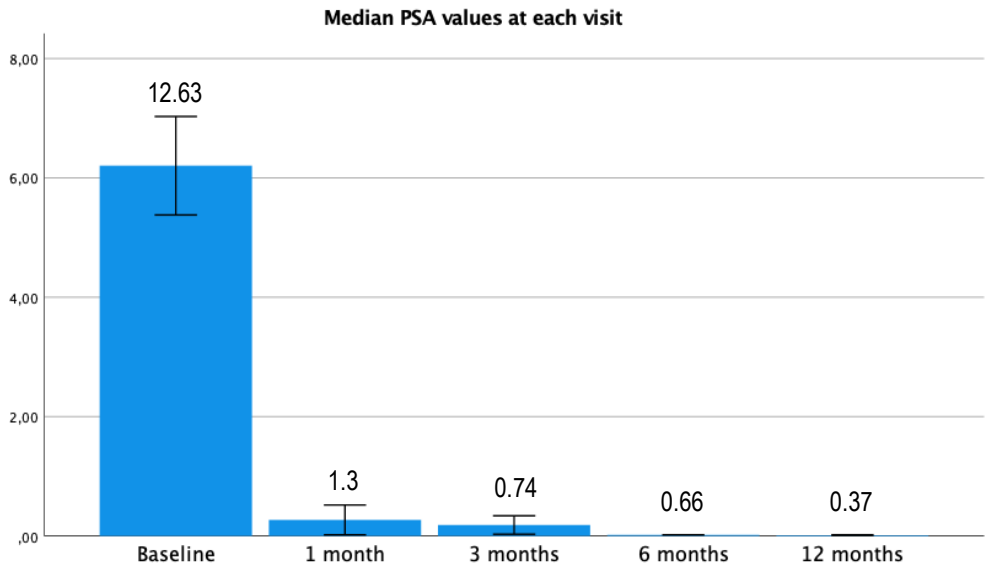

Figure 5. Evolution of PSA values at each visit.

5. DISCUSSION

In June 2019 a prospective phase II clinical trial investigating a novel radiation schedule for patients with intermediate and high-risk prostate cancer was set up in the Radiation Oncology department in Hospital Universitario Cruces. This novel approach, consisting of the combination of single fraction 15Gy HDR and SABR (25Gy in 5 daily fractions), shortens the overall treatment time to 6 days through the implementation of SABR (7).

This novel approach is a feasible, safe, effective and well-tolerated scheme without severe adverse events observed in the phase II clinical trial. Moreover, the majority of patients did not suffer from any adverse event. Patient reported outcomes (PROMS)

confirm these results, as no significant decline from baseline values could be found in any domain.

The combination of single-fraction 15Gy HDR-BT and EBRT is considered to be one of the most effective radiotherapeutic interventions for the treatment of localized prostate cancer. It has also proven to be a safe procedure with optimal local and biochemical disease control in previous studies (41,43). Nowadays, when it comes to radiation techniques, two aspects are considered to be essential: dose escalation (16,40) and hypofractionation (56). Both aspects were combined in this phase II trial, with HDR-BT used as a boost previous to hypofractionated radiation therapy (SABR). Both procedures are considered to be the best radiation techniques nowadays when it comes to conformality and precision.

There is a current interest in searching hypofractionated, shorter treatment times, which causes cost to decrease and patient quality of life to increase/maintain, while maintaining disease control. SABR is a very interesting treatment option, as it allows for the application of a lower number of fractions of radiotherapy (41,56). This is one of the first studies to demonstrate that the combination of SABR and HDR-BT is a safe and well-tolerated procedure.

SABR is a novel radiation technique that allows the administration of elevated doses of radiation in few fractions. Through the use of lineal accelerators dosimetric values similar to those obtained by brachytherapy can be achieved. The implementation of this technique is allowed by important advances in the field of radiation oncology, such as Intensity-Modulation Radiation Techniques (IMRT) and Image-guided Radiation Techniques (IGRT). More adjusted treatment volumes can be defined, thus reducing the dose administered to surrounding healthy tissues. Total treatment time is significantly reduced (7).

The combination of brachytherapy and SBRT has been studied by few institutions, and to date very few articles have been published on the subject. One of the first studies was published in 2018 by Charas et al. (61). High risk, node negative patients were treated with LDR-BT followed by conventionally fractionated EBRT (19 patients) or SBRT (87 patients). Early toxicity and tumour control outcomes were then compared between both groups. The SBRT cohort was treated to 25Gy in 5 fractions, and the

EBRT cohort to 45Gy in 1.8Gy fractions. Toxicity outcomes were similar in both groups, although late GI G1 toxicity was lower in the SBRT group (15% vs. 66%, p<0,01). No severe (G3-4) adverse events were noted in either group. Tumour control outcomes appeared to be similar as well, with a median follow-up of 17.1 months for the SBRT group vs. 24.6 months for the CFRT group (57).

