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TOXICITY PROFILE AND PATIENT-REPORTED OUTCOMES FOLLOWING SALVAGE STEREOTACTIC BODY RADIOTHERAPY (SBRT) TO PELVIC LYMPH NODES AND PROSTATE BED AFTER PROSTATECTOMY

PERFIL DE TOXICIDAD Y CALIDAD DE VIDA CON SBRT DE RESCATE EN GANGLIOS PÉLVICOS Y LECHO PROSTÁTICO DESPUÉS DE PROSTATECTOMÍA

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Toxicity Profile and Patient-Reported outcomes following Salvage Stereotactic Body Radiotherapy (SBRT) to Pelvic Lymph nodes and Prostate Bed after Prostatectomy.

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ABSTRACT

Most of the current literature on salvage stereotactic body radiotherapy (SBRT) has focused on evaluating toxicity and efficacy outcomes limited to the prostate fossa. To date, no studies have systematically assessed the inclusion of elective nodal irradiation (ENI) in this context. This retrospective, single-center cohort study included 62 patients with prostate adenocarcinoma who experienced biochemical recurrence following radical prostatectomy and were treated with salvage SBRT to the prostatectomy bed and pelvic lymph node areas at Clínica Los Nogales (Bogotá, Colombia) between March and October 2023. Toxicities were assessed using CTCAE v5.0, and health-related quality of life (HRQOL) was evaluated using the EPIC-26 questionnaire. Grade 1 genitourinary (GU) toxicity occurred in 50% of patients and grade 2 in 29.3%, with no grade ≥3 GU toxicity reported. Gastrointestinal (GI) toxicity was reported as grade 1 in 20.7% and grade 2 in 12% of patients, with no grade ≥3 GI events. Prior to SBRT, 17% of patients had preserved sexual function, and 31% had full urinary continence. These findings suggest that salvage SBRT including ENI is feasible and well tolerated, with low rates of acute toxicity. The greatest HRQOL impact was observed in the sexual domain, highlighting the importance of early detection of biochemical recurrence to guide treatment decisions and potentially avoid systemic therapy.

Keywords: salvage radiotherapy, stereotactic body radiotherapy, prostate cancer, elective nodal irradiation, toxicity

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Perfil de Toxicidad y Calidad de Vida con SBRT de Rescate en Ganglios Pélvicos y lecho Prostático después de Prostatectomía

RESUMEN

La literatura existente sobre radioterapia estereotáxica corporal (SBRT) de rescate se ha enfocado principalmente en los resultados de toxicidad y eficacia restringidos a la fosa prostática, sin estudios previos que evalúen sistemáticamente la irradiación nodal electiva (ENI) en este contexto. El objetivo principal de este estudio fue evaluar la incidencia de toxicidades genitourinarias (GU) y gastrointestinales (GI) agudas, así como la calidad de vida relacionada con la salud (HRQOL) durante los primeros tres meses posteriores a la administración de SBRT de salvamento dirigida al lecho prostático y áreas ganglionares. La toxicidad se midió utilizando los Criterios Comunes de Terminología para Eventos Adversos (CTCAE) versión 5.0 y calidad de vida mediante el cuestionario EPIC-26. Este estudio de cohorte, realizado en una sola institución, incluyó a 62 pacientes con adenocarcinoma de próstata que presentaron recaída bioquímica tras prostatectomía radical, tratados en la Clínica Los Nogales (Bogotá, Colombia) entre marzo y octubre de 2023. Según la escala CTCAE v5.0, el 50% de los pacientes presentó toxicidad GU grado 1 y el 29,3% toxicidad grado 2; no se observaron eventos grado 3. En cuanto a la toxicidad GI, el 20,7% presentó grado 1 y el 12% grado 2, sin toxicidades de grado 3. Antes del tratamiento, el 17% de los pacientes conservaba funcionalidad sexual y el 31% reportó continencia urinaria completa. La SBRT dirigida al lecho prostático y áreas nodales como terapia de rescate puede administrarse de forma segura, mostrando tasas bajas de toxicidad aguda sin complicaciones mayores. Estos resultados refuerzan la viabilidad y tolerabilidad de la SBRT en este escenario, destacando la importancia del diagnóstico temprano de la recaída bioquímica para optimizar el tratamiento y de ser posible, evitar la necesidad de terapia hormonal.

