UNIVERSIDAD CATÓLICA DE VALENCIA
"SAN VICENTE MÁRTIR"

HIGH-DOSE-RATE BRACHYTHERAPY BOOST IN PROSTATE CANCER: CLINICAL OUTCOMES, LATE RECTAL TOXICITY AND UNCERTAINTIES IN ORGAN AT RISK DELINEATION

Doctoral Thesis

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LIST OF ABBREVIATIONS AND ACRONYMS

ABS	American Brachytherapy Society
AJCC	American Joint Committee on Cancer
bDFS	Biochemical disease-free survival
BRFS	Biochemical relapse-free survival
COV	Coefficient of variation
^{60}Co	Cobalt 60
CT	Computed tomography
CTV	Clinical target volume
$D_{0.1cc}$	The minimum dose received by the most exposed 0.1 cm^3 volume of the rectum
D_{1cc}	The minimum dose received by the most exposed 1.0 cm^3 volume of the rectum
D_{2cc}	The minimum dose received by the most exposed 2.0 cm^3 volume of the rectum
D_{5cc}	The minimum dose received by the most exposed 5.0 cm^3 volume of the rectum
D_{10cc}	The minimum dose received by the most exposed 10.0 cm^3 volume of the rectum
D_{10}	Dose covering 10% of the clinical target volume
D_{30}	Dose covering 30% of the clinical target volume
D_{90}	Dose covering 90% of the clinical target volume
D_{100}	Dose covering 100% of the clinical target volume
DVH	Dose-volume histogram
EAU	European Association of Urology

EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EQD_2	Biologically equivalent rectal dose
ESTRO	European Society for Radiotherapy and Oncology
GEC	Groupe Européen de Curiethérapie
GI	Gastrointestinal
GS	Gleason score
GU	Genitourinary
HDRBT	High-dose-rate brachytherapy
HIFU	High-Intensity Focused Ultrasound
^{192}I	Iridium 192
IOV	Interobserver variability
LDRBT	Low-dose-rate brachytherapy
LRT	Late rectal toxicity
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OAR	Organ at risk
PSA	Prostate serum antigen
PSAD	Prostate-specific antigen density
PTV	Planning target volume
SD	Standard deviation
TNM	The TNM classification of Malignant Tumours
TRUS	Trans-rectal ultrasonography
TURP	Transurethral resection of the prostate
UICC	International Union Against Cancer

US	Ultrasound
V_{75}	Volume receiving 75% of the prescribed dose
V_{80}	Volume receiving 80% of the prescribed dose
V_{100}	Volume receiving 100% of the prescribed dose
V_{125}	Volume receiving 125% of the prescribed dose
V_{150}	Volume receiving 150% of the prescribed dose
V_{200}	Volume receiving 200% of the prescribed dose

LIST OF PUBLICATIONS

PUBLISHED ARTICLES:

[1] **Chicas-Sett R**, Celada-Alvarez F, Roldan S et al. Interobserver variability in rectum contouring in high-dose-rate brachytherapy for prostate cancer: A multi-institutional prospective analysis. *Brachytherapy 2017*; doi: 10.1016/j.brachy.2017.09.015

[2] **Chicas-Sett R**, Farga D, Perez-Calatayud MJ et al. High-dose-rate brachytherapy boost for prostate cancer: analysis of dose-volume histogram parameters for predicting late rectal toxicity. *Brachytherapy 2017*; doi: 10.1016/j.brachy.2017.03.002

[3] **Chicas-Sett R**, Celada-Alvarez F, Roldan S, et al. An evaluation of the robustness of organ-at-risk recommendations made by GEC/ESTRO according to interobserver variability: a single-center experience. *J Contemp Brachytherapy* 2016; 8:349–355.

STUDIES PRESENTED IN CONFERENCES:

[4] **Chicas Sett R**, Ibañez Roselló B, Celada Álvarez F, Roldán S, Rodríguez Villalba S, Santos Olías M, Soler Catalán P, Lliso Valverde F, Tormo Micó A, Pérez Calatayud J. *Interobserver variability of rectum delineation in Prostate HDR brachytherapy: A multiinstitutional-prospective analysis.* Poster presented at **XIX Congreso SEOR**, hold in Santander (Spain) in June 2017.

[5] **Chicas Sett R**, Farga Albiol D, Perez Calatayud MJ, Celada Alvarez F, Roldan S, Fornes Ferrer V, Ibañez Rosello B, Carmona Meseguer V, Burgos Burgos J, Tormo Micó A. *Dose-volume histogram predictors for late rectal toxicity in prostate HDR-brachytherapy.* Poster presented at **XIX Congreso SEOR**, hold in Santander (Spain) in June 2017.

[6] **Chicas Sett R**, Ibañez Roselló B, Celada Álvarez F, Roldán S, Rodríguez Villalba S, Santos Olías M, Soler Catalán P, Lliso Valverde F, Tormo Micó A, Pérez Calatayud J. *Interobserver variability of rectum delineation in Prostate HDR brachytherapy: A multiinstitutional-prospective analysis.* **Oral presentation** at **XIX Congreso SEOR**, hold in Santander (Spain) in June 2017.

[7] **Chicas Sett R**, Farga Albiol D, Perez Calatayud MJ, Celada Alvarez F, Roldan S, Fornes Ferrer V, Ibañez Rosello B, Carmona Meseguer V, Burgos Burgos J, Tormo Micó A. *Dose-volume histogram predictors for late rectal toxicity in prostate HDR-brachytherapy.* **Oral presentation** at **XIX Congreso SEOR**, hold in Santander (Spain) in June 2017.

[8] **Chicas-Sett R**, Celada F, Burgos J, Farga D, Perez-Calatayud M, Roldan S, Collado E, Ibañez B, Perez-Calatyud J, Tormo A. *Dose escalation with HDR brachytherapy for intermediate- and high-risk prostate cancer*. Poster presented at **ESTRO 36 Congress**, hold in Vienna (Austria) in May 2017.

[9] **Chicas-Sett R**, Farga-Albiol D, Perez-Calatayud MJ, Celada F, Roldan S, Burgos J, Ibanez-Rosello B, Benlloch JM, Perez-Calatayud J, Tormo A. *Assessing the relationship between dose-volume histogram parameters and late rectal toxicity in HDR brachytherapy for prostate cancer.* Poster presented at **ABS 2017 Annual Meeting**, hold in Boston, Massachusetts (USA) in April 2017.

[10] **Chicas-Sett R**, Perez-Calatayud J, Bautista-Ballesteros J, Celada F, Roldan S, Torregrosa A, Betancourt J, Farga-Albiol D, Carmona V, Tormo A. *An evaluation of the robustness of the organ-at-risk recommendations made by GEC/ESTRO according to inter- and intra-observer variability: A single center experience.* Poster presented at **World Congress of Brachytherapy**, hold in San Francisco, California (USA) in June 2016.

[11] **Chicas-Sett R**, Bautista-Ballesteros J, Celada-Alvarez F, Roldan S, Torregrosa A, Betancourt J, Burgos J, Farga D, Perez M, Carmona V, Tormo A, Benlloch J, Perez-Calatayud J. *Robustness of the OARS recommendations made by GEC/ESTRO according to inter-observer variability.* Poster presented at **ESTRO 35 Congress**, hold in Turín (Italy) in April 2016.

[12] **Chicas Sett R**, Roldan S, Celada F, Soler A, Burgos J, Gimeno J, Perez-Calatayud J. *Early toxicity outcomes: A single 15 Gy fraction HDR brachytherapy as pre-treatment EBRT boost in prostate*

cancer. Poster presented at **57th Annual Meeting (ASTRO)**, hold in San Antonio, Texas (USA) in October 2015.

[13] **Chicas Sett R,** Soler A, Fernandez J, Burgos J, Pons O, Roldan S, Celada F, Gimeno J, Tormo A, Perez-Calatayud J. *Early toxicity outcomes: A single 15 Gy fraction HDR brachytherapy as pre-treatment ERBT boost in prostate cancer*. Poster presented at **3rd ESTRO Forum**, hold in Barcelona (Spain) in April 2015.

[14] **Chicas Sett R,** Soler A, Fernandez J, Burgos J, Pons O, Roldan S, Celada F, Gimeno J, Tormo A, Perez-Calatayud J. *Early toxicity outcomes: A single 15 Gy fraction HDR brachytherapy as pre-treatment ERBT boost in prostate cancer*. **Oral presentation** at **3rd ESTRO Forum**, hold in Barcelona (Spain) in April 2015.

[15] **Chicas Sett R**, Celada FJ, Roldan S, Soler AM, Burgos J, Garcia-Mora MC, Collado E, Farga D, Perez-Calatayud J, Tormo A. *Single fraction HDR-BT as pre-treatment EBRT boost in prostate cancer*. **Oral presentation** at **XVIII Congreso de SEOR**, hold in Valencia (Spain) in June 2015.

CHAPTER I

SUMMARY

1.1 Summary

Prostate cancer is one of the most commonly diagnosed cancers in the developed world, having caused 293,000 deaths in 2013 (Global Burden of Disease Cancer, *et al.*, 2013). According to the Spanish Network of Cancer Registries (REDECAN), 33,370 new cases were diagnosed in 2015 in Spain. In 2014, prostate cancer was ranked fifth in terms of cancer deaths among Spanish men (Instituto de Salud Carlos III, 2014).

High-risk prostate cancer is an aggressive form of the disease with a higher risk of distant metastasis and mortality. This classification represents a significant portion of the nearly 28,000 prostate cancer deaths per year in the United States and the 5,855 deaths in Spain (American Cancer Society 2015; Instituto de Salud Carlos III, 2014). There are different treatment options for locally advanced prostate cancer, such as active surveillance, radical prostatectomy, and radiotherapy. The use of radiotherapy in the radical treatment of intermediate- and high-risk prostate cancer has been well studied in several prospective randomized trials (Zelefsky *et al.*, 2008; Coen *et al.*, 2002). This option can be administered through EBRT, BT, and either HDRBT or LDRBT given alone or combined with EBRT.

HDRBT is a brachytherapy technique, and when combined with EBRT, it allows for dose escalation, administration of the complete dose to the target (the prostate), and minimisation of the dose received by the surrounding normal tissues. Current international treatment guidelines recommend the use of HDRBT combined with EBRT, which is also

known as “HDRBT boost”. According to the ABS, GEC/ESTRO, and ESTRO/EUA/EORTC, this treatment modality improves local control compared with monotherapy, as well as the outcomes in certain patients with intermediate- and high-risk disease (Zaorsky *et al.*, 2017).

There are no specific recommendations about the best dose fractionation scheme for HDRBT boost. Several studies have reported various treatment schemes, which has made it difficult to compare the results of acute and late toxicity. In recent years, there has been a transition in the number of fractions delivered. Initially, as many as four boost fractions were used, but currently, the evidence supports large boost fractions with a single HDRBT boost (Morton *et al.*, 2013). This trend has been accompanied by important biological effects, as well as practical and cost-saving advantages. Furthermore, virtually all-geometric uncertainty is eliminated, as there is no risk of inter-fraction variability. For these reasons, there has been much interest in this technique, which has also been adopted by several centres for high-risk patients. This thesis is motivated by the need for clinical outcomes, including improvements in prevention and decrease of rectal toxicity.

The purpose of this thesis was threefold. Firstly, to determine the clinical outcomes of a cohort of patients diagnosed with prostate cancer and treated with HDRBT boost using real-time TRUS based planning in combination with EBRT (**see Chapter IV, Paper I**). Secondly, determining the occurrence of late rectal toxicity in our patients’ cohort and evaluating its potential relationship with D_{2cc} parameter. This was based in the rectal constraint recommended by GEC/ESTRO, given the absence of another rectal dose constraints from similar studies of HDRBT

combined with EBRT for prostate cancer **(**see **Chapter IV, Paper I)**. Thirdly, we proposed to evaluate the D_{2cc} robustness in HDRBT for prostate cancer using the interobserver variability in the rectum contouring. A first pilot study was performed with a limited number of patients and physicians of the same center (see **Chapter IV, Paper II**). Lastly, in order to evaluate the outcomes from the pilot study, a multicentre prospective study was performed (see **Chapter IV, Paper III**). Below is a summary of the information contained in each of the papers of this thesis.

Chapter I provides a summary describing the findings of the research that were carried out by the doctoral candidate.

Chapter II provides a general introduction and justification of the thesis.

Chapter III contains the general aim, specific objectives and the study design of the thesis.

In **Chapter IV (Paper I),** we review our institution´s experience with HDRBT boost for localized prostate cancer. The first purpose of this study was to analyse the clinical outcomes, particularly local control, overall survival, and late rectal toxicity. The second purpose was to determine the significance of dose-volume histogram parameters for predicting LRT after single-fraction HDRBT boost and EBRT in prostate cancer patients.

A cohort of 300 patients diagnosed with locally advanced prostate cancer and treated with HDRBT boost plus EBRT were followed prospectively. The patient data were used for both purposes. The treatment comprised a single-fraction HDRBT boost of 15 Gy plus EBRT

(46 Gy delivered in 23 fractions) or an HDRBT boost of 9.5 Gy plus EBRT (60 Gy delivered in 30 fractions) if the seminal vesicles were infiltrated using real-time transrectal ultrasound-based planning. The toxicity was evaluated every 3 months after the end of the combined treatment using the Common Terminology Criteria for Adverse Events version 4.0. For the second analysis, the minimum dose received by the most exposed rectum volumes of 0.1 and 2 cm^3 ($D_{0.1cc}$/D_{2cc}) was determined and analysed by estimating the biologically equivalent rectal dose according to the GEC/ESTRO recommendations.

The clinical results showed an estimated 5-year bDFS rate of 90% and OS of 87% with a median follow-up of 33 (2 – 68) months. Only 18 patients had a follow-up less than 18 months because death occurred before then. In total, 10 patients (3.3%) experienced biochemical failure in this period. In the OS analysis, death occurred in 28 patients, and only one patient died of prostate cancer. The remaining 27 patients died from other causes, including ischemic cardiopathy (10 patients), secondary cancers (6 patients), pulmonary embolism (1 patient), and other causes (10 patients). To date, clinical outcomes obtained in this study are comparable with results from prospective and retrospective studies, which reported local control rates for intermediate- and high-risk disease of 69 - 97% and 63 - 80%, respectively, with evidence level 1 (Zaorsky *et al.*, 2017).

In the toxicity analysis, 62 patients (20.7%) experienced rectal toxicity. Of those patients, based on the highest grade of late rectal toxicity, 39 patients (13%) had Grade 1, 20 patients (7%) had Grade 2, and 3 patients (1%) had Grade 3. No Grade 4 toxicity was reported. These

LRTs were composed of 10.3% diarrhoea, 9.3% proctitis, and 1% rectal haemorrhage. All patients with rectal haemorrhage were treated with an argon laser, which produced good results without any medical complications.

In the second part of this study, based on the latest GEC/ESTRO recommendations (which proposed that D_{2cc} should be constrained to ≤ 75 Gy EQD_2), we found that the means ± standard deviation for $D_{0.1cc}$ and D_{2cc} were 80.3 ± 4.4 and 69.7 ± 3.6 for patients with Grade 0 - 1 and 80.4 ± 4.0 and 70.1 ± 2.7 for patients with Grade ≥ 2, respectively (see **Paper I**). Subgroup analysis according to the treatment scheme group stratification did not show statistical differences in $D_{0.1cc}$ or D_{2cc} between patients with Grade 0 - 1 and Grade ≥ 2 LRT ($p > 0.05$). All 23 patients (100%) developed Grade ≥ 2 LRT and received doses ≥ 65 Gy EQD_2. Of those patients, only seven patients who were given a dose ≥ 75 Gy EQD_2 developed Grade ≥ 2 LRT.

Ordinal regression analysis was used to evaluate the potential relationship between D_{2cc} and LRT. A significant association was found between D_{2cc} and the probability of developing LRT of Grade 1 – 3 ($p = 0.04$). To avoid potential bias, a subgroup analysis was performed without the 18 patients with a follow-up less than 18 months. The results were very similar, thus confirming the association between D_{2cc} and LRT ($p = 0.05$).

The results provided in **Paper I** have clinical implications. First, our experience suggests that single-fraction HDRBT boost using real-time TRUS-based planning is safe and effective. Second, despite the low incidence of LRT, it might be necessary to take precaution when

administering rectal doses > 65 Gy EQD_2. Further investigations will be needed to confirm these results.

The following two chapters evaluate the robustness of $D_{2cc} \leq 75$ Gy EQD_2 suggested by the GEC/ESTRO as a rectal dose constraint via IOV. This was based on accurate delineation of volumes as a crucial step in radiotherapy treatment, and these variations can have implications for the patient in terms of cure rates and toxicities. In addition, DVHs can be affected by variability in volume contouring, resulting in differences in plan acceptability among physicians.

Chapter IV (**Paper II**) evaluates the robustness of $D_{2cc} \leq 75$ Gy EQD_2 suggested by the GEC/ESTRO as a rectal dose constraint via intra-observer variability and IOV in a pilot study in an experienced single centre. This study included five representative patients (5 sets of US images) diagnosed with prostate cancer and treated using HDRBT boost and EBRT. An expert group was established with 2 radiation oncologists, 1 radiologist, and 1 urologist who is usually involved in prostate brachytherapy and prostate US.

As a first step, in the absence of rectal delineation guidelines for OARs in HDRBT for prostate cancer, this group had previously agreed on rectal delineation criteria in consensus. The HDRBT was performed before the EBRT as an intraoperative procedure under epidural anaesthesia, and the dose was delivered in a single fraction using real-time TRUS-based planning. This gave control over the patient setup error, intra-fraction organ movement, and patient movement, but there were still brachytherapist-dependent uncertainties in rectum delineation. Thus, the IOV was calculated using the coefficient of variation (COV).

For dosimetric impact analysis, DVHs ($D_{0.1cc}$, D_{1cc}, and D_{2cc}) were analysed according to the GEC/ESTRO recommendations and subjected to intra- and interobserver comparison. The effect of IOV on the total dose was analysed by estimating the biologically equivalent rectal dose (EQD2), assuming that the rectum received the prescribed EBRT dose (in our study, 46 Gy), as described in more detail in **Chapter IV (Paper II).** The results indicated were an IOV < 5% for D_{2cc}, with strong impacts on clinical threshold levels ($D_{2cc} \leq 75$ Gy EQD_2) in some cases. For example, the highest interobserver rectal delineation variation yielded a rectal dose difference of up to 5.8 Gy EQD_2 in the worst-case scenario. For the intraobserver variability, the test revealed no statistically significant differences in $D_{0.1cc}$, D_{1cc}, or D_{2cc}. The results in this study are very limited, but they create a need to investigate the strong impacts near the clinical rectal dose threshold and the comparison of these results in other centres.

Chapter IV (**Paper III)** is based on the results provided from **Paper II**, where we tested the robustness of D_{2cc} via IOV in a single-institution study. We performed a follow-up study to evaluate the IOV of rectum delineation for HDRBT, to determine its dosimetric consequences, and to analyse the robustness of the aforementioned constraints in a multi-institutional study involving five different radiation oncologists. According to a systematic review of the literature on the evaluation of IOV in radiotherapy volume delineation, 119 studies including several targets have been published, such as the breast, lung, head and neck, brain, and sarcoma. However, only 31 studies have evaluated this variability in OAR volume delineation, and only 3 of these have been

realised in brachytherapy and include the evaluation of dosimetry (Vinod *et al.*, 2016). There is no specific recommendation in the design of these studies. They are highly variable with different numbers of observers, metrics of comparison, and use of statistical tests. For this reason, we performed this study with the same conditions as the pilot study but with more cases and involving physicians from others expert centres. Thus, both studies were comparable.

We found that the interobserver coefficients of variation (± standard deviation) for $D_{0.1cc}$, D_{1cc}, and D_{2cc} were 5±1.84%, 4±1.26%, and 4±1.33%, respectively. The impact on the total dose was determined by the mean dose differences observed for $D_{0.1cc}$, D_{1cc}, and D_{2cc}, which were 10 Gy, 7.3 Gy, and 6.6 Gy respectively. We believe our findings are of great interest because they show that the D_{2cc} determination is robust given the IOV < 5%. In addition, consensus rectal contouring guidelines appear to be a desirable tool for reducing delineation. Further investigations should be performed in order to compare these results and to suggest general recommendations in everyday clinical practice for OAR contouring in the HDRBT for prostate cancer.

Lastly, **Chapter V** presents a general discussion, **Chapter VI** provides the conclusions and **Chapter VII** contains the references used in the current thesis.