Another study is the one published in 2020 by Den et al. (41). In this study, the safety and feasibility of an approach consisting on the delivery of HDR-BT with SBRT for men with intermediate-risk localized prostate cancer were determined. A total number of thirty-nine men were treated and divided into SBRT dose cohorts of 10, 7 and 5 fractions. Patients were monitored for safety (via evaluation of toxicity using the CTCAE v.4 scale), efficacy (by measuring PSA), and HRQoL (through the EPIC questionnaire). With a median follow-up of 36 months, the biochemical disease-free survival rate was of 95.5%, thus suggesting promising efficacy. Toxicity rates were comparable to those previously reported with conventional approaches. Regarding HRQoL, PROMS were collected via the EPIC questionnaire, and no clinically significant differences were noted in any of the three domains (urinary, bowel, sexual) from baseline. One acute G3 GU adverse event was noted, whilst no acute G3 GI events or late G3 events occurred (41).

Following this research line, there are some clinical trials investigating the combination of HDR-BT and SBRT. One of them is the phase I clinical trial conducted by the Sidney Kimmel Cancer Center at Thomas Jefferson University (66). In this clinical trial, patients with intermediate risk localized prostate cancer are treated with HDR-BT followed by SBRT. The purpose of this study is to determine the safety of brachytherapy when combined with hypofractionated SBRT (58).

Thus, previous data suggests that the combination of BT and SBRT for localized prostate cancer may be a safe, efficient procedure with low toxicity, which is also suggested by preliminary data from our phase II clinical trial. However, longer follow-up is needed in order to obtain more robust results.

Apart from the combination of two novel techniques for the treatment of localized prostate cancer, another remarkable aspect in this study is the implementation of ICHOM methodology for the evaluation of a novel treatment protocol. A future long-

term follow-up of all ICHOM dimensions will enable the comparison between this treatment protocol and the standard protocol in our institution.

6. CONCLUSIONS

- The combination of 15Gy HDR prostate brachytherapy and prostate SBRT (25 Gy in 5 daily fractions) is safe based on parameters linked to toxicity and tolerance. It is a well – tolerated scheme without severe adverse events observed in our prospective phase II trial. The majority of patients did not suffer any adverse events, and no significant decline could be found in any HRQoL domain from baseline values.
- Longer follow-up is needed in order to decide whether this treatment can substitute the previous standard of care.

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ANNEX I: NCCN RISK STRATIFICATION SYSTEM FOR LOCALIZED PROSTATE CANCER

Risk group	Clinical / pathological features
Very low	• T1c AND • Grade group 1 AND • PSA < 10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density < 0.15ng/mL
Low	• T1 to T2a AND • Grade group 1 AND • PSA <10ng/mL AND • Does not qualify for very low risk
Favorable intermediate	• No high- or very high-risk features • No more than one intermediate risk factor: o T2b to T2c OR o Grade group 2 or 3 o PSA 10 to 20 ng/mL AND • Grade group 1 or 2 AND • Percentage of positive biopsy cores <50%
Unfavorable intermediate	• No high- or very high-risk features • Two or three of the intermediate risk factors: o T2b to T2c o Grade group 2 or 3 o PSA 10 to 20 ng/mL AND/OR • Grade group 3 AND/OR • Percentage of positive biopsy cores ≥50%
High	• No very high-risk features AND • T3a OR • Grade group 4 or 5 OR • PSA >20 ng/mL
Very high	• T3b to T4 OR • Primary Gleason pattern 5 OR • Two or three high-risk features OR • >4 cores with Grade group 4 or 5

NCCN: National Cancer Comprehensive Network.
Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®): Prostate Cancer. Version 4.2018 (35).

ANNEX II: TUMOR NODE METASTASIS STAGING SYSTEM

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Source: EAU guidelines (16).

ANNEX III: AJCC/UICC TNM STAGING SYSTEM

When T is…	And N is…	And M is…	And PSA is…	And Grade Group is…	Then the stage group is…
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	<20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

In case PSA or Grade Group were not available, grouping should be determined by T category and/or either PSA or Grade Group as available. TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

Source: AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing (37).

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