Palabras clave: radioterapia estereotáxica, cáncer de próstata, recaída bioquímica, toxicidad aguda, calidad de vida

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INTRODUCTION

The estimated incidence rate of prostate cancer in Colombia ranges from 20 to 30 cases per 100,000 men, 30–60% of patients will develop recurrent disease after any local therapy in prostate cancer, (1,2). The rationale for using SBRT in patients with prostate cancer is the low α/β value of about 1.5 Gy (3,4.) The organs at risk in close proximity to the prostate like the bladder, rectum or urethra for instance have a higher α/β value of 3–6 (5). Therefore, using a larger fraction dose is expected to improve the therapeutic ratio and consequently the probability of tumor control.

Gokhan et al showed no severe acute and late toxicity with postoperative ultra-fractionated SBRT. Late GU grade 2 toxicity rates of about 15%, in addition to excellent biochemical control rates(6)

The NRG Oncology-RTOG 0534 SPPORT group show that extending salvage radiotherapy to treat the pelvic lymph nodes when combined with short-term ADT results in meaningful reductions in progression after prostatectomy in patients with prostate cancer.(7)

The population continues to grow and age, with a consequent increase in cancer incidence that drives a greater demand for radiotherapy. According to the Department of Health in England, there is a 2.3% annual growth in demand for radiotherapy. Radiotherapy is a highly cost-effective treatment. It represents only 5% of the national expenditure on cancer treatment in England and is the second most effective cancer treatment after surgery.

Of all cancer patients who are cured, 40-50% have received radiotherapy as part of their curative treatment, and 16% of all cancer patients cured are completely attributable to radiotherapy, according to a report by the National Radiotherapy Implementation Group (NRIG) of England (9).

In developing countries, the only alternative available to the shortage of radiotherapy equipment is extreme hypofractionation to increase installed capacity due to lack of access. Extending the adoption of SBRT in LATAM can provide a path forward to increase access to radiotherapy .(8)

The limited supply, high current demand, and the enormous challenge of meeting future demand require strategies from national regulatory bodies, insurers, and service providers to meet current and future demand specially in prostate cancer. Strategies are needed to control the dramatic increase in costs due to aging, higher expenditures on expensive procedures and advanced treatment modalities by addressing the inefficiency of healthcare

delivery. The use of hypofractionated radiotherapy has advantages for the patient by reducing transportation costs, lodging expenses, and costs of work incapacity for the labor system. For the radiotherapy center, it reduces patient absenteeism during treatment and improves patient adherence. (10)

That is why this study was developed to evaluate the Toxicity profile and patient-reported outcomes following salvage Sbrt to pelvic lymphnode and prostate bed after prostatectomy.

Main Endpoint

The primary endpoint was to evaluate the incidence rate of acute genitourinary (GU) and gastrointestinal (GI) toxicities and to evaluate the health-related quality of life (HRQOL) within the first three months following salvage stereotactic body radiotherapy (SBRT) to the prostatectomy bed and elective nodal irradiation (ENI).

Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and the Expanded Prostate Cancer Index Composite-26 (EPIC-26) questionnaire, which evaluates health-related quality of life (HRQOL).

Materials and Methods

Study Design

This single-institution, prospective cohort study included 62 patients diagnosed with adenocarcinoma of the prostate who experienced biochemical relapse after radical prostatectomy. All patients had a prostate-specific antigen (PSA) level ≥ 0.1 ng/mL and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Patients were treated with stereotactic body radiotherapy (SBRT) targeting the prostatectomy bed and pelvic lymph node areas as salvage therapy at Clínica Los Nogales in Bogotá, Colombia, between March and October 2023. Androgen deprivation therapy (ADT) was administered at the discretion of the treating physician. This study was approved by the Institutional Review Board of our institution (Study Number).