1.2 Summary in Spanish / Resumen en Español.

El cáncer de próstata es uno de los cánceres más frecuentes en los países desarrollados, causando 293,000 muertes en el año 2013 (Global Burden of Disease Cancer, *et al.*, 2013). Según la Red Española de Registros de Cáncer (REDECAN), en España en el año 2015 se diagnosticaron 33,370 nuevos casos. En 2014, el cáncer de próstata ocupó el quinto lugar en términos de mortalidad por cáncer en hombres españoles (Instituto de Salud Carlos III, 2014).

De acuerdo a la clasificación del cáncer de próstata en diversos grupos de riesgo, el alto riesgo es una forma agresiva de la enfermedad, con mayor riesgo de metástasis a distancia y mortalidad, representando una parte significativa de las 28,000 muertes por cáncer de próstata al año en los Estados Unidos de América, y 5,855 muertes en España (American Cancer Society 2015; Instituto de Salud Carlos III, 2014).

Existen diferentes opciones de tratamiento para el cáncer de próstata localmente avanzado, como la vigilancia activa, la prostatectomía radical y la radioterapia. El uso de la radioterapia en el tratamiento radical del cáncer de próstata de riesgo intermedio y alto riesgo, ha sido ampliamente estudiado en múltiples estudios prospectivos aleatorizados (Zelefsky *et al.*, 2008; Coen *et al.*, 2002). Esta opción puede ser administrada mediante radioterapia externa (EBRT), braquiterapia (BT), así como braquiterapia de alta tasa de dosis (HDR) o braquiterapia de baja tasa de dosis (LDR), administrada de forma exclusiva o combinada con EBRT.

La BT HDR es una técnica de braquiterapia que combinada con EBRT, permite realizar una escalada de la dosis, administrando de esta

forma la dosis completa al volumen tumoral (próstata), y minimizando la dosis recibida por los tejidos sanos adyacentes. Actualmente, las guías de tratamiento internacional recomiendan el uso de BT HDR combinada con EBRT, también conocida como "BT HDR boost". Según la ABS, GEC/ESTRO y la ESTRO/EUA/EORTC, esta modalidad de tratamiento mejora el control local en comparación con la monoterapia, optimizando los resultados en determinados pacientes con riesgo intermedio y alto riesgo (Zaorsky *et al.*, 2017).

No existen recomendaciones específicas respecto al mejor esquema de fraccionamiento de dosis para la sobreimpresión con BT HDR. Diversos estudios han reportado distintos esquemas de tratamiento, y por ello es difícil comparar los resultados sobre la toxicidad aguda y tardía. En los últimos años ha habido una transición en el número de fracciones administradas. En un principio, se utilizaban 4 fracciones para la sobreimpresión con BT HDR, y actualmente la evidencia apoya la utilización de dosis más elevadas en una única fracción (Morton *et al.*, 2013). Esta tendencia presenta ventajas con respecto al efecto biológico, desde el punto de vista práctico y coste-efectivo, además de eliminar algunas incertidumbres geométricas al no existir riesgo de variabilidad inter-fracción. Por este motivo, ha habido mucho interés en esta técnica, siendo adoptada por numerosos centros en pacientes de alto riesgo. Esta tesis ha sido desarrollada ante la necesidad de obtener resultados clínicos en el uso de una fracción única de BT HDR, así como de mejorar la prevención y disminución de la toxicidad rectal.

Tres son los objetivos principales de esta tesis. En primer lugar, determinar los resultados clínicos obtenidos a partir de una cohorte de

pacientes diagnosticados con cáncer de próstata y tratados con una sobreimpresión de BT HDR, mediante una planificación en tiempo real guiada por ultrasonido trans-rectal (TRUS) en combinación con EBRT (ver **capítulo IV, artículo I**). En segundo lugar, determinar la incidencia de toxicidad rectal tardía en nuestra cohorte de pacientes y evaluar una potencial relación con el parámetro D_{2cc}. Para ello, nos basamos en el límite de dosis recomendado por la GEC/ESTRO, ante la ausencia de estudios similares de BT HDR combinada con EBRT para el cáncer de próstata que sugieren otros límites de dosis rectal **(**ver **Capítulo IV, artículo I)**. En tercer lugar, se propuso evaluar la robustez del parámetro D_{2cc} en la BT HDR para el cáncer de próstata mediante la variabilidad inter-observador en el contorneo del recto. Se realizó un primer estudio piloto con un número limitado de pacientes y especialistas de un único centro (ver **Capítulo IV, artículo II**). Por último, con el propósito de evaluar los resultados del estudio piloto, se realizó un estudio prospectivo multicéntrico (ver **Capítulo IV, artículo III**).

A continuación, presentamos un resumen de la información contenida en cada uno de los capítulos de la tesis.

En el **Capítulo I,** se presenta un resumen de los objetivos y resultados obtenidos en la tesis.

En el **Capítulo II,** se presenta una introducción general y la justificación de la tesis.

El **Capítulo III** contiene el propósito general de estudio, los objetivos específicos y el diseño del estudio.

En el **Capítulo IV (artículo I),** revisamos la experiencia de nuestra institución con la sobreimpresión con BT HDR en el cáncer de próstata localizado. Inicialmente, el objetivo de este estudio fue analizar los resultados clínicos, específicamente el control local, la supervivencia global y la toxicidad tardía. En segundo lugar, se determinó la significancia de los parámetros de los histogramas dosis-volumen (DVH) para predecir toxicidad rectal tardía (LTR) después de la sobreimpresión con BT HDR en fracción única y EBRT en pacientes con cáncer de próstata.

Se realizó un seguimiento prospectivo sobre una cohorte de 300 pacientes diagnosticados con cáncer de próstata localmente avanzado y tratados con una sobreimpresión de BT HDR más EBRT. Los datos obtenidos se utilizaron con el fin de alcanzar ambos objetivos. El tratamiento consistió en una sobreimpresión de BT HDR en fracción única de 15 Gy combinada con EBRT (46 Gy administrados en 23 fracciones), o en una sobreimpresión de BT HDR en fracción única de 9.5 Gy combinada con EBRT (60 Gy administrados en 23 fracciones) en caso de infiltración en las vesículas seminales, realizándose mediante una planificación basada en TRUS en tiempo real. La toxicidad fue evaluada cada 3 meses a partir de la finalización del tratamiento combinado mediante los Criterios de Terminología de Eventos Adversos, versión 4.0. Para el segundo análisis, la dosis mínima recibida por el volumen rectal más expuesto en los 0.1 y 2 cm^3 ($D_{0.1cc}$/D_{2cc}) se determinó y se evaluó mediante la estimación de la dosis rectal biológicamente equivalente según las recomendaciones de GEC/ESTRO.

Los resultados clínicos mostraron un intervalo estimado de supervivencia libre de recaída bioquímica (bDFS) a los 5 años del 90% y una supervivencia global (OS) del 87%, con un seguimiento medio de 33 (2-68) meses. Solamente 18 pacientes tuvieron un seguimiento menor a 18 meses, debido a que fallecieron antes de completarlo. En total, 10 pacientes (3.3%) recayeron durante este período. En el análisis de OS, 28 pacientes fallecieron, pero solamente 1 paciente debido al cáncer de próstata. Los 27 pacientes restantes murieron por otras causas, como cardiopatía isquémica (10 pacientes), cánceres secundarios (6 pacientes), embolismo pulmonar (1 paciente) y otras causas (10 pacientes). Hasta el momento, los resultados obtenidos en estudios prospectivos y retrospectivos respecto al control local para el grupo de riesgo intermedio y alto riesgo es de 69%-97% y 63%-80% respectivamente. Este resultado ha sido obtenido con un nivel de evidencia 1 (Zaorsky *et al.*, 2017).

Respecto al análisis de toxicidad, 62 pacientes desarrollaron toxicidad rectal. De ellos, y basado en el mayor grado de toxicidad rectal tardía presentada, 39 pacientes (13%) tuvieron Grado 1, 20 pacientes (7%) Grado 2 y 3 pacientes (1%) Grado 3. No se reportó toxicidad Grado 4. Las LRT fueron diarrea en el 10.3%, proctitis en el 9.3% y rectorragia en el 1%. Todos los pacientes con rectorragia fueron tratados con láser de argón, obteniendo buenos resultados y en ausencia de complicaciones médicas.

En la segunda parte del estudio, y basándonos en las últimas recomendaciones de GEC/ESTRO (en las cuales se propuso una dosis límite para el $D_{2cc} \leq 75$ Gy EQD_2), encontramos que la media ± desviación estándar para el $D_{0.1cc}$ y D_{2cc} fue de 80.3 ± 4.4 y 69.7 ± 3.6 en

pacientes con Grado 0-1, y de 80.4 ± 4.0 y 70.1 ± 2.7 en pacientes con Grado ≥ 2, respectivamente (ver **Capítulo IV; estudio I**). Además se realizó un análisis de subgrupo estratificado según el esquema de tratamiento, no encontrándose diferencias estadísticamente significativas en los parámetros $D_{0.1cc}$ y D_{2cc} entre los pacientes con LRT Grado 0-1 y los pacientes con Grado ≥ 2 ($p > 0.05$). Los 23 pacientes (100%) que desarrollaron LRT Grade ≥ 2 recibieron dosis ≥ 65 Gy EQD_2. De ellos, únicamente 7 pacientes recibieron una dosis ≥ 75 Gy EQD_2.

Se realizó un análisis de regresión ordinal para evaluar la potencial relación entre D_{2cc} y la LRT, y se encontró una asociación significativa entre el D_{2cc} y la probabilidad de desarrollar LRT de Grado 1-3 ($p = 0.04$). Para evitar posibles sesgos, se realizó un análisis de subgrupo excluyendo los 18 pacientes con un seguimiento inferior a 18 meses. Los resultados obtenidos fueron muy similares, confirmándose la asociación entre el D_{2cc} y la LRT ($p = 0.05$).

Los resultados recogidos en el **Capítulo IV (estudio I)** tienen diversas implicaciones clínicas. En primer lugar, nuestra experiencia sugiere que el uso de la fracción única con BT HDR planificada mediante TRUS en tiempo real es segura y efectiva. En segundo lugar, a pesar de la baja incidencia de LRT, deberían tomarse medidas de precaución cuando se administran dosis rectales > 65 Gy EQD_2. Estos resultados deberían ser confirmados en futuros estudios.

El **Capítulo IV (estudio II)** evaluó la robustez del parámetro $D_{2cc} \leq$ 75 Gy EQD_2 recomendado por GEC/ESTRO como dosis límite en el recto mediante un estudio piloto realizado en un centro especializado, determinando la variabilidad intra e inter-observador. En este estudio, se

incluyeron 5 pacientes representativos (5 conjuntos de imágenes por ultrasonidos (US)) diagnosticados con cáncer de próstata y tratados mediante una sobreimpresión de BT HDR y EBRT. Se estableció un grupo de expertos, formado por 2 oncólogos radioterápicos, 1 radiólogo y 1 urólogo entrenados en braquiterapia de próstata y ecografía prostática. Ante la ausencia de guías de contorneo para los órganos de riesgo (OARs) en BT HDR para el cáncer de próstata, este grupo estableció un consenso sobre los criterios de contorneo. La BT HDR fue realizada antes de la EBRT como un procedimiento intra-operatorio bajo anestesia epidural, y la administración de la dosis fue realizada en una fracción única utilizando una planificación basada en TRUS en tiempo real. Este procedimiento aportó un mejor control sobre el posicionamiento del paciente, el movimiento del órgano intra-fracción, pero persistían las incertidumbres en el contorneo del recto al ser un procedimiento dependiente del médico braquiterapista. Se calculó la variabilidad inter-observador (IOV) mediante la determinación del coeficiente de variación (COV). Para el análisis del impacto dosimétrico, se analizaron los histogramas dosis-volumen (DVH) para obtener los parámetros $D_{0.1cc}$, D_{1cc} y D_{2cc} según las recomendaciones de GEC/ESTRO, utilizándose en la comparación intra e inter-observador. El efecto de la IOV en la dosis total se analizó estimando la dosis rectal biológicamente equivalente (EQD_2), asumiendo que el recto recibió la dosis de EBRT prescrita (en nuestro estudio, 46 Gy), como se describe con más detalle en el **Capítulo IV (estudio II)**. Los resultados obtenidos fueron una IOV < 5% para el D_{2cc}, con un fuerte impacto en la dosis límite ($D_{2cc} \leq 75$ Gy EQD_2) en algunos casos. Por ejemplo, una alta variación inter-observador en el

contorneo del recto produciría una diferencia en la dosis rectal de hasta 5.8 Gy EQD_2 en el peor de los casos. Respecto a la variabilidad intra-observador, el análisis estadístico no encontró diferencias estadísticamente significativas en los parámetros $D_{0.1cc}$, D_{1cc} y D_{2cc}.

En dicho estudio se concluyó que los resultados obtenidos son limitados, pero crean la necesidad de investigar el fuerte impacto cerca de la dosis rectal límite y de comparar estos resultados con los de otros centros.

El **Capítulo IV (estudio III)** se basó en los resultados obtenidos del **estudio II**, donde evaluamos la robustez del D_{2cc} mediante la IOV en un estudio de un único centro. A partir de dichos resultados, se realizó un estudio de seguimiento para evaluar la IOV en el contorneo del recto en la BT HDR, determinar las consecuencias dosimétricas y analizar la robustez de la dosis límite antes mencionadas en un estudio multicéntrico en el que participaron 5 oncólogos radioterápicos.

Mediante una revisión sistemática de la literatura sobre la evaluación de la IOV en la delimitación de volúmenes en radioterapia, hemos encontrado 119 estudios publicados incluyendo varios objetivos, por ejemplo, la mama, pulmón, cabeza y cuello, cerebro, sarcoma, etc. Sin embargo, solo 31 estudios han evaluado esta variabilidad en el contorneo de volúmenes en órganos de riesgo, y solo 3 de estos estudios se han realizado en braquiterapia incluyendo la evaluación dosimétrica (Vinod *et al.*, 2016). No hay una recomendación especifica en relación al diseño de este tipo de estudios, debido a que poseen una amplia variedad respecto al número de observadores, medidas de comparación y al uso de pruebas estadísticas. Por este motivo, realizamos este estudio en las mismas

condiciones que en el estudio piloto, pero aumentando el número de casos e incluyéndose especialistas de otros centros con experiencia. Así, los dos estudios fueron comparables.

Encontramos que los coeficientes de variación inter-observador (± desviación estándar) para los parámetros $D_{0.1cc}$, D_{1cc} y D_{2cc} fueron 5±1.84%, 4±1.26% y 4±1.33% respectivamente. El impacto en la dosis total se determinó mediante la diferencia de dosis calculada para el $D_{0.1cc}$, D_{1cc} y D_{2cc}, los cuales fueron 10 Gy, 7.3 Gy y 6.6 Gy, respectivamente. Creemos que nuestros resultados son de gran interés, ya que muestran la robustez del parámetro D_{2cc} al determinar una IOV < 5%. Además, la utilización de una guía de contorneo rectal establecida mediante consenso, parece ser una herramienta de gran utilidad para precisar el contorneo. Se necesitarían más estudios para comparar estos resultados y proponer recomendaciones generales para la practica clínica diaria en el contorneo de OAR en la BT HDR en el cáncer de próstata.

Por último, en el **Capítulo V** se presenta una discusión general, el **Capítulo VI** contiene las conclusiones y el **Capítulo VII** las referencias utilizadas en la presente tesis.

CHAPTER II

INTRODUCTION

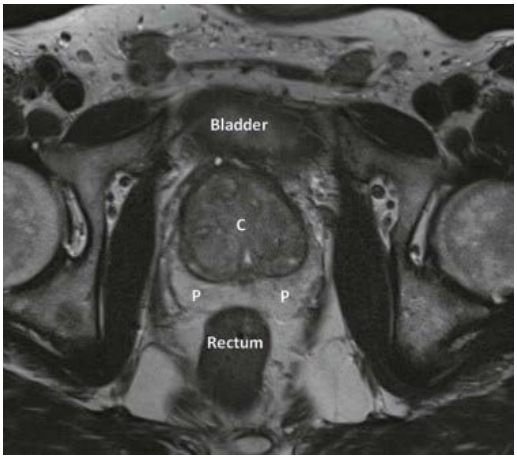
Recent evidence suggests that the constant technological innovations in radiotherapy and brachytherapy have improved clinical disease management for individual patients with localized prostate cancer. HDRBT is being used as a method for dose escalation, particularly in intermediate- and high-risk groups. The main focus of this thesis is assessing the quality of the HDRBT treatment through clinical outcomes and treatment-induced toxicity. The aim of such treatments is to improve the care of patients with this disease.

2.1 Anatomy of the prostate

The prostate gland is a part of the male reproductive system. In adulthood, the prostate has a volume of up to 20-30 ml. This pelvic organ is located immediately below the bladder, in front of the rectum, and behind the pubic symphysis (Figure 2-1). The seminal vesicles lie posterosuperiorly between the bladder and the rectum. The neurovascular bundles responsible for erectile function pass from superior to inferior along both posterolateral sides of the prostate (Caokley *et al.*, 2000).

The prostate can be divided into three parts (Figure 2-1). The superior part corresponds with the base, the middle part is the midprostate, and the inferior part is the apex (Caokley *et al.*, 2000). According to McNeal (1988), the prostate consists of three different zones: the peripheral zone (70%), the central zone (20%), and the peri-urethral transition zone (10%).

A.



B.

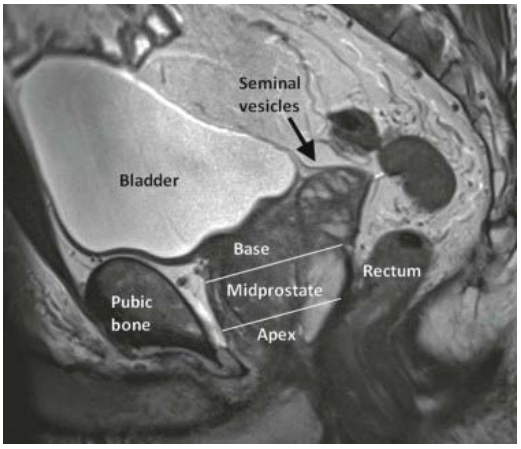


Figure 2-1.

(A) Axial T2-weighted MR image showing the prostate and its zonal anatomy. The peripheral zone (P) is shown as a crescent-shaped hyperintense structure, and the central gland (C) is depicted as a structure with heterogeneous signal intensity. (B) Sagittal T2-weighted image showing the craniocaudal segmentation of the prostate and its relation to the adjacent structures.

All of these anatomical relationships correspond to organs that are at risk in radical treatments such as HDR brachytherapy, especially with the rectum, urethra, neurovascular bundles, and bladder. Thus, any dose administered to these organs that exceeds the threshold dose explains most of the toxicities associated with prostate cancer radiation treatment.

2.2 Prostate cancer

Prostate cancer is one the most common cancers in the developed world, with 1.4 million cases and 293,000 deaths having occurred in 2013 (Global Burden of Disease Cancer *et al.*, 2015; Siegel *et al.*, 2012). According to the Spanish Network of Cancer Registries (REDECAN), it is estimated that 33,370 new cases were diagnosed in 2015 in Spain (Galceran *et al.*, 2015). In 2014, a total of 5,855 deaths by prostate cancer were reported in Spain, and the disease is ranked fifth in terms of cancer deaths among Spanish men (Instituto de Salud Carlos III, 2014). The current incidence might be explained by the increased use of assays for serum levels of prostate-specific antigen (PSA) in symptomatic and asymptomatic patients, which makes it possible to diagnose cases of clinically silent disease.

2.3 Diagnosis of prostate cancer

The diagnosis of prostate cancer is based on the microscopic evaluation of prostate tissue obtained via needle biopsy. According to general recommendations, a systematic prostate biopsy is performed using TRUS to obtain 10 to 12 tissue samples (Heidenreich *et al.*, 2014)

2.3.1 Clinical presentation

Prostate tumours are usually slow growing, and symptoms may be absent initially. Given its localization around the urethra, symptoms for the disease most commonly affect urination. Symptoms include frequent urination, nocturia, difficulty in maintaining a steady stream of urine, hematuria, and dysuria. These symptoms also occur in other prostate diseases, including benign prostate hyperplasia. Problematically, both benign prostate hyperplasia and prostate cancer commonly coexist in the prostate, and both can lead to an increase in serum PSA (Mohler *et al.*, 2016). Thus, further invasive investigations are required to confirm the diagnosis, such as biopsy.

2.3.2 Prostate-specific antigen (PSA)

PSA is a glycoprotein produced by the acinar cells of the prostate and is normally present in small quantities in the serum among men (Hernández *et al.*, 2004). The level often increases in prostate disorders, including prostate cancer. Nevertheless, PSA is organ-specific but not cancer-specific, and elevated PSA levels can result from benign conditions such as benign prostatic hypertrophy or prostatitis. There is no PSA cut-off level that indicates prostate cancer. However, higher levels of PSA are associated with the risk of developing prostate cancer. The PSA level is also used in risk stratification for newly diagnosed prostate cancer patients, predictive staging nomograms, and monitoring treatment response (Heidenreich *et al.*, 2014).

2.3.3 Tumour grading and staging

The Gleason Grading System is the most commonly used system, where cancers are scored according to their microscopic appearance. The tumour tissue is graded on a scale from 1 to 5, with 5 indicating the poorest prognosis. The Gleason (GS) sum ranges from 2 to 10 (Epstein, 2005; Gleason, 1974). For the primary grade, pathologists identify which pattern corresponds with at least 50% of the tumour, and the secondary grade represents the minority of the tumour. High GS implies increased tumour aggressiveness and increased risk of local and distant tumour spread with a worse prognosis. Table 2-1 describes the Gleason patterns used in the scoring system.

Table 2-1. *Gleason Patterns*

Pattern 1	The cancerous prostate cells closely resemble normal prostate cells. The glands are small, well formed, and closely packed.
Pattern 2	The glands are larger and have more tissue between them.
Pattern 3	The tissue still has recognizable glands, but the cells are darker. Some cells have left the glands and have started to invade the surrounding tissue.
Pattern 4	The tissue has few recognizable glands. Many cell are invading the surrounding tissue.
Pattern 5	The tissue does not have recognizable glands. There are often just sheets of cells throughout the surrounding tissue.

Currently, most therapeutic options for patients with newly diagnosed prostate cancer are based on the GS from TRUS biopsies, which can be inaccurate due to sampling error. This is confirmed by the fact that the GS is upgraded in every third patient following radical prostatectomy (Epstein *al.*, 2012). Incorrect GS at biopsy may lead to incorrect risk stratification and possible over- or under-treatment.

Two consensus guidelines were established in 2005 and 2014 to update the Gleason grading for prostate cancer. The recommendation was that the percentage of pattern 4 must be recorded in all cases of GS 7 (3+4, 4+3) tumours (Epstein *et al.*, 2016; Moch *et al.*, 2016). There are some well-known limitations of Gleason scoring systems. For example, the category of GS 7 includes tumours with 3+4 = 7 and 4+3 = 7. Studies have shown better outcomes for GS 7 with primary pattern 3 versus 4. Thus, in 2014, a novel grading system was adopted to address some of these limitations, which includes five grade groups (GG) from 1 to 5, as described in Table 2-2 (Pierorazio *et al*., 2013). The latest recommendations suggest that the GG system should be used in parallel with the 2014 Gleason grading system (Epstein, 2016; Epstein, 2017).

The TNM classification is used to stage prostate cancer, where T represents tumour and its invasion into adjacent structures, N represents whether or not the regional lymph nodes are involved, and M represents the presence or absence of distant metastasis according to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) (Sobin, 2009). More details are described in Table 2-3.

***Table 2-2**. Prognostic grade groups*

Grade group		Description
GG 1	(GS ≤ 6)	PCa composed only of well-formed and separated glands
GG 2	(GS 3+4 = 7)	PCa with predominantly well-formed and separated glands and a lesser component of poorly formed/fused/glomeruloid/cribiform elements
GG 3	(GS 4+3 = 7)	PCa with predominantly poorly formed/fused/glomeruloid/cribiform elements with a minor component of well-formed and separated glands
GG 4	(GS 4+4 = 8, 3+5 = 8, or 5+3 = 8)	PCa with poorly formed/fused/glomeruloid/cribiform glands or tumours with well-formed and separated glands and lesser component without glands, or tumor predominantly without glands with a lesser component of well-formed and separates glands
GG 5	(GS 9 or 10)	PCa without gland/lumen or with necrosis, with or without poorly formed/fused/glomeruloid/cribiform elements

GG = grade group; GS = Gleason score; PCa = prostate cancer.

***Table 2-3.** AJCC Prostate Cancer Staging 7th Edition.*

Primary Tumor (T)	
Clinical (cT)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified be needle biopsy
T2	Tumour confined within prostate
T2a	Tumour involves one-half of one lobe or less

T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle (s)
T4	Tumour is fixed or invades adjacent structures others than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathologic (pT)	
pT2	Organ confined
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and/or pelvic wall
Regional Lymph Nodes (N)	
Clinical	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node (s)
Pathologic	
pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional nodes (s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node (s)
M1b	Bone (s)
M1c	Other site(s) with or without bone disease

2.3.4 Risk stratification

Patients with organ-confined (i.e. T1-T2) prostate cancer have better results if there is local tumour control. On the other hand, there is a group of patients that presents more aggressive forms of the disease, including PSA > 20 ng/ml and Gleason score >8 (Cahlon *et al.*, 2008). According to D´Amico et al. (1998), the risk of microscopic lymph node involvement and subsequent metastatic disease can be categorised in three groups, as described in the Table 2-4.

Table 2-4. *Prostate cancer risk groups.*

Group	Criteria
Low risk	T1-T2a; PSA ≤ 10ng/ml; Gleason score ≤ 6
Intermediate risk	T2b or PSA > 10 ≤20 ng/ml or Gleason score 7
High risk	≥ T2c or PSA > 20 ng/ml or Gleason score ≥ 8

PSA = prostatic serum antigen.

The National Comprehensive Cancer Center (NCCN) introduced in 2010 the very low risk category, which include T1c, Gleason score ≤ 6, PSA <10 ng/ml, < 3 positive biopsy cores, ≤ 50% cancer in each core and PSAD < 0.15 ng/ml/g. A very high-risk also was added, which include 2 from 3 risk factors form high risk or T3b-T4 (NCCN, 2012).

2.4 Treatment of prostate cancer

Based in the risk groups mentioned above, there is a wide range of treatment strategies available to treat prostate cancer including active surveillance, radical prostatectomy and radiotherapy (Mohler *et al.*, 2016).

Active surveillance is a concept in which patients with a newly diagnosed prostate cancer are offered close surveillance instead of an immediate curative approach (Godtman *et al.*, 2013; Klotz *et al.*, 2015). That option should be given to selected patients with very low risk, low risk and favourable intermediate-risk disease, particulary if they are young men with long life expectancy (Zumsteg *et al.*, 2013; NCCN, 2016). Active surveillance includes a series of PSA testing, physical examinations, prostate biopsies, or a combination of these to monitor progression of the disease in patients who may benefit of local treatment (Filson *et al.*, 2015). Results from various studies had shown a risk of metastasis and prostate cancer mortality ranged from 0% to 6.1% in this treatment option, supporting its use in selected patients (Klotz *et al.*, 2015; Welty *et al.*, 2015; Tosoian *et al.*, 2015; Godtman *et al.*, 2016; Hamdy *et al.*, 2016).

Watchful waiting is an approach for patients in whom a radical intent is not indicated, as the life expectancy should be <10 years. This is a

palliative approach with the goal of minimizing the side effects from treatment. It is a symptom-guide approach in which only complications to prostate cancer are treated, i.e. symptoms due to a local progression or a metastatic disease. The follow-up is patient ajusted, and no predefined follow-up scheme is used. Watchful waiting should only be applied to patients in whom radical treatment is not supposed to be of any benefit (Herden *et al.*, 2018).

In patients diagnosed with localized prostate cancer the two treatment options most used are the surgery and radiotherapy. In addition, there are available others ablative treatments such as high intensity focussed ultrasound (HIFU), cryotherapy and electroporation, but these treatments are not recommended as standard and should be used in a clinical trial. Wallis *et al.*, (2016) in a meta-analysis based mainly in observational studies suggested lower overall and prostate cancer mortality with surgery. However, the ProtecT trial (the first trial evaluating the effectiveness of active surveillance, radical prostatectomy and radiotherapy for men with localised prostate cancer) found not difference in prostate cancer mortality, overall mortality, or metastases. This trial enrolled 1,643 patients randomised to active surveillance (545), radical prostatectomy (553) or radical radiotherapy (545). The rate of cancer progression and spread was reduced by more than half in men in the radical prostatectomy and radiotherapy groups, compared with active surveillance. But significant difference was found in adverse events. For postoperative patients, incontinence or impotence was reported. While, patients treated with radiotherapy had better urinary control and sexual

function but more nocturia and bowel dysfunction than postoperative and active surveillance patients (Hamdy *et al.*, 2016; Donovan *et al.*, 2016)".

The radiotherapy can be administrated in form of external beam radiotherapy (EBRT), and brachytherapy, either HDR or LDR, given alone or combined with EBRT (Zaorsky *et al.*, 2016). Several randomised clinical trials supported the improvement in biochemical control though the use of dose escalation (Viani *et al.*, 2012). This dose escalation could be achievable using EBRT or brachytherapy. However, brachytherapy allows for dose escalation beyond that achievable with EBRT, with a further reduction in dose to the surrounding tissues. Currently, HDRBT is most often used in dose escalation combined with EBRT (Morton, 2005), supported in randomised trials where the results obtained had shown that HDRBT provides better disease control than that achieved with EBRT alone (Hoskin *et al.*, 2007; Pieters *et al.*, 2009)

2.5 High-dose-rate brachytherapy for prostate cancer

Brachytherapy, sometimes referred to as internal radiation therapy, is an excellent treatment option for prostate cancer. This technique is a focused way to deliver radiation in high dose fractions through the positioning of a radiation source directly into the prostate, with rapid dose fall off and subsequent sparing of adjacent normal tissue such as the rectum and bladder. Its use has been recommended by the major international societies in radiation oncology, such as American Brachytherapy Society (ABS), the Groupe Européen de Curiethérapie/European Society for Radiotherapy & Oncology (GEC/ESTRO), and the European Society for Radiotherapy &

Oncology/European Association of Urology/European Organization for Research and Treatment of Cancer (ESTRO/EAU/EORTC) (Yamada *et al.*, 2012; Salembier *et al.*, 2007; Hoskin *et al.*, 2013).

2.5.1 History

The HDRBT for prostate cancer emerged after the use of ^{125}I LDRBT in the 1970s. Several studies, including Mate *et al*. (1998) analysed the outcomes from prostate cancer series-using seed implants with the techniques available at that time. An inadequate dosimetry was found sometimes, mainly in the peripheral zone of the gland (site most frequently to find a tumour cells). For this reason, the ^{192}Ir HDRBT use was suggested as alternative, given that the higher energy ^{192}Ir isotope would enable dose delivery to the periphery of the prostate including the whole tumor and minimizing the dose to the bladder and rectum (Mate *et al.*, 1998).

In 1980 was introduced the TRUS guided remote afterloading system to deliver a high radiation dose to the prostate while limiting exposure of the surrounding tissues, with the aim to improve some limitations experimented with LDRBT, such as inability to adjust seeds once they are deposited, inability to optimize the dose delivered once the seeds are in place and variability between planned and actual seeds distribution (Zaorsky *et al.*, 2013).

In the beginning, HDRBT was used as a method of dose escalation in combination with EBRT for patients with intermediate- and high-risk disease. Several prospective and retrospective studies have demonstrated high rates of biochemical control, ranging from 84% to 98% for

intermediate-risk group, and 63% to 85% for high-risk group. There is a wide range of fractionations schemes available (1 – 4 fractions). Most recently a transition to fewer has been adopted, and in many centres a single fraction has been implemented, such as single HDR boost of 15 Gy (Morton *et al.,* 2013).

There are an emerging data for HDR monotherapy for patients with localized disease. Several studies have been published since 2000 (Yoshioka *et al.,* 2000; Yoshioka *et al.,* 2013; Yoshioka *et al.,* 2017). Acceptable outcomes have been reported, for example, Zamboglou *et al*. (2013) with a median follow-up of 53 months, reported rates of biochemical control ranging from 93% to 95%, with low rates of late grade 3 GU and GI toxicities.

2.5.2 Patients selection and indication

The use of HDRBT as monotherapy or boost combined with EBRT for prostate cancer depends mainly on the stage of the disease (Skowronek *et al.,* 2013). Eligible patients are divided into risk group as described above and selection criteria for treatment based on the risk groups. The NCCN guidelines indicate that HDRBT can be used as firs-line treatment in all risk groups as described in the Table 2-5 (Mohler *et al.*, 2016).

Table 2-5. *Patient selection criteria for HDRBT at different treatment stages according to National Comprehensive Cancer Network (NCCN, 2016).*

Indication	Type of radiation therapy
	HDRBT
Low risk disease Gleason score ≤ 6, PSA < 10ng/ml, T1, T2a	Monotherapy
Intermediate risk disease Gleason score 7, PSA 10-20 ng/ml, T2b, T2c	Boost or monotherapy
High risk disease Gleason score >7, PSA ≥ 20 ng/ml, ≥T3a	Boost (preferred)

PSA = Prostate serum antigen; EBRT = External beam radiotherapy

Based in the evidence, the HDRBT monotherapy is recommended for low- and favourable intermediate-risk with level 2, compared with EBRT. In the unfavourable intermediate- and high-risk groups, the HDRBT boost is the better treatment option with an evidence level 1 based in retrospective and prospective trials (Shen *et al.*, 2012; Morris *et al.*, 2015).

2.5.3 Contraindications

The TRUS-guidance brachytherapy contraindications can be divided in absolute and relatives. The absent of a rectum is an absolute contraindication because the procedure cannot be performed. Relative contraindications for HDRBT can be summarized as follow: distant metastases, history of transurethral resection of the prostate (TURP), pubic arc interference, a low peak urinary flow rate of < 10cm^3/s, a postvoid residual volume >100cm^3, collagen vascular disease and lithotomy position or anaesthesia not possible (Zaorsky *et al.*, 2016; Davis *et al.*, 2012; Yamada *et al.*, 2012; Hoskin *et al.*, 2013).

2.5.4 Technical aspects

HDRBT is a temporary type of brachytherapy where the high dose-rate radioactive source is inserted into the prostate during the applicators implantation procedure. The two main isotopes used are iridium 192 (^{192}Ir) or cobalt 60 (^{60}Co). The procedure is performed under general or spinal anaesthesia with the patient in lithotomy position. HDRBT allows for improved accuracy of needle placement and radiation dose distribution through the use of intraoperative optimization software.

According to GEC/ESTRO recommendations, the HDRBT should be performed under TRUS guidance with template, TRUS fixation and stepping unit, and treatment planning software (Hoskin *et al.*, 2013). ABS also recommends TRUS, CT or MRI for treatment planning (Yamada *et al.*, 2012).

2.5.5 Volumes for treatment planning

Treatment planning can be performed with ultrasound, CT or MRI-based images. According to GEC/ESTRO the next volumes should be defined in every patient (Hoskin *et al.*, 2013):

(a) Clinical target volume (CTV): include the prostate capsule and any macroscopic extracapsular disease or seminal vesicle involvement. A 3 mm margin should be added to cover the microscopic disease.

(b) Organ at risk (OAR) includes: rectum, urethra, bladder, penile bulb and neurovascular bundle.

2.5.6 Dose prescription and constraints

For treatment approval plan, GEC/ESTRO and ABS recommends that the CTV V_{100} should be >90% (Hoskin *et al.*, 2013; Yamada *et al.*, 2012). Given the heterogeneity in dose fractionation, the ABS does not provide normal tissue constraints and only refers OARs constraints used by experienced HDR centres. For example, in the Table 2-6 describes OARs constraints in two centres using HDRBT boost as a single fraction (Yamada *et al.*, 2012).

Table 2-6 *Constraints in experienced centres for HDRBT for prostate cancer.*

Institution	Dose fractionation	Urethra	Rectum
UCSF	Boost 15 Gy x 1	V_{125} < 1cc V_{150} = 0 cc	V_{75} < 1 cc
Toronto	Boost 15 Gy x 1	D_{10} < 118% Max < 125%	V_{80} < 0.5 cc

UCSF = University of California San Francisco; V_{125} = fractional volume covered by 125% of the prescription dose; V_{150} = fractional volume covered by 150% of the prescription dose; V_{75} = fractional volume covered by 75% of the prescription dose; V_{80} = fractional volume covered by 80% of the prescription dose; D_{10} = dose that covers the highest 10% of the organ.

On the other hand, GEC/ESTRO in its last update recommend dose constraints for OARs with conversion into the EQD_2 (Hoskin *et al.*, 2013), as shown in the Table 2-7.

Table 2-7. *Dose constraints for OARs proposed by GEC/ESTRO*

Urethra	Rectum
$D_{0.1} \leq 120$ Gy EQD_2 $D_{10} \leq 120$ Gy EQD_2 $D_{30} \leq 105$ Gy EQD_2	$D_{2cc} \leq 75$ Gy EQD_2

At this time, there is no data available on dose constraints to penile bulb and neurovascular bundles for HDRBT in prostate cancer.

2.5.7 Fractionation and treatment sequence

To date, there are no a specific dose-fractionation regimen for HDRBT boost in prostate cancer. There is wide variability in dose schedules currently in clinical practice. The ABS has not recommended a particular dose fractionation regimen supported in the excellent outcomes reported in the literature with the different schemes (Yamada *et al.*, 2012). Meanwhile, GEC/ESTRO suggest various fractionations options, as shown in Table 2-8 (Hoskin *et al.*, 2013). In general, EBRT is associated through standard fractionations to doses between 36 – 50 Gy (Yamada *et al.*, 2012).

***Table 2-8**. HDRBT planning doses*

Dose	Number of fractions
15 Gy	3
11 – 22 Gy	2
12 – 15 Gy	1

According to GEC/ESTRO the use of HDRBT monotherapy currently is undertaken into the clinical study. Efficacy and tolerability to date have been encouraging for the latest published series (Yoshioka *et al.*, 2011; Hoskin *et al.*, 2012; Prada *et al.*, 2012). The main dose fractionations regimens are summarized in the Table 2-9 (Yamada *et al.*, 2012; Hoskin *et al.*, 2013).

***Table 1-9.** HDRBT planning doses for monotherapy*

ABS	GEC/ESTRO
31.5 Gy in 3 fractions	34 Gy in 4 fractions
34 – 38 Gy in 4 fractions	36-38 Gy in 4 fractions
36 – 45 Gy in 6 fractions	31.5 Gy in 3 fractions
	26 Gy in 2 fractions

Three temporal approaches for combining EBRT and HDRBT have been described (Zaorsky *et al.*, 2013; Zaorsky *et al.*, 2014). Figure 2-2 describes the sequences of combination between HDRBT and EBRT.
If EBRT is delivered first, HDRBT is delivered 1-6 weeks later. Another options are when EBRT can be interdigitated with HDRBT. Lastly, HDRBT can be delivered first and EBRT delivered 1-3 weeks later. Is important to note, that when HDRBT is delivered before EBRT, there is a reduction of pre-implant radiation-induce oedema and GU symptoms.

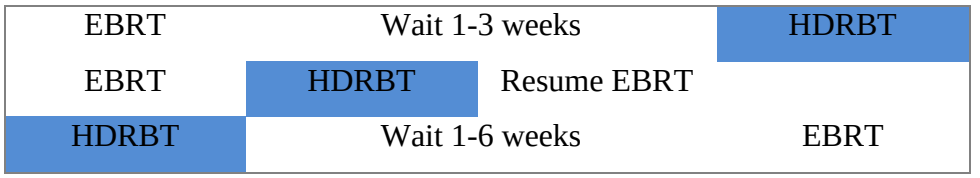


Figure 2-2. *Possible treatment schemes combination between HDRBT boost and EBRT for prostate cancer.*

2.5.8 Evidence of HDRBT Boost

HDRBT has an important role in the treatment of prostate cancer in combination therapy (EBRT plus HDRBT) for intermediate- and high-risk disease. Currently, the evidence for this treatment modality includes two randomized trials (Hoskin *et al.*, 2007; Sathya *et al.*, 2005).

Sathya *et al*. (2005) performed the first randomized phase III study with localized prostate cancer patients. In that study 104 patients were treated with EBRT alone (66 Gy) or HDRBT boost (35 Gy) plus EBRT (40 Gy). The primary goal of this trial was biochemical or clinical failure, and a statistically significant benefit in favour of the combination therapy (HDRBT + EBRT) was reported after a 98 months of follow-up.

The second trial, published by Hoskin *et al.* (2007) included a total of 220 patients who were randomised to receive HDRBT boost versus EBRT alone. After a median follow-up of 30 months, favourable outcomes for combined HDRBT and EBRT were reported. This trial was updated in 2012, where the authors reported a recurrence-free survival of 116 months for patients receiving HDRBT boost compared with 74 moths for EBRT alone after a follow-up of 85 months (Hoskin *et al.*, 2012).

The findings of major studies at least 5 to 10 years of median follow-up, prospective or retrospective and with at least 300 patients have reported BRFS rates of 69-96% and 63-97% for intermediate- and high-risk, respectively (De Bari et al., 2015). In a systematic review of prospective studies using HDRBT boost, the reported 5-year BRFS for intermediate- and high-risk were 80-98% and 59-96%, respectively Zaorsky *et al.* (2014).

2.5.9 Toxicity of HDRBT Boost

As reported in the literature, HDRBT boost treatment is very well tolerated and accepted by the patients. According to Morton (2004), the most significant late toxicity of HDRBT boost is urethral stricture, which has been reported to occur in up to 8% of the patients.

Several prospective clinical trials have shown rates of Grade 3-4 genitourinary (GU) and gastrointestinal (GI) toxicities of 0-12% and 0-8% respectively (Duchesne *et al.*, 2007; Kalkner *et al.*, 2007; Martinez *et al.*, 2003; Myers *et al.*, 2012; Vargas *et al.*, 2006).

Hoskin et al. (2012) in their randomised phase III study reported a late G3-4 toxicity of 31% for GU and 6% for GI, and found no significant difference between HDRBT + EBRT arm and ERBT alone arm for toxicity. In addition, Challapalli *et al*. (2012) also reported a wide range rate (2-20%) for Grade 3 GU toxicity and the erectile dysfunction was reported between 10-47% of patients.

The clinical outcomes suggest that the use of HDRBT boost is safe. However, there are also studies that have reported high rate of toxicity. For example, Mohammed *et al.* (2012) based in 1903 prostate cancer

patients from four prospective non-randomised trials reported highest toxicity in the EBRT + HDRBT group. They found a rate of 10% for late urethral strictures compared to 2% in the EBRT group. In reference to GI toxicity, this study found a rate of 26% for any GI toxicity ≥ Grade 2 compared with 16% and 2 % for EBRT and brachytherapy alone, respectively.

2.6 Uncertainties in volumes delineation

Current developments in radiotherapy and brachytherapy focus on increasingly accurate planning techniques, and as a requirement for this goal it necessary to achieve a high accuracy and precision for target and OARs delineation.

During the planning process, the inadequate definition of the target and OARs might introduce a systematic error in all other steps of the treatment planning and delivery process. In other words, that could potentially lead to a reduction of the dose delivered to the target, corresponding with lower local control, and increased toxicity in the patients (Van de Steene *et al.*, 2002; Lee *et al.*, 2002; Kim *et al.*, 1995; Jansen *et al.*, 2010).

The variation between observers (commonly "inter-observer variability" or "IOV") in volumes delineation can have implications for the patients in terms of local control, surveillance and toxicities. In addition, this variation may also affect the dose volume histograms (DVHs) and resulting in differences in plan acceptability among physicians.

Among the methods for quantifying the magnitude of uncertainties in volume delineations, involving mean, range, standard deviation, the ratio of the largest and the smallest delineated volume (V_{max}/V_{min}), coefficient of variation (COV), conformity index, kappa (k) index, etc. (Fotina *et al.*, 2012).

Several studies evaluating IOV in radiotherapy or brachytherapy in volume delineation have been published. However, the comparison between studies and the applicability of the results is very difficult, because there is not a standardized method in its design, for example, the studies using different number of observers, datasets, metrics and statistical tests. In most cases, the dosimetric impacts not are quantified and reported (Vinod *et al.*, 2016).

As of today, in the systematic review of uncertainties in volume delineation published by Vinod *et al*. (2016), there are 119 studies available evaluating IOV in volume delineation in different clinical sites, such as breast, bladder, prostate, lung, oesophagus, stomach, pancreas, liver, rectum, head and neck, brain, cervix, uterus, lymphoma, sarcoma and OARs. These studies include as image modalities CT, MRI and US, and the majority of studies have been focused on target delineation. Further research is necessary for IOV analysis in OARs delineation, and thus to quantify the dosimetric impact, which will make possible reducing the mobility in the patients.

CHAPTER III

AIM, OBJECTIVES AND STUDY DESIGN

3.1 Aim

The aim of the work presented in this thesis is to evaluate the significance of Dose Volume Histogram parameters ($D_{0.1cc}$ and D_{2cc} [the minimum dose received by the most exposed 0.1 and 2.0 cm^3 volume of the rectum]) for predicting late rectal toxicity (LRT) of a cohort of patients diagnosed with prostate cancer and treated with HDRBT boost using real-time TRUS based planning in combination with EBRT. This relationship will be assessed based on the rectal constraint recommended by GEC/ESTRO. In addition, the robustness of D_{2cc} constraint has not been clearly investigated; therefore, two consecutive studies will be made to determine the interobserver variability in the rectum contouring. A first pilot study will performed with a limited number of patients and physicians of the same center. Lastly, in order to evaluate the outcomes from the pilot study, a multicentre prospective study will performed.

3.2 Objectives

Each chapter in this thesis is designed to address specific objectives outlined as follows:

1. To undertake a descriptive clinical study to determine the occurrence of rectal toxicity in prostate cancer patients focusing on late rectal toxicity.

2. To carry out a clinical analysis to investigate the control local and overall survival rates in prostate cancer patients treated with HDRBT boost in combination with EBRT.

3. To determine the significance of the dose-volume histogram parameter for predicting late rectal toxicity after single-fraction HDRBT boost in combination with EBRT

4. To conduct a pilot prospective study to investigate the degree of interobserver variability in rectum delineation in the HDRBT and assesses the robustness of D_{2cc} parameter according to GEC/ESTRO recommendation.

5. To conduct a multiinstitutional prospective study with expert physicians to compare the outcomes obtained previously in the pilot study and reporting the dosimetric impacts in rectum delineation due to interobserver variability.

3.3 Study Design

In order to accomplish the objectives, four sub-analysis were performed, and presented using 3 peer-reviewed scientific papers. This section summarises the methods used, and in each one of them is described in more detail the specific analysis performed.

3.3.1 Sub-analysis 1 y 2 (Paper I): Clinical outcomes and rectal toxicity in HDR brachytherapy boost for prostate cancer.

a. *Analysis of rectal toxicity incidence, local control and overall survival in prostate cancer patients treated with HDRBT.*
b. *Analysis of relationship among D_{2cc} and late rectal toxicity (LRT)*

3.3.1.1 Patients

Three hundred patients with intermediate- or high-risk prostate cancer were included between August 2010 and March 2015 at Hospital Universitari i Politècnic La Fe. All patients were treated with curative intent by a combination of HDRBT and EBRT, and followed-up prospectively.

3.3.1.2 Radiotherapy treatment

Treatment comprised a single-fraction HDRBT boost of 15.0 Gy plus EBRT (46.0 Gy delivered in 23 fractions) or an HDRBT boost of 9.5 Gy plus EBRT (60 Gy delivered in 30 fractions) if the seminal vesicles were infiltrated using real-time transrectal ultrasound-based planning.

3.3.1.3 Evaluation of LRT

Rectal toxicity was evaluated every 3 months after the end of the combined treatment using the Common Terminology Criteria for Adverse Events, version 4.0 as is shown in **Table 3-1**. LRT was defined over 90-day period from the completion of treatment.

Table 3-1

General characteristics of Common Terminology Criteria for Adverse Events grading

Grade	General characteristic
1-Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention nor indicated.
2-Moderate	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
3-Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4-Life threatening	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

ADL = Activities of daily living; AE = adverse event.

3.3.1.4 Evaluation of DVH parameters

The minimum dose received by the most exposed 0.1 and 2.0 cm^3 volume od the rectum ($D_{0.1cc}/D_{2cc}$) was analysed by estimating the biologically equivalent rectal dose according to the recommendations of the Group Européen de Curiethérapie/European Society for Radiotherapy and Oncology.

3.3.1.5 Statistical Analysis

Descriptive statistics were calculated to summarize the patients', tumour and toxicity characteristics. Overall survival (OS) and biochemical DFS (bDFS) curves were estimating using Kaplan-Meier method. The rates of LRT between the two treatment regimens were compared using the X^2 test.

Dose-toxicity relationships influencing the probability of developing an LRT go grade ≥ 2 were analysed using an ordinal regression model. All statistical analyses were conducted using R statistical software, version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

3.3.2 Sub-analysis 3 (Paper II): Interobserver uncertainties in rectal contouring: A pilot study.

a. *Analysis of the D_{2cc} for rectal contouring via intra- and inter-observer variability.*

3.3.2.1 Cases (patients)

The HDRBT treatment planning data of 5 patients treated with combined radiotherapy (HDRBT and EBRT) at Hospital Universitari i Politècnic La Fe was included. All patients were diagnosed with prostate adenocarcinoma and treated according to the same treatment plan.

3.3.2.2 Treatment planning

Treatment comprised a single-fraction HDRBT boost of 15.0 Gy plus EBRT (46.0 Gy delivered in 23 fractions). The HDRBT was an

intraoperative procedure based on US imaging findings. The urethra and rectum were contoured as OARs.

3.3.2.3 Contouring protocol

An expert group comprising 2 radiation oncologists, 1 radiologist, and 1 urologist usually involved in prostate brachytherapy and prostate US was established. This group had previously determined rectal delineation criteria in consensus, as are shown in **table 3-2**.

Table 3-2.

Boundaries of the rectal contouring

Definition of borders	Description
Superior (cranial)	Where the urethra; contour begins.
Anterior	The posterior layer of Denonvilliers' fascia
Posterior	The rectal wall is visible on the TRUS screen.
Inferior (caudal)	Where the urethra contour ends.

TRUS = trans-rectal ultrasonography

Four observers delineated the rectum on 5 US images sets from 5 prostate cancer patients. The observer repeated the delineation procedure twice at a 1-week interval (for evaluating intra-observer variability).

3.3.2.4 Evaluation of DVH parameters

DVH were used to evaluate plans according to the GEC/ESTRO recommendations on HDRBT for prostate cancer. The $D_{0.1cc}$, D_{1cc} and

D_{2cc} rectum volumes parameters were determined. All dose values were biologically normalized to an EQD2 expressed in units of Gy $_{a/b=3}$.

3.3.2.5 Statistical Analysis

The mean, standard deviation, and range of each DVH parameter were evaluated for each patient. The interobserver COV was obtained by calculating the ratio of the SD to the mean for each patient. For the 5 patients, the differences in dose values between duplicated US image sets were analysed using the non-parametric Friedman test.

The intraobserver COV was defined as 2 SDs of the value resulting from the following equation: absolute value [first measurement – second measurement]/mean measurement. For the 5 patients, the differences in dose values between duplicated US image sets were analysed using the Wilcoxon signed-rank test.

The impact of contouring uncertainties on the total dose delivered to the rectum was evaluated by estimating the total dose (EBRT+HDRBT), assuming that the rectum received the prescribed EBRT dose (46 Gy).

Statistical analysis was performed using the SLSTAT software (version 2014.6.01; Addinsoft, Paris, France).

3.3.3 Sub-analysis 4 (**Paper III**): Interobserver variability in rectum contouring: A multi-institutional prospective study.

a. *Analysis of the interobserver variability (IOV) of rectum contouring, and its dosimetric consequences, for HDRBT in patients with prostate cancer across multiple institutions.*

3.3.3.1 Cases (patients)

The HDRBT treatment planning data of 10 patients treated with combined radiotherapy (HDRBT and EBRT) at Hospital Universitari i Politècnic La Fe was included. All patients were diagnosed with prostate adenocarcinoma and treated according to the same treatment plan.

3.3.3.2 Treatment planning

Treatment comprised a single-fraction HDRBT boost of 15.0 Gy plus EBRT (46.0 Gy delivered in 23 fractions). The HDRBT was an intraoperative procedure based on US imaging findings. The urethra and rectum were contoured as OARs.

3.3.3.3 Contouring protocol

Expert consensus rectal contouring was devised by the observers during a joint discussion at our department, and was based on a previous consensus established in a pilot study (Paper II), as shown in Table 3-2.

Five identical TRUS image sets were generated from the original HDRBT treatment planning. TRUS image sets only showed the urethra contour as a reference for longitudinal rectum delineation.

Each observer contoured the rectal wall on 10 TRUS image sets from 10 prostate cancer patients according to previously established multi-

institutional consensus guidelines. All the rectal wall contours were included in the original HDRBT plan, and cumulative DVH data were measured and collected for analysis.

3.3.3.4 Evaluation of DVH parameters

The minimal doses to 0.1 cm^3 ($D_{0.1cc}$), 1 cm^3 (D_{1cc}), and 2 cm^3 (D_{2cc}) of the rectum were determined according to the GEC/ESTRO recommendations. The mean and standard deviation (SD) of each DVH parameter were evaluated for each patient.

To quantify the IOV in rectum contouring, the coefficient of variation (COV), defined as the ratio of SD to the mean, was measured for all patients. The overall COV for the 10 patients was calculated to provide a measure of interobserver variation across the entire group.

For the assessment of the dosimetric impact due to variations in rectal delineation, the total dose delivered to the rectum (HDRBT + EBRT) was estimated under the assumption that the rectum received the prescribed EBRT dose (46 Gy). All dose values were biologically normalized to an EQD_2 expressed in units of $Gy_{\alpha/\beta=3}$.

3.3.3.5 Statistical analysis

The mean and COV values for $D_{0.1\ cc}$, D_{1cc}, and D_{2cc} were compared to evaluate the IOV in rectum contouring. The non-parametric Friedman test was used to compare the differences in dose values between all patients. P-values <0.05 were considered statistically significant. Statistical analysis was performed using the XLSTAT software (version 2017.19.01; Addinsoft, Paris, France).

CHAPTER IV

RESULTS - PUBLICATIONS

4. PAPER I:

CLINICAL OUTCOMES AND RECTAL TOXICITY IN HDR BRACHYTHERAPY BOOST FOR PROSTATE CANCER.

Most of the content of this chapter was based in the original research paper:

Chicas-Sett R, Farga D, Perez-Calatayud MJ, Celada F, Roldan S, Fornes-Ferrer V, Ibanez-Rosello B, Tormo A, Benlloch JM, Perez-Calatayud J. High-dose-rate brachytherapy boost for prostate cancer: analysis of dose-volume histogram parameters for predicting late rectal toxicity. *Brachytherapy 2017*; doi: 10.1016/j.brachy.2017.03.002.

[Q2/Radiology, Nuclear Medicine and Medical Imaging; JCR]

Kind permission was granted by the journal to reprint this article as a chapter of this thesis.

4.1 Introduction

High-dose-rate brachytherapy (HDRBT) combined with external beam radiotherapy (EBRT) is used as an alternative treatment to radical prostatectomy or EBRT alone in patients with intermediate- or high-risk prostate cancer (De Bari *et al.,* 2015). In 2009, Viani *et al.* published a meta-analysis of randomised and controlled trials reporting better outcomes in preventing biochemical failure with the use of dose escalation compared to conventional dose radiotherapy. The implementation of intensity-modulated radiotherapy has facilitated high-dose conformation and dose escalation. However, the higher radiation doses delivered to the organs at risk (OARs) during intensity-modulated radiotherapy are associated with increased gastrointestinal and genitourinary toxicity (Kuban *et al.,* 2008).

An alternative method of dose escalation has been demonstrated using a HDRBT boost in combination with EBRT (Demanes *et al*., 2009; Hoskin *et al.*, 2007; Martinez *et al.*, 2011; Zwahlen *et al.,* 20104). It has been supported in a radiobiological model of prostate cancer (Kal *et al*., 2003) in which a low alpha/beta ratio suggests that the prostate cancer cells have a greater sensitivity to high-dose per fraction radiotherapy than normal tissues. Application of the HDRBT boost has achieved an excellent conformity and rapid dose fall-off outside the target volume, reducing the dose to surrounding normal tissues (Smolska-Ciszewska *et al.*, 2015). In 2013, Morton *et al.* in a review of HDRBT reported disease-free survival (DFS) rates of >90.0% and >80.0% for patients with intermediate- and high-risk disease, respectively. Different dose and fractionation regimens have been included in the American

Brachytherapy Society (Yamada *et al.*, 2012) and in the Groupe Européen de Curiethérapie/European Society for Radiotherapy and Oncology (GEC/ESTRO) recommendations (Hoskin *et al.*, 2013) on HDRBT for prostate cancer. In our opinion, clinical data comparing the efficacy and toxicity of EBRT alone with EBRT plus a HDRBT boost are limited (Hoskin *et al.*, 2007; Zwahlen *et al.*, 2010; Hoskin *et al.*, 2012). In the latest task group report in 2016, the American Brachytherapy Society (Spratt *et al.*, 2016) suggested based on favourable outcomes with combination therapy that it might become the standard for the treatment of high-risk cancers.

Studies have demonstrated low treatment-related toxicity in patients treated with HDRBT. Zwahlen *et al.* (2010) reported acute rectal toxicity rates of ≤34.0%, ≤12.0%, and ≤3.0% for patients with Grade 1–3, respectively. Late rectal toxicity (LRT) was reported in 58.0% of patients with Grade 1 and 34.0% of patients with Grade 2, respectively (Zwahlen *et al.*, 2010). In general, LRT has been reported with an incidence of 3.0–7.0% (Hoskin *et al.*, 2012). Altered bowel habit, discomfort, diarrhoea, mucus discharge, and bleeding have mainly been described. Dose-volume histogram (DVH) parameters, including the minimum dose received by the most exposed 2.0 cm^3 volume of the OAR (D_{2cc}), have been reported as predictive factors of LRT of Grade ≥2 in patients with gynaecological carcinomas (Kim *et al.*, 2013; Lee *et al.*, 2012). In our opinion, limited studies of HDRBT for prostate cancer have been realised, especially for the evaluation of LRT. At this time, the American Brachytherapy Society (Yamada *et al.*, 2012) has not as yet proposed specific normal tissue constraints of HDRBT for prostate cancer and GEC/ESTRO (Hoskin *et*

al., 2013) in the last update has proposed a dose constraint of D_{2cc} ≤75.0 Gy $EQD2_{\alpha/\beta=3}$ for rectum.

Our group recently published the results of a pilot study (Chicas-Sett *et al.*, 2016) that assessed the robustness of the dose constraint (D_{2cc} ≤75.0 Gy biologically equivalent rectal dose [$EQD2_{\alpha/\beta=3}$]) of the rectum, according to the GEC/ESTRO recommendations (Hoskin *et al.*, 2013) on HDRBT for prostate cancer. An inter-observer variation of <5.0% with an $EQD2_{\alpha/\beta=3}$ for the reported D_{2cc} dose difference of ≤5.8 Gy was obtained (Chicas-Sett *et al.*, 2016). No dose-volume effects have been established between D_{2cc} and the occurrence of LRT. Thus, the purpose of the present study is to evaluate the significance of DVH parameters ($D_{0.1cc}$ and D_{2cc} [the minimum dose received by the most exposed 0.1 and 2.0 cm^3 volume of the rectum]) for predicting LRT in HDRBT-treated prostate cancer patients.

4.1.2 Materials and methods

4.1.2.1 Patients

Between August 2010 and March 2015, a total of 300 patients with histologically confirmed locally advanced prostate cancer were treated with curative intent by a combination of HDRBT and EBRT at our institute and were followed-up prospectively. All patients provided informed written consent for the use of their clinical data. The appropriate Ethical Review Board committee of our institution approved the study protocol.

Patients were classified into an intermediate- or a high-risk group according to the National Comprehensive Cancer Network guidelines (NCCN, 2016), based on initial serum prostate specific antigen level, Gleason score (determined by core biopsy), and clinical tumour stage (determined by magnetic resonance imaging). Almost all of the patients (*N* = 267; 89.0%) received androgen deprivation therapy. In unfavourable intermediate- and high-risk patients, neoadjuvant androgen deprivation therapy was performed (2–3 months) and was continued as concomitant and adjuvant treatment (6 months in the intermediate- and 24 months in the high-risk groups, respectively).

4.1.2.2 High-dose-rate brachytherapy boost treatment

HDRBT treatment planning was performed using an Oncentra Prostate® planning device, version 4.2 (Nucletron, an Elekta company, Veenendaal, The Netherlands). HDRBT was conducted as an intraoperative transrectal ultrasound-based treatment as recommended in the GEC/ESTRO guidelines (Hoskin *et al.*, 2013) and it was delivered to the patient with an ultrasound probe in place. The HDRBT procedure performed in this study has been described in detail elsewhere (Chicas-Sett *et al.*, 2016). The prescribed dose was a single-fraction of 15.0 Gy delivered to the whole prostate/seminal vesicles with a 3.0 mm margin (except in the vesical and rectal directions) or a single-fraction of 9.5 Gy if the seminal vesicles were infiltrated. In general, the prescribed dose was defined as the minimum dose received by 90.0% of the clinical target volume according to the GEC/ESTRO recommendations (Hoskin *et al.*, 2013). The urethra and rectum were contoured as OARs and their

respective dose constraints were reported according to the GEC/ESTRO recommendations (Hoskin *et al.*, 2013). The rectum contouring was established in our protocol by use of radiologic anatomic boundaries, as is shown in Fig. 4-1: a) the anterior surface corresponds with the posterior layer of Denonvillier´s fascia; and b) the posterior surface corresponds with the rectal wall visible on the US screen (Chicas-Sett *et al.*, 2016). $D_{0.1cc}$ and D_{2cc} values for rectum were systematically recorded. After treatment delivery, four gold fiducial markers were implanted for image-guided radiotherapy. HDRBT was performed first, followed by computed tomography simulation 2 weeks later. EBRT was conducted after an additional 2-week interval. In instances where complications could occur that would prohibit HDRBT, this plan would facilitate continuous high-dose treatment during EBRT.

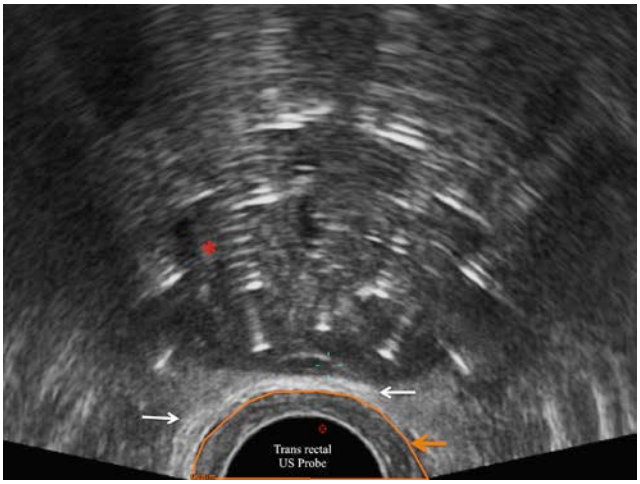


Fig. 4-1. *Transrectal ultrasound-based planning. Prostate and catheters inserted (*); the white arrows indicates the posterior layer of Denonvillier´s fascia; the orange line and arrow indicates the rectal contour.*

4.1.2.3 External beam radiotherapy treatment

EBRT treatment planning was performed 4 weeks after HDRBT using an Eclipse planning system, version 13.0 (Varian Medical Systems, Palo Alto, CA, USA).

EBRT was realised using volumetric-modulated arc therapy (RapidArc; Varian Medical Systems, Palo Alto, CA, USA) and image-guided radiotherapy, and daily cone beam computed tomography or orthogonal kV images were combined and gold fiducial marker matching was performed. The clinical target volume was defined as the prostate gland/seminal vesicles with a 3.0 mm margin in all directions**,** but this margin was only used in patients with capsular involvement. The planning target volume was defined as the clinical target volume with a 5.0 mm margin in all directions, except in the posterior direction in which the margin was 4.0 mm. The prescribed dose was defined such that 95.0% of the planning target volume should receive ≥95.0% of the prescribed dose (equivalent to D_{50}). The total dose of EBRT was 46.0 Gy (delivered in 23 fractions) for intermediate- and high-risk patients who received a HDRBT boost of 15.0 Gy, and 60.0 Gy (delivered in 30 fractions) for patients with infiltration of the seminal vesicles who received a HDRBT boost of 9.5 Gy.

4.1.2.4 Dose-volume histogram parameter analysis

The DVHs for each patient were generated for the single-fraction HDRBT treatment and the parameters were reported according to the GEC/ESTRO recommendations (Hoskin *et al.*, 2013) on HDRBT for prostate cancer. $D_{0.1cc}$ and D_{2cc} values for rectum were recorded for each

patient. The total dose delivered to the rectum was evaluated by estimating the total dose of HDRBT and EBRT, assuming that the rectum had received the prescribed EBRT dose of 46.0 or 60.0 Gy as described above. All dose values were normalised to an $EQD2_{\alpha/\beta = 3}$ with units expressed in Gy.

4.1.2.5 Late rectal toxicity scoring and follow-up

LRT was graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute, 2009). Morbidity was assessed 1 month after the end of EBRT and then every 3 months for the first year of follow-up, every 6 months for the subsequent 4 years, and annually thereafter. LRT was defined over a 90-day period from the completion of treatment. The highest graded event was considered for analysis. For the purpose of this study, the minimum interval from the end of EBRT to evaluation was 18 months, except in instances where death had occurred before then.

4.1.2.6 Statistical analyses

Descriptive statistics were calculated to summarise the patients', tumour, and toxicity characteristics. Overall survival (OS) and biochemical DFS (bDFS) curves were estimated using the Kaplan-Meier method. To analyse the effects of DVH parameters, a LRT of Grade ≥2 was used as the endpoint. The rates of LRT between the two treatment regimens were compared using the chi-square test. Dose-toxicity relationships influencing the probability of developing a LRT of Grade ≥2 were analysed using an ordinal regression model. In the multivariate

analysis, a step-wise ordinal regression model was used with all clinical and DVH parameters included to predict the risk of developing LRT. All statistical analyses were conducted using R statistical software, version 3.2.2. (The R Foundation for Statistical Computing, Vienna, Austria). A $p \leq 0.05$ was considered statistically significant.

4.1.3 Results

4.1.3.1 Descriptive data

The patient and treatment characteristics are summarised in Table 4-1. A total of 300 patients were included in our study. The median age was 71 (range, 46–84) years. Two hundred and forty patients (80.0%) were classified into the high-risk group and 60 patients (20.0%) were classified into the intermediate-risk group according to the National Comprehensive Cancer Network guidelines (NCCN, 2016). Two hundred and eighteen patients (72.7%) were treated with a HDRBT boost of 15.0 Gy plus EBRT (46.0 Gy delivered in 23 fractions) and 82 patients (27.3%) were treated with a HDRBT boost of 9.5 Gy plus EBRT (60.0 Gy delivered in 30 fractions).

4.1.3.2 Survival outcomes

The estimated 5-year OS and bDFS rates were 87.0% (95.0% confidence interval: 82.0–92.0%) and 90.0% (95.0% confidence interval: 83.0–98.0%), respectively, as shown in Fig. 4-2 and Fig. 4-3. The median follow-up duration was 33 (range, 2–68) months. Only eighteen patients

have had a follow-up less than 18 months, because the death had occurred before then.

Table 4-1.
Patient and treatment characteristics

Characteristic	Patients (*N* = 300)
Age (years), median (IQR)	71 (46–84)
Stage, *N* (%)	
T1c	19 (6.3)
T2a	38 (12.7)
T2b	49 (16.3)
T2c	51 (17.0)
T3a	73 (24.3)
T3b	70 (23.3)
Gleason score, *N* (%)	
0–6	115 (38.3)
7	120 (40.0)
>7	65 (21.7)
Initial PSA (ng/mL), *N* (%)	
0–10	126 (42.0)
10–20	90 (30.0)
>20	84 (28.0)
NCCN group, *N* (%)	
Intermediate-risk	59 (19.7)
High-risk	241 (80.3)
ADT, *N* (%)	
Short-term (6 months)	46 (15.3)
Long-term (24 months)	221 (73.7)
None	33 (11.0)
Treatment regimen, *N* (%)	
HDRBT (15.0 Gy) + EBRT (46.0 Gy)	218 (72.7)
HDRBT (9.5 Gy) + EBRT (60.0 Gy)	82 (27.3)
Brachytherapy therapy	
CTV (cm^3), median (IQR)	38 (21–135)

ADT = androgen deprivation therapy; CTV = clinical target volume; EBRT = external beam radiotherapy; HDRBT = high-dose-rate brachytherapy; IQR = interquartile range; NCCN = National Comprehensive Cancer Network; PSA = prostate specific antigen.

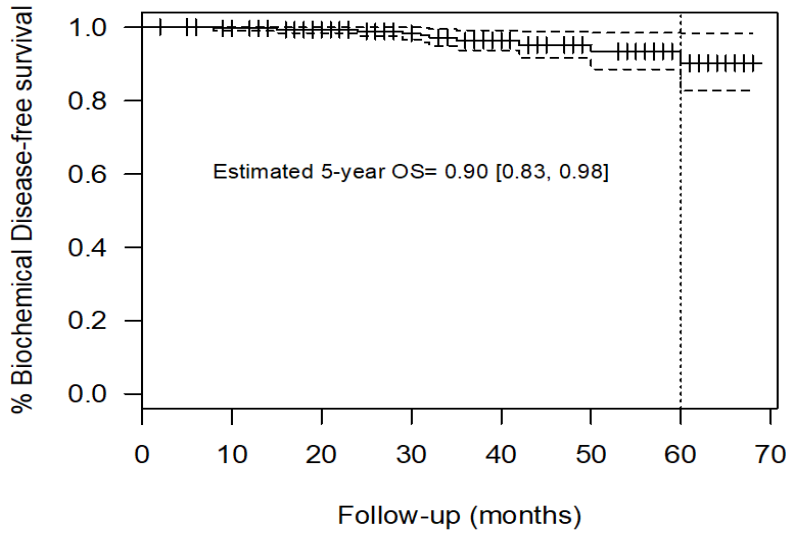


Fig. 4-2. *Kaplan-Meier curve of overall survival (OS).*

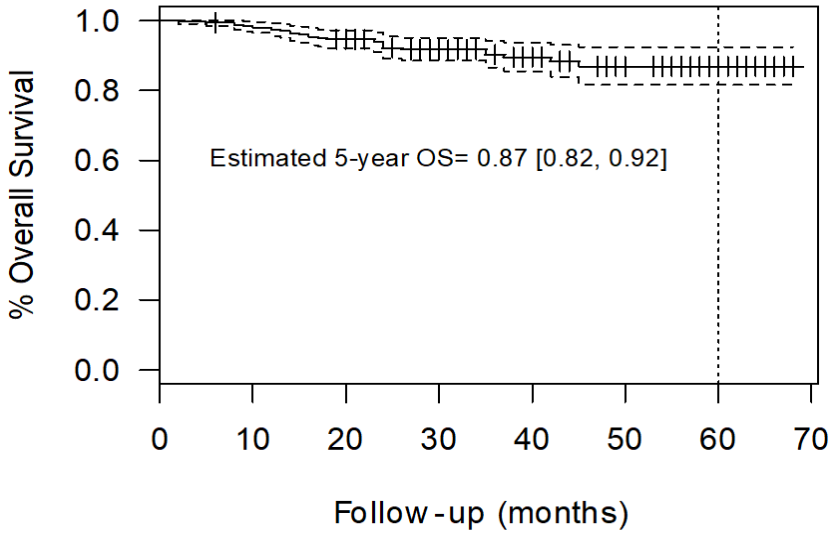


Fig. 4-3. *Kaplan-Meier curve of biochemical disease-free survival (bDFS).*

4.1.3.3 Late rectal toxicity

LRT occurred in 62 patients (20.7%). Concentrating on the highest grade of LRT in each patient, 238 patients (79.3%) had Grade 0 (i.e., no LRT during follow-up), 39 patients (13.0%) had Grade 1, 20 patients (6.7%) had Grade 2, and 3 patients (1.0%) had Grade 3 LRT. No LRT of Grade 4 was reported. There was no overall significant difference in LRT between the two treatment regimens ($p > 0.05$), as demonstrated in Table 4-2. The most frequently reported adverse events included diarrhoea in 31 patients (10.3%), proctitis in 28 patients (9.3%), and rectal haemorrhage in 3 patients (1.0%), which are categorised according to the grade of LRT in Table 4-3. The 3 patients (1.0%) with Grade 3 rectal haemorrhage required ablation with an argon laser.

Table 4-2

Comparison of late rectal toxicities between different treatment regimens

Grade, *N* (%)	Treatment regimen		*p*-value
	HDRBT (15.0 Gy) + EBRT (46.0 Gy) (*N* = 218)	HDRBT (9.5 Gy) + EBRT (60.0 Gy) (*N* = 82)	
0–1	203 (93.1)	74 (90.2)	0.550
≥2	15 (6.9)	8 (9.8)	

EBRT = external beam radiotherapy; HDRBT = high-dose-rate brachytherapy

Table 4-3

Comparison of dose distribution and late rectal toxicity (LRT)

DVH parameter (Gy), mean (SD)	LRT	
	Grade 0–1	Grade ≥2
$D_{0.1cc}$	80.3 (4.4)	80.4 (4.0)
D_{2cc}	69.7 (3.6)	70.1 (2.7)

$D_{0.1cc}$ and D_{2cc} = the minimum dose received by the most exposed 0.1 and 2.0 cm^3 volume of the rectum; DVH = dose-volume histogram; SD = standard deviation

4.1.3.4 Dose-volume histogram parameters

The mean ± standard deviation for $D_{0.1cc}$ and D_{2cc} were 80.3 ± 4.4 and 69.7 ± 3.6 for patients with Grade 0–1 and 80.4 ± 4.0 and 70.1 ± 2.7 for patients with Grade ≥2 LRT, respectively, as demonstrated in Table 4-3. No significant difference in $D_{0.1cc}$ or D_{2cc} was observed between patients with Grade 0–1 or Grade ≥2 LRT ($p > 0.05$).

Twenty-three (100%) patients who developed Grade ≥2 LRT received doses ≥65 Gy $EQD2_{\alpha/\beta=3.}$ Only 7 patients who were given a dose ≥75 Gy $EQD2_{\alpha/\beta=3}$ developed Grade ≥2 LRT.

Ordinal regression analysis revealed an association between D_{2cc} and the probability of developing LRT of Grade 1–3 ($p = 0.04$). In Fig. 4-4, an increase in D_{2cc} is associated with a reduction in the probability of developing LRT of Grade 0 and a concomitant increase in the probability of developing LRT of Grade 1–3.

A similar sub-analysis was made including only patients with a follow-up greater than 18 months (N = 272). The result was the same, an

association between D_{2cc} and the probability of developing LRT of Grade 1–3 (p = 0.05) was found.

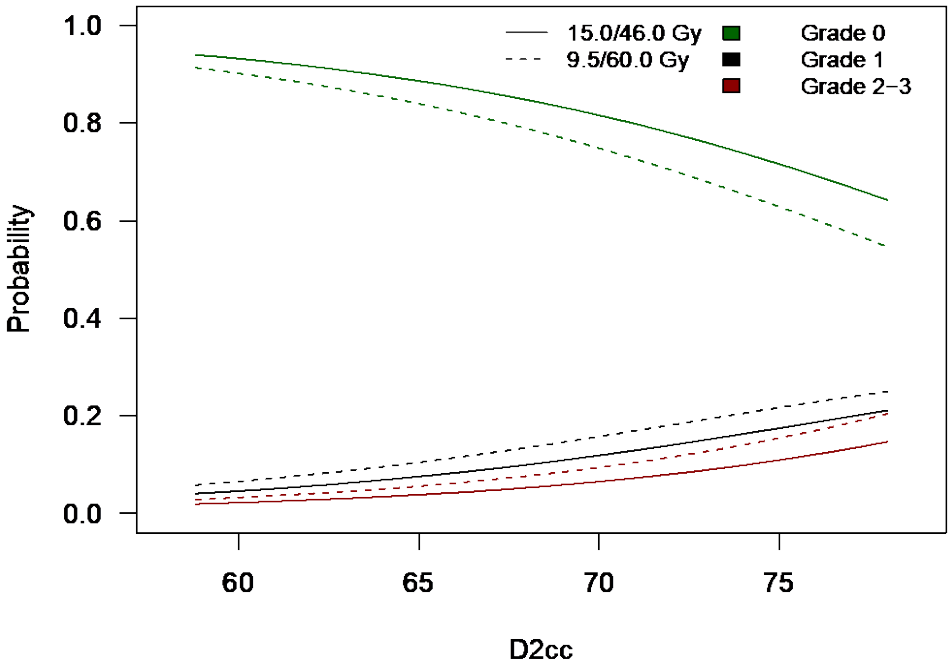


Fig. 4-4. *Relationship between D_{2cc} and late rectal toxicity (LRT). D_{2cc} values are represented on the x-axis and probability values (0–1) according to LRT (Grade 0–3) are represented on the y-axis. D_{2cc} = the minimum dose received by the most exposed 2.0 cm^3 volume of the rectum.*

4.1.4 Discussion

There is a wealth of evidence from retrospective and prospective clinical trials data indicating that HDRBT in combination with EBRT is

associated with excellent outcomes for disease control, primarily in the group of patients with high-risk prostate cancer (Galalae *et al.*, 2009). Among the prospective studies available in the literature, Demanes *et al.* (2009) analysed the largest cohort of patients (N = 411) treated with HDRBT in combination with EBRT and reported 5-year bDFS rates of 87.0% and 63.0% for patients in the intermediate- and high-risk groups, respectively. Prostate specific antigen failure-free rates of 61.0–90.0% have also been reported for patients in the high-risk group (De Bari *et al.*, 2015). Similar results were summarized in 2012 by the American Brachytherapy Society in its consensus guidelines on HDRBT for prostate cancer (Yamada *et al.*, 2012). Our data revealed promising 5-year OS and bDFS rates of 87.0% and 90.0%, respectively.

The most frequently observed rectal complications in our study included diarrhoea in 31 patients (10.3%), discomfort in 28 patients (9.3%), and rectal haemorrhage in 3 patients (1.0%). Zwahlen *et al.* (2010) published similar findings of LRT associated with HDRBT. Although the overall incidence of gastrointestinal toxicity is low, LRT of Grade ≥2 remains a significant problem for the quality of life of the patients (De Bari *et al.*, 2015). In our study, the incidence and severity of LRT is concordant with previous studies with rates of 6.7% and 1.0% observed for Grade 2 and Grade 3 LRT, respectively. Zaorsky *et al.* (2014) published gastrointestinal toxicity rates of 7.0% and <6.0% for Grade 2 and Grade ≥3 gastrointestinal toxicity, respectively.

The American Brachytherapy Society consensus guidelines (Yamada *et al.*, 2012) on HDRBT for prostate cancer has not established dose constraints for normal tissues and has only suggested using constraints

reported by experienced HDRBT centres for OARs. Meanwhile, the latest GEC/ESTRO update in 2013 (Hoskin *et al.*, 2013) has proposed a dose constraint (D_{2cc} ≤75.0 Gy $EQD2_{\alpha/\beta = 3}$) of the rectum and reporting $D_{0.1cc}$ parameter, which has been based on the experience gained in gynaecological brachytherapy (Pötter *et al.*, 2006). Publications such as that of George *et al.* (2011) have reported that D_{2cc} and $D_{0.1cc}$ can predict rectal toxicity in brachytherapy-treated cervical cancer patients. Chopra *et al.* (2015) has also demonstrated a correlation among dose volume metrics and toxicity Grade ≥2 in pelvic interstitial brachytherapy, reporting a lower dose threshold for interstitial brachytherapy than dose threshold described for intracavitary brachytherapy. However, no dose-volume effects have been established between D_{2cc} or $D_{0.1cc}$ and the occurrence of LRT in prostate cancer patients treated with HDRBT. To the best of our knowledge, this is the first study to evaluate the potential of these parameters to predict LRT in HDRBT-treated prostate cancer patients.

In our present study, multivariate and regression analyses revealed that only D_{2cc} was significantly associated with the risk of developing LRT of Grade ≥2 (p = 0.04). As demonstrated in Fig. 4-4, dose-response analysis suggested that an increase in D_{2cc} correlated with an increase in the risk of developing LRT. Although all patients (N=23) with LRT of Grade ≥2 received doses ≥ 65 Gy $EQD2_{\alpha/\beta = 3}$, we treated to realise a dose-stratified analysis for D_{2cc} in order to establish a threshold dose. However, this was not possible. A low incidence of LRT of Grade ≥2 (N = 23 patients; 7.7%) and closer $D_{2.0cc}$ values (median: 70.1 [range, 58.8–

78.0] Gy) have made it difficult to determine a dose cut-off for LRT of Grade ≥2. In addition, to assess the D_{2cc} constraint recommended by GEC/ESTRO (D_{2cc} ≤75.0 Gy $EQD2_{\alpha/\beta = 3}$), it should be noted that 12 patients who developed some grade of toxicity presented with a D_{2cc} of >75.0 Gy and of those patients, 7 (58.3%) had LRT of Grade ≥2. Of the 3 patients (1.0%) who experienced rectal haemorrhage (radiation proctitis confirmed by colonoscopy), one patient (33.3%) had a D_{2cc} of 77.3 Gy, while the remaining two patients had a D_{2cc} of 74.8 Gy and 70.4 Gy, respectively.

Based on our data, we concluded that a significant relationship exists between D_{2cc} and the occurrence of LRT of Grade ≥2. Our analysis included a cohort of 300 patients, but with a lower number of adverse events (*N* = 23; 7.7%). However, the same evaluation criteria (Common Terminology Criteria for Adverse Events, version 4.0) were used in all patients, making it easy to compare the frequency of rectal toxicities. In addition, follow-up was performed prospectively. However, our findings need to be investigated further. Identification of a suitable dose cut-off could improve the optimisation of HDRBT treatment and reduce the risk of LRT.

4.1.4.1 Limitations

There were some limitations of our study. First, its single institution retrospective design and the fact that the data were mostly based on clinical observations. Second, due to the median follow-up period of 33 months, we may have underestimated the frequency of LRT.

4.1.5 Conclusions

D_{2cc} is associated with the occurrence of LRT in HDRBT-treated prostate cancer patients. Although this study has been unable to determine the threshold dose to minimize the occurrence of LRT of Grade ≥2, we believe that it has the potential to promote development of long-term prospective and multiinstitutional investigations that allow to confirm our findings and establishing the threshold dose.

4.2 PAPER II:

INTEROBSERVER UNCERTAINTIES IN RECTAL CONTOURING: A PILOT STUDY

Most of the content of this chapter was based in the original research paper:

Chicas-Sett R, Celada-Alvarez F, Roldan S, Torregrosa A, Betancourt J, Bautista-Ballesteros J, Farga D, Ibañez B, Tormo A, Perez-Calatayud J. An evaluation of the robustness of organ-at-risk recommendations made by GEC/ESTRO according to interobserver variability: a single-center experience. *J Contemp Brachytherapy* 2016; 8:349–355.

[Q3/Radiology, Nuclear Medicine and Medical Imaging; JCR]

Kind permission was granted by the journal to reprint this article as a chapter of this thesis.

4.2.1 Introduction

High-dose-rate brachytherapy (HDRBT), defined by Morton et al. as a method of conformal dose escalation to the prostate (Morton, 2014), involves the placement of sealed sources of radiation in contact with the tumour using after-loading devices. This type of therapy plays an important role in the management of prostate cancer. Notably, dose escalation strategies, which allow the delivery of high radiation doses, have yielded improved local control in patients with prostate cancer. Accordingly, HDRBT is considered a very acceptable option when used in combination with external beam radiotherapy (EBRT) (Yamada *et al.*, 2012). A significant number of EBRT and HDRBT boost studies have reported biochemical relapse-free survival (BRFS) rates of 63–97% in intermediate and high-risk patients (De Bari *et al.*, 2015). Hoskin *et al.*, in a randomized phase III trial, observed a significant improvement in BRFS with EBRT + HDRBT versus EBRT alone, along with a 31% reduction in the risk of recurrence (Hoskin *et al.*, 2012).

In addition, HDRBT monotherapy is gaining relevance as a promising treatment for prostate cancer. However, its administration is under protocol and the majority of related studies have involved a relatively short follow-up period (Demanes *et al.*, 2011). In 2013, Zamboglau *et al*. published a study with the longest follow-up period to date (52.8 months) and reported biochemical control rates exceeding 90% (including intermediate and high-risk groups) [6]. In 2015, Kukielka *et al*. published local control outcomes as high as 96.9%. Similar urinary

toxicity has been observed in patients treated with HDR monotherapy (Cendales *et al.*, 2015).

The primary goal of HDRBT is the delivery of a high radiation dose to the target tissue; however, this goal is restricted by the presence of the surrounding organs at risk (OAR) such as the rectum, which limit the planned total dose for a definitive treatment (Bolling *et al.*, 2007). A high dose to the rectum may cause adverse effects such as local inflammation, fibrosis, telangiectasia, ulceration, necrosis, and fistula, which are directly related to the magnitude of the administered dose (Pötter *et al.*, 2006). Although rare, rectal complications after combined EBRT and HDRBT have been reported and cannot be completely prevented. Although the majority of studies have reported grade 2 toxicity with this combination therapy, proctitis, rectal ulceration, and fistula formation have also been described (Ghilezan *et al.*, 2006).

The effects of the doses to the target and normal tissues can be analysed and calculated by planning systems from dose-volume histograms (DVH). DVH values can be expressed in absolute (cc) or relative volumes (%). The usage of different doses, techniques, and fractionation schedules among departments, however, may present a challenge in the identification of universal quality parameters for the evaluation of brachytherapy treatment plans (Kirisits *et al.*, 2009). In this light, various parameters and indices for OAR documentation (most exposed 0.1-, 1-, 2-, 5-, 10-cc volumes; $D_{0.1cc}$; D_{1cc}; D_{2cc}, D_{5cc}, D_{10cc}, respectively) and the target volume (V_{100}, V_{150}, and V_{200}, or percentages of the clinical target volume [CTV] receiving 100%, 150%, and 200% of the prescribed dose, respectively; D_{100} and D_{90}, or the doses covering

100% and 90% of the CTV, respectively) have been proposed in the context of Groupe Européen de Curiethérapie (GEC) and European Society for Radiotherapy & Oncology (ESTRO) recommendations for the treatment of cervical cancer (Pötter *et al.*, 2006). These parameters were subsequently extrapolated, used, and suggested as comparable universal dosimetric parameters in the recommendations by Hoskin *et al*. regarding HDRBT for prostate cancer (Hoskin *et al.*, 2013; Kovacs *et al.*, 2005).

Because the use of different EBRT and HDRBT schemes result in considerable dose heterogeneity, it is difficult to obtain a generalized OAR constraint. The GEC/ESTRO accordingly recommends the use of an absolute dose-volume constraint expressed in $Gy_{\alpha/\beta=3}$ for every fractionation based on an EQD_2 total dose (Hoskin *et al*., 2013). The $D_{2cc} \leq 75$ Gy EQD_2 has been indicated for specific cases involving the rectum, and has also been supported by Crook et al., who reported absolute volumes rather than relative doses because the latter are subjective and very sensitive to the number of contoured slides and contoured shape of the wall (Crook *et al.*, 2005).

Interobserver variation when contouring clinical target volumes (CTVs) is known as an important source of systematic error in the radiotherapy treatment process. Accordingly, several studies have assessed interobserver variability. For example, in gynaecological brachytherapy, delimitation of the high-risk CTV has been used to demonstrate acceptable interobserver variability (Petric *et al.,* 2008; Dimopoulos *et al.,* 2009; Petric *et al.,* 2013; Duane *et al.,* 2014). However, limited data are available on the impacts of contouring errors on doses to the OARs. Given the above issues, this pilot study aimed at

determining the degree of interobserver variability with regard to rectal contouring during HDRBT treatment planning, and to analyse the robustness of D_{2cc} as an acceptable parameter according to the GEC/ESTRO recommendations in our Radiation Oncology Department.

4.2.2 Material and methods

This single-centre retrospective study included 5 sets of ultrasound (US) images from prostate cancer patients that were used for HDRBT planning. Four expert physicians performed rectal contouring.

4.2.2.1 Study Cases

The HDRBT treatment planning data of 5 patients treated with combined radiotherapy (HDRBT and EBRT) at La Fe Polytechnic and University Hospital were included. All patients were diagnosed with prostate adenocarcinoma and treated according to the same treatment plan. These patients were selected to provide a range of different prostate sizes for this study (Table 4-4), as well as for other characteristics.

Table 4-4. Baseline characteristics of the patient group.

Case/patient	Prostate Volume (mm^3)	Age	PSA (ng/mL)	Tumour	Gleason Score
1	35.71	63	5.17	T3a	6
2	28.14	72	20.40	T3a	7
3	44.78	78	27.37	T1	7
4	39.47	71	30.00	T2	6

5	53.70	70	9.20	T2	7

Abbreviation: PSA, prostate-specific antigen.

4.2.2.2 Treatment Planning

HDRBT treatment planning was performed on an Oncentra Prostate® planning device (version 4.2; Nucletron, an Elekta company, Veenendaal, Netherlands). EBRT planning was performed on an Eclipse planning device (version 13.0; Varian Medical Systems, Palo Alto, CA, USA).

The treatment was designed such that HDRBT was performed first, followed by CT simulation 2 weeks later and EBRT after an additional 2-week interval (i.e., 4 weeks after HDRBT). In the instance of a complication that would prohibit HDRBT, this plan would allow a continuous high-dose treatment during EBRT.

Brachytherapy was administered in a 15-Gy single fraction, and the intraoperative procedure was based on US imaging findings. The patient was placed in a lithotomy position, and transversal images were captured in 1-mm slices using a trans-rectal ultrasound (TRUS) probe. The CTV was defined as the entire prostate gland, and the planning target volume (PTV) was defined as the CTV plus a 3-mm margin (except in the rectal and vesical directions). The urethra and rectum were contoured as OARs.

Dose distributions were optimized by determining the dwell positions and dwell times for the source within each needle and calculating the D_{90} for the target volume and D_{2cc} for the OARs. The needles were inserted through a transperineal template, using live TRUS images for guidance. Treatment was delivered using a HDR ^{192}Ir source. Needles were

removed after treatment, and 4 gold fiducials were implanted for EBRT image guidance.

EBRT was planned using computed tomography (CT) images. The CTV was defined as the prostate gland, and the PTV was defined as the CTV with a 5-mm margin in all directions except posteriorly, where the margin was 4 mm. Volumetric modulated arc therapy (RapidArc, Varian Medical Systems) and image-guided radiation therapy were used, and daily cone beam CT or orthogonal kV images were combined. The prescribed dose was defined such that 95% of the PTV should receive at least 95% of the prescribed dose (46 Gy).

4.2.2.3 Contouring

An expert group comprising 2 radiation oncologists, 1 radiologist, and 1 urologist usually involved in prostate brachytherapy and prostate US was established. This group had previously determined rectal delineation criteria in consensus.

Two identical US image sets were generated from the original HDRBT contouring plan. Image assembly was anonymized to avoid bias. US image sets were obtained with a Primus 6.5 MHz ultrasound device (Hitachi, Ltd., Tokyo, Japan). Axial images of the prostate were captured from the base through the apex. Rectums were contoured on 5 image sets by 4-blinded observers.

Each observer contoured the rectal wall on the axial slides in 5-mm slide increments according to the previously established consensus criteria. All observers were blinded to the other physicians' contours and

were only provided the urethra contour as a reference for longitudinal rectum delineation.

In our study, the radiologic anatomic boundaries of the rectum, according to the previous consensus, were: (i) 10 mm upward of the CTV volume in the cranial direction; (ii) 10 mm below of the CTV volume in the caudal direction; (iii) the posterior layer of Denonvillier´s fascia in the anterior direction; and (iv) the rectal wall visible on the US screen in the posterior direction (see Figures 4-5 and 4-6).

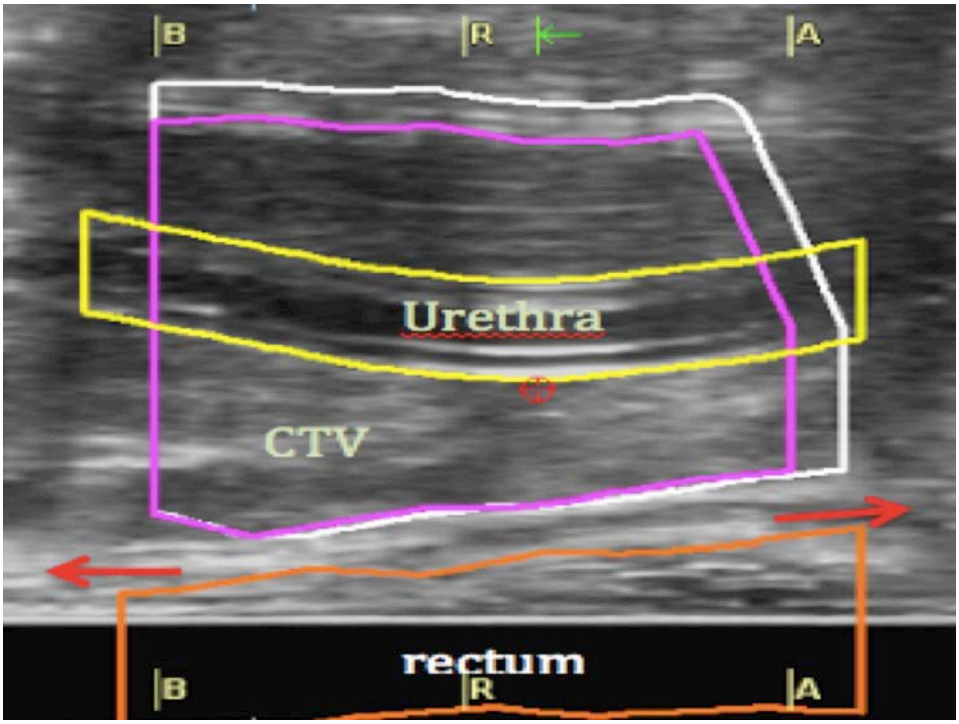


Figure 4-5. *Sagittal ultrasound (US) image showing the prostate and different rectal contours. The rectal structure includes a 10 mm margin that is*

craniocaudal with respect to the clinical target volume (CTV; red arrow). The shaded region (orange) indicates the rectal contour delineated by each observer.

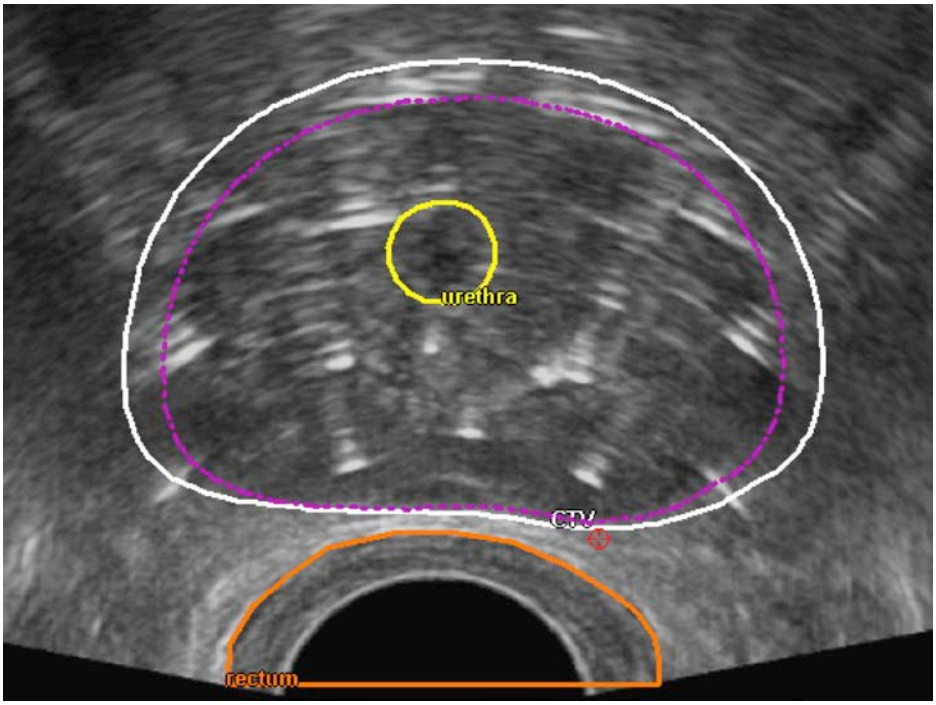


Figure 4-6. *Transverse ultrasound image showing an example of a rectal contour (orange line).*

4.2.2.4 Study Design

Four observers delineated the rectum on 5 US image sets from 5 prostate cancer patients. The observers repeated the delineation procedure

twice at a 1-week interval. Forty rectal contours (4 observers × 5 patients × 2 records for each case) were created and made available for analysis. Only the main investigator, who supervised the delineations performed by the 4 observers but did not actively participate in the delineation process, controlled the data registry and adequate identification of the patients and data. Figure 4-7 presents the scheme of the study.

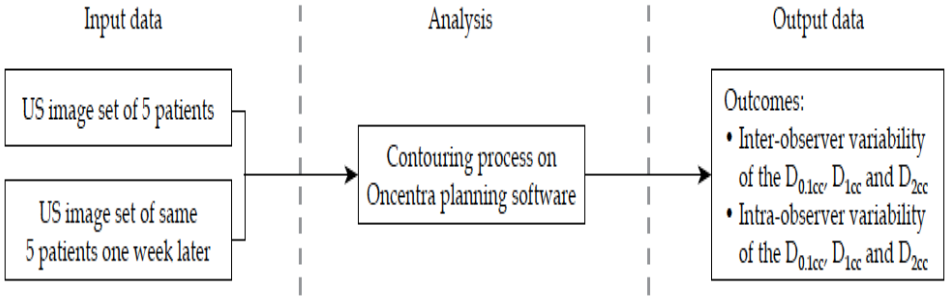


Figure 4-7. *Scheme of the study design. US-ultrasound; $D_{0.1cc}$, D_{1cc}, and D_{2cc}, most exposed 0.1-, 1-, and 2-cc volumes of the rectum.*

4.2.2.5 Dose Volume Histogram Analyses

DVHs were used to evaluate plans according to the GEC/ESTRO recommendations on HDRBT for prostate cancer (Hoskin *et al.*, 2013). For each patient, the plan from a single HDRBT fraction selected for contouring was used to calculate the DVH parameters. Using the source configuration from the optimized plans, the $D_{0.1cc}$, D_{1cc}, and D_{2cc} for the rectum were calculated for the observed contour set for each case.

For each DVH parameter, the mean value and standard deviation (SD) were calculated for each observer. To compare variability in the different DVH parameters according to Duane et al., the coefficient of variation (COV) was used to provide a measure of the data dispersion as a proportion of the mean (Duane *et al.*, 2014).

The 4 observers determined the means and SDs of the 2 measurements recorded for the matched US image sets for each parameter. The overall mean of these 4 measurements was then calculated for each patient. The interobserver COV was obtained by calculating the ratio of the SD to the mean for each patient. In the end, the overall COV for the 5 patients was calculated to provide a measure of interobserver variation across the entire group (Duane et al., 2014). For the 5 patients, the differences in dose values between duplicated US image sets were analysed using the non-parametric Friedman test. Statistical analyses were conducted using XLSTAT software (version 2014.6.01; Addinsoft, Paris, France).

The impact of contouring uncertainties on the total dose delivered to the rectum was evaluated by estimating the total dose (EBRT + HDRBT), assuming that the rectum received the prescribed EBRT dose (46 Gy) as described above. All dose values were biologically normalized to an EQD_2 expressed in units of $Gy_{\alpha/\beta=3}$.

The intraobserver COV was calculated to determine intraobserver variability. This value was defined as 2 SDs of the value resulting from the following equation: absolute value [first measurement – second measurement]/mean measurement, where the absolute value is the absolute difference between the 2 measurements made by the same

observer (Duane *et al.*, 2014). For the 5 patients, the differences in dose values between duplicated US image sets were analysed using the Wilcoxon signed-rank test. Statistical analyses were conducted using XLSTAT software (version 2014.6.01; Addinsoft, Paris, France). The test revealed no statistically significant differences in the $D_{0.1cc}$, D_{1cc} and D_{2cc} dose parameters (P = 0.059, 0.418, and 0.281, respectively).

4.2.3 Results

4.2.3.1 Interobserver Variation: Impact on Reported Dose Volume Histogram

The mean reported $D_{0.1cc}$, D_{1cc}, and D_{2cc} values for the rectum from 2 sessions of contouring are summarized for each patient in Table 4-5.
The overall mean of the interobserver COV for all patients and all observers is presented in Table 4-6. Greater interobserver variation was observed for $D_{0.1cc}$. However, the larger SD of 2.62 for case 5, relative to the SDs of 0.28-0.5 for the other cases, might be explained by interobserver variation. The global test revealed significant differences in the $D_{0.1cc}$, D_{1cc}, and D_{2cc} for the rectum among the observers ($p<0.05$) using the Friedman test.

4.2.3.2 Interobserver Variation: Impact on Evaluated Total Rectum Dose

The greatest interobserver variation in the $D_{0.1cc}$ group was 16.8% greatest for case 5, with $D_{0.1cc}$ values ranging from 1.47–18.42 Gy, indicating that the potential total reported rectum $D_{0.1cc}$ ranged from

82.55–98.22 Gy. Similar magnitudes of interobserver variation were observed for D_{1cc} and D_{2cc}. The greatest interobserver variations for D_{1cc} and D_{2cc} were also observed in case 5, with values of 6.4% and 4.5%, respectively. The reported range of variability in D_{2cc} was 0.61–2.53 Gy, indicating that the potential total reported rectal D_{2cc} ranged from 71.10–77.25 Gy. The higher interobserver variability described above for D_{2cc} corresponds to a worst-case scenario of a rectal contouring variation that might result in a recorded dose difference of up to 5.8 Gy, as shown in Table 4-7.

Table 4-5. *Values of the most exposed 0.1, 1, and 2-cc volumes ($D_{0.1cc}$, D_{1cc}, and D_{2cc}, respectively) of the rectum for each patient and observer based on a single 15-Gy high-dose-rate brachytherapy plan. Data are shown as the means of values obtained at 2 different time points. Interobserver mean, range and standard deviation for each patient are represented in the right side.*

$D_{0.1cc}$ (Gy)							
Case	Observer A	Observer B	Observer C	Observer D	Mean	Range	SD
1	12.41	11.98	12.30	11.79	12.12	11.79-12.41	0.28
2	12.48	12.16	12.63	11,79	12.27	11.79-12.63	0.37
3	12.45	12.45	12.68	11.96	12.39	11.96-12.68	0.30
4	13.62	12.43	13.22	12.91	13.04	12.43-13.62	0.50
5	13.56	15.65	19.16	13.65	15.51	13.56-19.16	2.62
D_{1cc} (Gy)							
1	10.35	11.47	10.50	10.13	10.61	10.13-11.47	0.59
2	10.43	11.13	10.54	9.84	10.49	9.84-11.13	0.53
3	10.89	11.52	10.82	10.50	10.93	10.50-11.52	0.43
4	11.40	11.60	11.51	11.23	11.44	11.23-11.60	0.16
5	11.61	13.15	12.98	11.79	12.38	11.61-13.15	0.79

	D_{2cc} (Gy)						
1	9.69	9.37	9.58	9.24	9.47	9.24-9.69	0.21
2	9.36	9.12	9.48	8.72	9.17	8.72-9.48	0.34
3	9.82	9.92	9.86	9.61	9.80	9.61-9.92	0.13
4	10.32	9,71	10.49	10.22	10.19	9.71-10.49	0.34
5	10.62	11.13	11.76	10.81	11.08	10.62-11.76	0.50

Table 4-6*. Overall interobserver coefficients of variation (%) for the recorded most exposed 0.1, 1, and 2-cc volumes ($D_{0.1cc}$, D_{1cc}, and D_{2cc}, respectively) of the rectum based on the single 15-Gy high-dose-rate brachytherapy plan.*

	Dosimetric Parameters		
	$D_{0.1cc}$	**D_{1cc}**	**D_{2cc}**
COV	5.71	4.46	4.06

Abbreviation: COV, coefficient of variation.

Table 4-7. *Range (standard deviation) of the biologically equivalent dose (EQD_2) of the most exposed 2-cc volume (D_{2cc}) of the rectum for each patient, based on the single 15-Gy high-dose-rate brachytherapy plan plus 46-Gy external beam radiotherapy.*

Case/Patient	D_{2cc} (Gy)	Dose difference (Gy)

1	68.60 – 70.62 (0.91)	2.0
2	66.45 – 69.67 (1.41)	3.2
3	70.25 – 71.66 (0.61)	1.4
4	70.70 – 74.30 (1.54)	3.6
5	74.95 – 80.71 (2.53)	5.8

4.2.3.3 Intraobserver Variation: Impact on Reported Dose Volume Histogram Parameters

The intraobserver variation for the reported D_{2cc} ranged from 2.5% to 6.3%. Variations in rectal delineation were consistent for each patient. Given that the $D_{0.1cc}$, D_{1cc}, and D_{2cc} values for observer 1 were similar in both US image sets, we tested for differences in dose values between duplicate US image sets for this observer using the Wilcoxon signed-rank test.

4.2.4 Discussion

To date, advances in technology and clinical experience have led to major progress in HDRBT for prostate cancer. However, the delineation of target volumes and OARs remains dependent on the observer. Variability in the delineation of these elements can limit the brachytherapy dose distribution, representing a main source of uncertainty that can impact clinical and treatment outcomes (Nieh *et al.*, 2008; Fotina *et al.*, 2012; Allozi *et al.*, 2010; Weiss *et al.*, 2003). Hence, quantification of the dosimetric impact of this delineation variability is necessary.

Studies of variability in contouring of target volumes and OARs are well represented in the literature (Collier *et al.,* 2003). Many such studies (e.g., a study by Wong *et al.,* 2006) indicate that delineation guidelines could improve interobserver homogeneity. Furthermore, in other studies (such as that Buch *et al.,* 2015) the use of high-resolution image as contrast enhanced magnetic resonance imaging could improve the dosimetry to OARs. Although the GEC/ESTRO recommendations for HDRBT of prostate cancer have been published and updated in 2013 with the inclusion of D_{2cc} and $D_{0.1cc}$ doses for the rectum (Hoskin *et al.,* 2013) to our knowledge, we are the first group to report the effects of interobserver and intraobserver variability on rectal delineation in the context of HDRBT treatment for prostate cancer.

In the present study, despite the use of contouring consensus-based rectal delineation criteria, significant interobserver differences were detected in the dose parameters; specifically, the average interobserver COVs for $D_{0.1cc}$, D_{1cc}, and D_{2cc} were 5.71%, 4.46%, and 4.06%, respectively. Although rectal contouring was consistent among the observers, caudal limit contouring was difficult because of the varied interpretations of the rectal border and delimitation of the sphincter muscle. This difficulty was clearly observed in the analysis of case 5, wherein a COV of 16.8% was calculated for $D_{0.1cc}$. This variability is expected because $D_{0.1cc}$ represents the smallest dose point of the largest dose near the rectum wall and is therefore highly sensitive to inaccuracies in contouring. No statically significant intraobserver differences in the dose parameters were reported.

Evidence for variations in the delineation of OARs has been primarily reported from gynaecological studies using the GEC/ESTRO recommendations. Hellebust *et al*. (2013) reported interobserver delineation variability of 5–8% for the D_{2cc} of the rectum in a study of the dosimetric impact of magnetic resonance imaging-based cervical cancer brachytherapy. Saarnak *et al*. (2000) reported a higher variability rate (approximately 11%). In our study, we obtained an interobserver COV <5% for D_{2cc}, although random dosimetric variations were observed in individual cases. The low dose variability observed in our study might be associated with proper training of the physicians and implementation of the consensus contouring guidelines. However, no previously published data regarding HDRBT for prostate cancer were available for comparison.

The impact on the total received dose (HDRBT + EBRT) corresponded with an EQD_2 range of 1.4–5.8 Gy. This difference in doses was similar to the range published by Hellebust (2–3 $Gy_{\alpha/\beta=3}$) (Hellebust *et al.*, 2013). Nesvacil *et al.* (2013) reported a slightly higher inter-fractional dose difference range of 4–8 Gy EQD_2 for OARs in a multicentre study.

Regarding rectum delineation, the observers emphasized the quality of the US images, but also noted difficulty with correctly contouring the final area of the rectum proximal to the anus in some cases. In one particular case, the large prostate volume led to uncertainty when contouring the anterior limit of the rectum proximal to the prostate, although this difficulty might have been limited to this particular case or to inherent uncertainties of the observers. This incident was relevant to the dosimetric analysis because the upper limit of the EQD_2 (5.8 Gy)

represents the total dose received by the rectum at a dose range of 74.95–80.71 Gy, which exceeds the recommended dose according to the GEC/ESTRO.

The impact of dosimetric variability is more significant in high-dose regions near the target volume than in low-dose regions. However, whereas the OARs are associated with low doses, factors such as interobserver variability in delineation could lead to severe toxicity of the OARs. George *et al.* (2012) referred to side effects after radiotherapy (EBRT and brachytherapy) for cervical carcinoma; specifically, the presence of telangiectasias correlated with the 2-cm^3 high-dose rectal volume, and ulcerations were limited to the small 0.1-cm^3 high-dose volumes. In our study, we observed dose uncertainties up to 5.8 Gy, which was higher than the range of 2–3 Gy published by George *et al.* (2012) (no correspondence with critical consequences). Nevertheless, dosimetric uncertainties become important with respect to interobserver variability when the OAR doses approach the maximum limit in an attempt to optimize the brachytherapy treatment.

The sample size is a limitation in this study. It is relatively small and a larger or multicentre study should be made before extrapolation to population. However, we believe that the results obtained, establish a starting point of the robustness of D_{2cc} as an acceptable parameter according to the GEC/ESTRO recommendations in our experienced Radiation Oncology Department.

4.2.5 Conclusion

In general, we obtained acceptable interobserver variability in the EQD_2 for the reported D_{2cc}, although a high impact on clinical threshold levels (D_{2cc} ≤75 Gy EQD_2) was present in some cases. Interobserver variability was lowest for D_{2cc} (<5%), in agreement with previously published studies on brachytherapy for gynaecological cancers. In our study, the impact of interobserver variation on the EQD_2 for the reported D_{2cc} had the potential to yield a worst-case scenario dose difference of up to 5.8 $Gy_{\alpha/\beta=3}$. Although the GEC/ESTRO recommendations provide a common language for reporting dose information, future studies are needed to identify correlations of interobserver delineation variability with adverse effects and clinical outcomes.

The outcomes obtained in this pilot study should be validated. In addition, a multicentre study is needed as a follow-up to this small, single-centre study.

4.3 PAPER III:

INTER-OBSERVER VARIABILITY IN RECTUM CONTOURING: A MULTI-INSTITUTIONAL PROSPECTIVE STUDY

Most of the content of this chapter was based in the original research paper:

Chicas-Sett R, Celada-Alvarez F, Roldan S, Rodriguez-Villalba S, Santos-Olias M, Soler-Catalan P, Ibanez-Rosello B, Arribas L, Tormo A, Benlloch JM, Perez-Calatayud J. Interobserver variability in rectum contouring in high-dose-rate brachytherapy for prostate cancer: A multi-institutional prospective analysis. Brachytherapy 2018;17:208-213. doi: 10.1016/j.brachy.2017.09.015.

[Q2/Radiology, Nuclear Medicine and Medical Imaging; JCR]

Kind permission was granted by the journal to reprint this article as a chapter of this thesis.

4.3.1 Introduction

The latest studies on the treatment of high-risk prostate cancer suggest that high-dose-rate brachytherapy (HDRBT) as a boost to external beam radiotherapy (EBRT) reduces the risk of relapse and increases survival (Hoskin *et al.*, 2012; Morris *et al.*, 2015; Kalbasi *et al.*, 2015; Kuban *et al.*, 2011). In 2016, Kishan *et al*. published a multi-institutional comparative analysis on the treatment of high-risk prostate cancer with radiotherapy or radical prostatectomy, in which they reported better systemic control with the use of EBRT and brachytherapy. The American Brachytherapy Society (ABS) has reported similar outcomes in its latest task group report of 2016 (Spratt *et al.*, 2016).

HDRBT is a technique that permits the selective treatment of the prostate through the use of radioactive sources; it delivers high doses of radiation to the tumour while avoiding organs-at-risk (OARs) such as the urethra, bladder, and rectum (Moon *et al.*, 2017). This makes it a promising alternative dose-escalating technique in patients with this disease.

In the radiotherapy/brachytherapy planning process, a number of uncertainties exist when devising the most optimal treatment plan. These include the variation in volume delineation of the target tumour and OARs, which can be attributed to (or influenced by) the observers (Weiss *et al.*, 2003). Such interobserver variability (IOV) may have a direct impact on dosimetry and clinical results. Some studies on delineation have been performed to minimize the IOV, and guidelines have been published. However, such variation continues to exist despite the technological advances in radiotherapy.

At this time, there is no a consensus guideline for rectum contouring for HDRBT for prostate cancer. In their latest recommendations for HDRBT, the Group Européen de Curiethérapie (GEC) and European Society for Radiotherapy & Oncology (ESTRO) suggested that rectum contouring should include the outer wall as a minimum (Hoskin *et al.*, 2013), while the ABS recommends that the rectum be defined by contouring the external and mucosal surface (Yamada *et al.*, 2012) The GEC/ESTRO have proposed that the minimum dose received by the most exposed 2.0 cm^3 volume (D_{2cc}) be constrained to a $\leq$75 Gy biologically equivalent dose (EQD_2) in their latest guidelines (Hoskin *et al.*, 2013).

In order to evaluate the robustness of the above-mentioned dose constraint to the rectum, we previously performed an IOV pilot study on rectal delineation, and found the interobserver variability to be <5% for D_{2cc}, but with a strong dosimetric impact up to 5.8 Gy as the worst-case scenario. This study was performed after a consensus for rectum contouring was achieved between radiation oncologists, radiologists, and urologists at the same radiotherapy centre (Chicas-Sett *et al.*, 2016).

Several studies have analysed the IOV in radiotherapy volume contouring; most that investigated volume delineation uncertainties in radiotherapy focused on targets (Vinod *et al.*, 2016). Only three of 31 published studies have evaluated OAR delineation variability on brachytherapy. Recently, a significant relationship between the dose volume histogram (DVH) parameter (D_{2cc}) of the rectum and the occurrence of late rectal toxicity in HDRBT-treated patients with prostate cancer was discovered (Chicas-Sett *et al.*, 2017). Given the aforementioned factors, the purpose of this study was to evaluate the IOV of rectum contouring for HDRBT to treat prostate cancer, determine the dosimetric consequences, and analyse the robustness of the GEC/ESTRO recommendations regarding D_{2cc} constraint in a multi-institutional study.

4.3.2 Materials and methods

This was a multi-institutional prospective trans-rectal ultrasonography (TRUS) planning study, based in a clinical HDRBT and EBRT combined protocol for patients with high-risk prostate cancer. Five academic radiation oncologists (observers) experienced in prostate HDRBT from four institutions participated in the study; each observer contoured the rectum on the TRUS-images of 10 patients.

4.3.2.1 Study cases

Ten patients with high-risk prostate cancer who underwent HDBRT and EBRT at our department were enrolled. All patients were classified as high-risk according to the National Comprehensive Cancer Network guidelines (NCCN, 2016) based on serum prostate-specific antigen level,

Gleason score, and clinical tumour stage. Tumour and HDRBT treatment characteristics are listed in Table 4-8. Selected cases included a range of different prostate sizes or clinical target volumes (CTVs) representing common situations in HDRBT prostate contouring. The Institutional Ethics Review Board approved this study.

4.3.2.2 Image acquisition and treatment planning

Planning TRUS image sets were obtained for each patient using a Primus 6.5 MHz ultrasound device (Hitachi, Ltd., Tokyo, Japan). As part of the HDRBT treatment, the ultrasound scan was uploaded to the Oncentra Prostate® planning device (version 4.2; Nucletron, Veenendaal, Netherlands) to reconstruct the three-dimensional prostate and OAR volumes. Each patient was placed in the lithotomy position under anaesthesia. The ultrasonography probe was inserted into the rectum, and two prostate stabilizing needles were inserted prior to image acquisition. The planning system recorded in vivo axial images captured at 1-mm slice intervals. Axial images of the prostate were captured from the base through the apex after the needles were positioned.

HDRBT was considered an intraoperative procedure, in which a single 15 Gy dose was delivered while the TRUS probe was in place. In our protocol, the CTV was defined as the entire prostate gland, while the planning target volume (PTV) was defined as the CTV plus a 3-mm margin (except in the posterior and superior directions). The urethra and rectum were also contoured. Immediately after HDRBT delivery, the

needles were removed and four gold fiducial markers were implanted for EBRT image guidance in the next treatment phase.

EBRT treatment planning was performed using the Eclipse planning system; version 13.0 (Varian Medical Systems, Palo Alto, CA, USA) based on computed tomography (CT) images. The EBRT dose was 46 Gy in 23 fractions of 2 Gy each. The CTV was defined as the prostate and seminal vesicles. The PTV was the CTV plus a 5-mm margin; except in the posterior (rectal) direction where the margin was 4 mm. EBRT was delivered using volumetric modulated arc therapy (RapidArc, Varian Medical Systems, Palo Alto, CA, USA). A combination of cone beam CT and orthogonal kV imaging was used for image guidance during radiation therapy.

In general, our clinical protocol for high-risk prostate cancer includes a combination of HDRBT (as boost) and EBRT. In order to guarantee continuous high-dose delivery, our protocol is to administer the HDRBT first; this allows the treatment to be completed with continuous EBRT should any complications arise during brachytherapy. Additionally, this sequence allows the implantation of the gold fiducial markers. CT simulation is then performed two weeks after HDRBT, following which EBRT is performed after an additional two-week interval (i.e., four weeks after HDRBT).

Table 4-8. *Patient characteristics*

Patient	Tumour Stage	PSA (ng/mL)	Gleason score	Prostate volume (cm^3)

1	T3a	N0	M0	5.2	6	35.7
2	T3a	N0	M0	20.4	7	28.1
3	T1	N0	M0	27.4	7	44.8
4	T2b	N0	M0	30.0	6	39.5
5	T2b	N0	M0	9.2	7	53.7
6	T2b	N0	M0	16.6	7	66.5
7	T2c	N0	M0	22.1	7	43.3
8	T3a	N0	M0	14.6	8	26.4
9	T1c	N0	M0	12.5	7	57.6
10	T1c	N0	M0	16.3	7	47.5

PSA = prostate-specific antigen.

4.3.2.3 Interobserver contouring protocol

Expert consensus rectal contouring was devised by the observers during a joint discussion at our department, and was based on a previous consensus established in a pilot study published in 2016 (Chicas-Sett *et al.*, 2016), as shown in Table 4-9.

Five identical TRUS image sets were generated from the original HDRBT treatment planning. TRUS image sets only showed the urethra contour as a reference for longitudinal rectum delineation. The rectal wall was contoured on the axial slides in 5 mm slide increments according to the previously established consensus criteria, as shown in Figure 4-8.

Table 4-9. *Boundaries of the rectal contouring*

Definition of borders	Description
Superior (cranial)	Where the urethra; contour begins.
Anterior	The posterior layer of Denonvilliers' fascia

Posterior	The rectal wall is visible on the TRUS screen.
Inferior (caudal)	Where the urethra contour ends.

TRUS = trans-rectal ultrasonography

4.3.2.4 Study design

Each observer contoured the rectal wall on 10 TRUS image sets from 10 prostate cancer patients according to previously established multi-institutional consensus guidelines, as described above. Each observer was blinded to any information pertaining to the patients or HDRBT plans. Two authors were present for the contouring session to facilitate loading images, patient data registry access, and recording information. All the rectal wall contours were included in the original HDRBT plan, and cumulative DVH data were measured and collected for analysis.

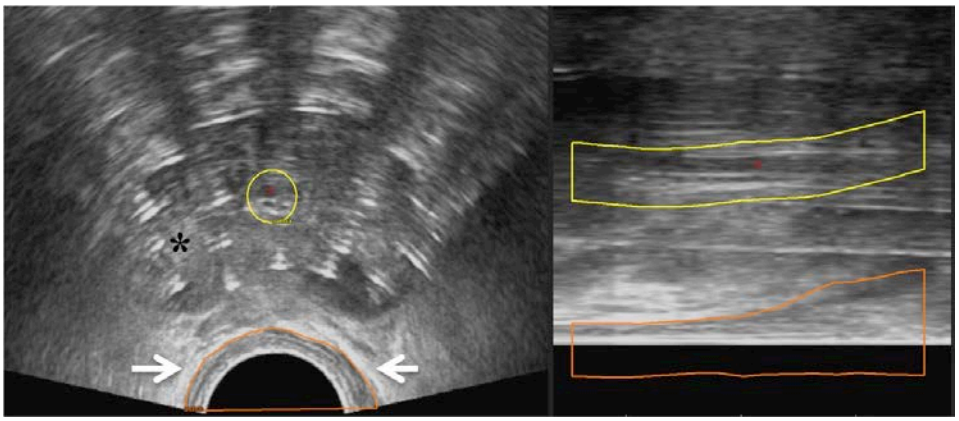


Fig. 4-8. *Transrectal ultrasonography-based prostate high-dose-rate brachytherapy contouring.*

Prostate and catheters inserted (*); the white arrows indicate the posterior layer of Denonvilliers' fascia; the orange line indicates the rectal contour and the yellow line indicate the urethral contour

4.3.2.5 DVH analysis: IOV and dosimetric impact

The minimal doses to 0.1 cm^3 ($D_{0.1cc}$), 1 cm^3 (D_{1cc}), and 2 cm^3 (D_{2cc}) of the rectum were determined according to the GEC/ESTRO recommendations (Hoskin *et al.*, 2013). The mean and standard deviation (SD) of each DVH parameter were evaluated for each patient.

To quantify the IOV in rectum contouring, the coefficient of variation (COV), defined as the ratio of SD to the mean (Chicas-Sett *et al.*, 2016), was measured for all patients [15-16]. The overall COV for the 10 patients was calculated to provide a measure of interobserver variation across the entire group.

For the assessment of the dosimetric impact due to variations in rectal delineation, the total dose delivered to the rectum (HDRBT + EBRT) was estimated under the assumption that the rectum received the prescribed EBRT dose (46 Gy). All dose values were biologically normalized to an EQD_2 expressed in units of $Gy_{\alpha/\beta=3}$.

4.3.2.6 Statistical analysis

The mean and COV values for $D_{0.1\,cc}$, D_{1cc}, and D_{2cc} were compared to evaluate the IOV in rectum contouring. The non-parametric Friedman test was used to compare the differences in dose values between all patients. P-values <0.05 were considered statistically significant.

Statistical analysis was performed using the XLSTAT software (version 2017.19.01; Addinsoft, Paris, France).

4.3.3 Results

4.3.3.1 IOV

The reported $D_{0.1\ cc}$, D_{1cc}, and D_{2cc} values in the rectum of each patient as reported by all observers are listed in Table 4-10. The overall interobserver means of the $D_{0.1\ cc}$, D_{1cc}, and D_{2cc} parameters were 86.1 (range 75.4–95.7) Gy, 75.3 (range 68.2–81.4) Gy, and 70.9 (range 63.7–76.0) Gy, respectively. The interobserver mean variability for $D_{0.1\ cc}$, D_{1cc}, and D_{2cc} was statistically significant in all cases ($p \leq 0.0001$).

The observed SD ranges for the interobserver COV between the five observers were 1.0–6.9%, 1.5–5.2%, and 0.8–4.0% for $D_{0.1\ cc}$, D_{1cc}, and D_{2cc}, respectively. The overall interobserver COVs for each parameter are shown in Table 4-11. Significant differences in interobserver COVs were found for all parameters among the observers ($p<0.05$).

Table 4-10. *Mean $D_{0.1cc}$, D_{1cc} and D_{2cc} values of rectal contouring as determined by five observers.*

	Rectum					
Patients	$D_{0.1cc}$ (Gy)		D_{1cc} (Gy)		D_{2cc} (Gy)	
1	82.0	(0.8)	73.5	(1.1)	68.9	(0.8)
2	84.2	(4.6)	72.9	(2.3)	68.5	(2.5)
3	84.2	(4.5)	75.5	(3.3)	71.3	(3.1)

4	88.5	(5.5)	78.7	(4.1)	74.2	(3.6)
5	97.1	(6.8)	81.4	(3.9)	76.0	(3.2)
6	88.7	(5.8)	78.5	(4.1)	73.9	(3.5)
7	75.1	(2.3)	68.2	(1.7)	64.7	(1.4)
8	79.2	(4.2)	68.5	(2.3)	64.0	(1.8)
9	88.3	(3.2)	79.1	(2.7)	74.0	(2.4)
10	94.1	(4.1)	76.5	(3.9)	73.1	(4.0)

Doses are expressed in Gy (EQD_2) based on a single 15 Gy high-dose-rate brachytherapy plan plus 46 Gy EBRT. The numbers in parentheses are standard deviations.
COV = coefficient of variation; $D_{0.1cc}$ and D_{2cc} = the minimum dose received by the most exposed 0.1 and 2.0 cm^3 volume of the rectum.

Table 4-11. *The interobserver coefficient of variation for $D_{0.1cc}$, D_{1cc} and D_{2cc}*

	COV		
	$D_{0.1cc}$	D_{1cc}	D_{2cc}
Rectum	4.8 (1.8)	3.9 (1.2)	3.7 (1.3)

COV = coefficient of variation; $D_{0.1cc}$, D_{1cc} and D_{2cc} = the minimum dose received by the most exposed 0.1, 1 and 2 cm^3 volume of the rectum. Shown are mean percentages (standard deviations).

4.3.3.2 Dosimetric impacts

An interobserver variation of 4.8% for the $D_{0.1cc}$ corresponds to a mean dose difference of 10 Gy, indicating that the potential total dose

reported for $D_{0.1cc}$ ranged from 72.4 to 104.4 Gy EQD_2. A slightly lower mean dose difference (7.3 Gy) was obtained for D_{1cc}; a COV of 3.9%

Patients	Range (Gy)	Dose difference (Gy)
1	67.9–70.1	2.2
2	66.0–72.0	6.1

corresponded to potential total doses ranging from 65.5 to 87.5 Gy EQD_2. Finally, with an IOV of 3.7%, the impact on the D_{2cc} was 6.6 Gy (mean), corresponding to a potential total dose of 61.7–80.7 Gy EQD_2. Table 4-12 lists the ranges and dose differences for the D_{2cc} for all patients. Patient 10, in whom a dose difference of 10.7 Gy EQD_2 for D_2cc was found, exemplified the worst-case scenario. There was difficulty in contouring the apex region for this patient, which may have been due to the echogenicity of the needles.

3	67.7–76.0	8.3
4	70.6–78.7	8.1
5	72.1–80.7	8.6
6	70.4–79.2	8.5
7	63.3–66.2	2.9
8	61.7–65.8	4.1
9	70.7–77.4	6.6
10	67.1–77.8	10.7

Values are based on 15-Gy high-dose-rate brachytherapy planning plus 46-Gy external beam radiotherapy.
EQD_2 = biologically equivalent dose; D_{2cc} = the minimum dose received by the most exposed 2.0 cm^3 volume of the rectum.

Table 4-12. *Range of the biologically equivalent doses of the D_{2cc} of the rectum for each patient.*

4.3.4 Discussion

In radiotherapy planning, uncertainties in the delineation of targets and OARs can lead to systematic errors and poor accuracy, which in turn have a pronounced dosimetric impact. This can detract from the advantages of modern radiotherapy or brachytherapy in terms of clinical outcomes (local control and toxicities). Several studies have investigated the interobserver variability in volume delineation, and have mainly focused on GTV or CTV rather than OAR contouring (Vinod *et al.*, 2016; Weiss *et al.*, 2003). The quantification of the dosimetric impact of IOV on volume delineation has been evaluated in a limited number of studies; however, due to the heterogeneity in methodologies, the results cannot necessarily be applied to general protocols or guidelines (Peters *et al.*,

2010; Weber *et al.*, 2012). In a 2016 review, Vinod *et al.* noted that only 12 of 31 studies of IOV in OARs had evaluated the dosimetric impact.

Following the aforementioned publication of the GEC/ESTRO recommendation of constraints for HDRBT, we devised the current multi-institutional study to compare outcomes with those obtained in a previous pilot single-institution study (Chicas-Sett *et al.*, 2016). Our study was performed under the same conditions, but included experienced observers from multiple centres.

Given that there is no general recommendation regarding optimal case vs. observer ratios in interobserver studies, we included 10 patients and five observers based on published studies of variability of interobserver contouring of OARs in brachytherapy. In these studies, the median number of observers and cases reported were five (range 3–14) and 10 (range 8–14), respectively (Duane *et al.*, 2014; Damato *et al.*, 2014; Saarnak *et al.*, 2000). The observers reviewed and approved the contouring consensus used in our prior pilot study owing to the lack of published recommendations (Chicas-Sett *et al.*, 2016).

In this study, our results concerning the IOV in rectum contouring for prostate HDRBT revealed smaller COVs in the DVH parameters. The COVs for $D_{0.1cc}$, D_{1cc}, and D_{2cc} were 4.8%, 3.9% and 3.7%, respectively. These results were similar to those obtained in the pilot study (Chicas-Sett *et al.*, 2016). To date, however, there have been no studies that evaluated the IOVs in rectum delineation for prostate HDRBT. Only three gynaecological brachytherapy studies have evaluated the IOVs in OAR delineation; all used CT images (Duane *et al.*, 2014; Damato *et al.*, 2014; Saarnak *et al.*, 2000). For example, Duane *et al*. reported an interobserver

COV for D_{2cc} of 9% for the rectum, while Hellebust *et al*. reported an IOV of 5–8% for the same (Duane *et al.*, 2014; Hellebust *et al.*, 2013). The low IOV observed in the present study is consistent with that obtained in the pilot study. This may be attributed to the use of rectal delineation criteria derived from a prior consensus, as well as the involvement of experienced physicians in prostate HDRBT.

A literature review indicates that 67% (8/12) of studies on IOVs in OARs show significant differences in DVHs (Duane *et al.*, 2014; Damato *et al.*, 2014; Saarnak *et al.*, 2000; Nelms *et al.*, 2012; Feng *et al.*, 2011; Perna *et al.*, 2011; Lorenzen *et al.*, 2013). However, most of these studies were analysed using different methodologies and statistical tests, making comparisons between them difficult. In our case, both our previous and current studies determined the COV for each parameter, and the dosimetric impacts were quantified by calculating the EQD_2 dose difference from the total received dose (HDRBT + EBRT) in the rectum.

The mean dose difference for a total EQD_2 D_{2cc} of 6.6 Gy in the rectum ranged from 2.2 to 10.7 Gy in our study. This variability for D_{2cc} is comparable to that previously reported in our pilot study, where the dose difference variability reached 5.8 Gy in the worst-case scenario (Chicas-Sett *et al.*, 2016). We also found that the upper limit in the total EQD_2 dose received by the rectum exceeded the GEC/ESTRO recommended dose in six cases, (Table 4-11).

In a recent study, we found that the D_{2cc} for the rectum in prostate HDRBT was significantly associated with the occurrence of Grade ≥2 late rectal toxicity (LRT) in a clinical study involving 300 patients. While it was not possible to determine the threshold dose, all patients who

presented with Grade ≥2 LRT reported a D_{2cc} ≥65 Gy EQD_2 (Chicas-Sett *et al.*, 2017). In a previous gynaecological series, George et al. (George *et al.*, 2012) reported side effect such as telangiectasias and ulcerations associated with D_{2cc} and $D_{0.1cc}$, respectively. Hence, the dosimetric uncertainties in rectum delimitation for prostate HDRBT should be carefully determined.

There are few studies of IOV for OAR delineation in HDRBT (Vinod *et al.*, 2016), most of which utilized CT or magnetic resonance imaging. However, our multi-institutional study is the first to investigate IOVs for rectum contouring in prostate HDRBT by TRUS. Despite the absence of established guidelines, the use of rectal contouring parameters arrived at by consensus in an expert brachytherapist group made it possible to achieve a low IOV for the dosimetric parameters, particularly for D_{2cc}. Further multi-institutional studies are necessary to enhance the applicability of our findings.

4.3.6 Conclusion

In conclusion, we achieved a low IOV for the D_{2cc} in rectum contouring for prostate HDRBT. However, the quantification of the dosimetric impact requires special consideration, since variations close to the clinical threshold levels were present in some cases. The use of consensus rectal contouring guidelines appears to be an effective tool for minimizing the extent of IOV. Further investigations are required to validate our results, and a general contouring guideline for rectum delineation will be an asset to radiation oncologists once it is incorporated into the prostate HDRBT recommendations.

CHAPTER V.

GENERAL DISCUSSION

Chapters 4 through 6 present a series of three different studies involving the use of HDRBT boost in combination with EBRT for prostate cancer patients. The following is a general discussion of the most important points of each chapter. Where necessary, the reader is referred to a specific discussion section provided in each chapter for additional in-depth information.

The study presented in **Chapter 4** was the starting point for all other studies in this thesis. This chapter is divided into two parts. The first part focuses on determining the clinical outcomes, local control, overall survival, and late rectal toxicity. This study was based on an analysis of 300 patients followed prospectively. Our sample size was comparable with those of major studies published about the use of HDRBT boost combined with EBRT (De Bari *et al.*, 2015). In patients treated with a single-fraction HDRBT boost and EBRT, we found estimated 5-year bDFS rates of 90% and OS of 87% with a median of follow-up of 33 months. These results correspond well with other studies, where the range of bDFS and OS rates were similar.

To date, clinical outcomes obtained from prospective and retrospective studies have reported local control rates for intermediate- and high-risk disease of 69 - 97% and 63 - 80%, respectively, with evidence level 1 (Zaorsky *et al.*, 2017). Furthermore, among the late toxicities developed in this group of patients, late rectal toxicity has the highest negative impact on quality of life. Most studies have reported low incidence in LRT rates, but the results are still poorly comparable due to heterogeneity in the dose fractionation.

In our study, we found that 20.7% of the patients experienced rectal toxicity. Of those patients, based on the highest grade of late rectal toxicity, 39 patients (13%) had Grade 1, 20 patients (7%) had Grade 2, and 3 patients (1%) had Grade 3. Several systematic reviews have reported rates of Grade 3 - 4 GI toxicity in the range of 0 - 8% (Zaorsky *et al.*, 2014). Diarrhoea, proctitis, and rectal haemorrhage are among the most frequent adverse events in treatment with HDRBT and EBRT. We found very similar rates of LRT, including 10.3% for diarrhoea, 9.3% for proctitis, and 1% of rectal haemorrhage. Determining the incidence and prevalence of LRT in these treatments is important for improving the quality of planning treatment and researching dosimetric prediction parameters that allow us to decrease or prevent the occurrence for that toxicity.

Given these findings, the second part of **Chapter 4** involves determining the significance of dose-volume histogram parameters for predicting LRT after single-fraction HDRBT boost and EBRT in prostate cancer patients. All of this was based on the GEC/ESTRO recommendations, which suggested using a rectal dose constraint of D_{2cc} ≤ 75 Gy EQD_2 in the last update of the HDRBT guidelines for prostate cancer (Hoskin *et al.*, 2013). Dosimetric parameters ($D_{0.1cc}$ and D_{2cc}) were collected and analysed, and no significant difference was found in $D_{0.1cc}$ and D_{2cc} for each treatment scheme. An ordinal regression analysis revealed a significant association between D_{2cc} and the probability of developing LRT of Grades 1 – 3 (p = 0.04). Due to the low incidence of LTR, it was not possible to establish a threshold dose for LRT ≥ Grade 2.

However, we observed that 100% of the patients with LRT Grade ≥ 2 received doses ≥ 65 Gy EQD_2.

Our study was the first to evaluate this association in HDRBT for prostate cancer. Other studies have found evidence of an association between D_{2cc} and the occurrence of LRT in gynaecological HDRBT (George *et al.,* 2011; Chopra *et al.,* 2015). The findings of this study with respect to the association of D_{2cc} with the occurrence of LRT ≥ Grade 2 suggests taking precautionary measures in rectal doses ≥ 65 Gy EQD_2. Further investigations are necessary to evaluate the robustness of the dose constraint for the rectum suggested by the GEC/ESTRO. Therefore, in **Chapter 5** and **Chapter 6**, we hope to contribute to this aspect in evaluating the uncertainties in rectum delineation via interobserver variability (IOV).

The study presented in **Chapter 5** evaluates the robustness of D_{2cc} ≤ 75 Gy EQD_2 suggested by GEC/ESTRO as a rectal dose constraint. **Chapter 4** reveals a significant association between D_{2cc} and the risk of developing LRT ≥ Grade 2, but other uncertainties in the process of radiotherapy could be implicated. HDRBT was performed as a single-fraction TRUS image in vivo with the patient under epidural anaesthesia. This gave control over the patient setup error, intra-fraction organ movement, and patient movement, but there are still uncertainties in rectum delineation continue that depend on the individual brachytherapist. For this reason, this study evaluated the IOV in rectum contouring in an expert centre as a pilot study.

The observer group included two radiation oncologists, a radiologist, and a urologist. A previous contouring consensus was established for the

purpose of comparing the dosimetric parameters between observers. We found an IOV of <5% for D_{2cc}, with strong impacts on clinical threshold levels ($D_{2cc} \leq 75$ Gy EQD_2) in some cases. Although similar studies are not available for prostate cancer, studies on gynaecological HDRBT have reported very similar values. For example, Hellebust *et al*. (2013) found an IOV of 5 - 8% for the D_{2cc} of rectum delineation in a study on the dosimetric impact of MRI-based cervical cancer brachytherapy. The results obtained in this study are very limited but create a need to investigate the strong impacts near the clinical rectal dose threshold and for comparison of these results in other centres.

In **Chapter 6**, we describe a study that was inspired by the fact that there are currently no consensus guidelines for rectum contouring for HDRBT in patients with localized prostate cancer who were treated with combined HDRBT and EBRT. In the latest guidelines, the GEC/ESTRO proposed that the minimum dose received by the most exposed 2-cm^3 volume (D_{2cc}) be constrained to ≤ 75 Gy EQD_2. We previously tested the robustness of this parameter in a single-institution study, and we performed this follow-up study to evaluate the IOV of rectum contouring for HDRBT, to determine its dosimetric consequences, and to analyse the robustness of the aforementioned constraints in a multi-institutional study involving five different radiation oncologists.

We found that the interobserver coefficients of variation (± standard deviation) for $D_{0.1cc}$, D_{1cc}, and D_{2cc} were 5±1.84%, 4±1.26%, and 4±1.33%, respectively. The impact on the total dose was determined by the mean dose differences observed for $D_{0.1cc}$, D_{1cc}, and D_{2cc}, which were 10 Gy, 7.3 Gy, and 6.6 Gy, respectively. We believe our findings will be

of great interest because they show that the D_{2cc} determination is robust given the IOV < 5%. In addition, the consensus rectal contouring guidelines appear to be a desirable tool for reducing delineation uncertainties.

CHAPTER VI

CONCLUSIONS

Paper I:

1. Our data revealed promising 5-year OS and bDFS rates of 87.0% and 90.0%, respectively.

2. The most frequently observed rectal complications in our study included diarrhoea in 31 patients (10.3%), discomfort in 28 patients (9.3%), and rectal haemorrhage in 3 patients (1.0%).

3. LRT is concordant with previous studies with rates of 6.7% and 1.0% observed for Grade 2 and Grade 3 LRT, respectively.

4. D_{2cc} is associated with the occurrence of LRT in HDRBT-treated prostate cancer patients. Although this study has been unable to determine the threshold dose to minimize the occurrence of LRT of Grade ≥2, we believe that it has the potential to promote development of long-term prospective and multiinstitutional investigations that allow to confirm our findings and establishing the threshold dose.

Paper II:

5. In general, we obtained acceptable interobserver variability in the EQD_2 for the reported D_{2cc}, although a high impact on clinical threshold levels (D_{2cc} ≤75 Gy EQD_2) was present in some cases. Interobserver variability was lowest for D_{2cc} (<5%), in agreement with previously published studies on brachytherapy for gynaecological cancers.

6. In our study, the impact of interobserver variation on the EQD_2 for the reported D_{2cc} had the potential to yield a worst-case scenario dose difference of up to 5.8 $Gy_{\alpha/\beta=3}$. Although the GEC/ESTRO recommendations provide a common language for reporting dose information, future studies are needed to identify correlations of interobserver delineation variability with adverse effects and clinical outcomes.

7. The outcomes obtained in this pilot study should be validated. In addition, a multicentre study is needed as a follow-up to this small, single-centre study.

Paper III:

8. We achieved a low IOV for the D_{2cc} in rectum contouring for prostate HDRBT. However, the quantification of the dosimetric impact requires special consideration, since variations close to the clinical threshold levels were present in some cases.

9. The use of consensus rectal contouring guidelines appears to be an effective tool for minimizing the extent of IOV.

Further investigations are required to validate our results, and a general contouring guideline for rectum delineation will be an asset to radiation oncologists once it is incorporated into the prostate HDRBT recommendations.

CHAPTER VII

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