This study adhered to the principles of medical research, the confidentiality of the data was assured, and the patients agreed under informed consent to accept their participation.

Eligibility Criteria

Inclusion Criteria

- Men with adenocarcinoma of the prostate who experienced biochemical recurrence or persistence following radical prostatectomy.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
- Signed informed consent.

Exclusion Criteria

- Patients with previous pelvic radiation .
- Simultaneous treatment of other tumor.

Treatment and Assessments

Radiotherapy Delivery

Radiotherapy was administered using a Varian Halcyon linear accelerator with 6 MV energy photons, equipped with cone-beam CT for image guidance prior to each fraction. The treatment schedule followed an every-other-day regimen.

A extreme hypofractionation or SBRT schedule was used, with a total dose of 30 Gy administered in 5 fractions to the prostate bed or positive lymph nodes in PET PSMA (if the patient has PSMA PET) and 25 Gy to pelvic (ganglia) nodal regions. Bladder filling and bowel preparation (enemas) were advised for treatment planning.The treatment was planned with a CT scan using a supine position with immobilization and fusion with PET in case of positive lesions (devices, and a multi-leaf collimator was used.)

The clinical target volume (CTV1) encompassed the prostate bed, while the clinical target volume (CTV2) included the pelvic lymph nodes.Pelvic nodal regions were contoured following established global guidelines NRG/RTOG , with the upper boundary of the pelvic contour delineated at the bifurcation of the aorta or L4-L5.

The planning target volume (PTV) was defined as the CTV plus 4 mm margin in all directions except 3 mm posteriorly, the goals dose constraint for target and organs at risk are shown in RTOG. At the beginning of the study, The Expanded Prostate Cancer Index Composite (EPIC 26) was performed to determine the symptoms prior to the study.

Acute toxicities were evaluated in the first 90 days after the beginning of radiation therapy, were scored weekly during radiation therapy in morbility consultation and at 3 months after the initiation of radiation therapy, The first control was in the final consultation once the radiotherapy ended, the second control was after 60 days and the last control was carried out after completing the 90 days of completion of treatment by telephone contact for all patients. Toxicity assessments were performed at baseline and at each follow-up visit using the EPIC26 short form

RESULTS

Table 1

	Total N=(58)	
Demographics		
Age at doagnosis (years)		
Median (range in years)	67 (51-76)	
Pathological T-Stage		
T2	11	(19,0 %)
T2a	1	(1,7 %)
T2b	2	(3,4 %)
T2c	5	(8,6 %)
T3	3	(5,2 %)
T3a	19	(32,7 %)
T3b	16	(27,6 %)
Unknown	1	(1,7 %)
ISUP Grade Group (GG)		
GG1: GS 3+3	13	(22,4 %)
GG2: GS 3+4	13	(22,4 %)
GG3: GS 4+3	15	(25,9 %)
GG4: GS 8	12	(20,7 %)
GG5: GS 9 or 10	4	(6,9 %)
Unknown	1	(1,7 %)
Positive surgical margin		
NO	28	(48,3 %)
YES	29	(50,0 %)
Unknown	1	(1,7 %)

Type of post-operative SBRT		
Adjuvant	2	(3,2 %)
Salvage	56	(96,8 %)
PSA at baseline		
Median (IQR range)	0,39 (0,23 - 0,85)	
ADT use		
No	14	(24,1 %)
Yes	44	(75,9 %)
Median Duration of ADT (range in months)	6(3 - 36)	
Duration of follow-up (months)		
Median (range in months)	8(5-12)	

Before initiating SABR, 17% of patients retained sexual functionality, and 31% exhibited complete urinary continence.

We evaluated the maximum grade of acute toxicity (0–90 days post-SABR) both gastrointestinal (GI) and genitourinary (GU), as reported by patients during follow-up

We evaluated the highest grade of acute gastrointestinal (GI) and genitourinary (GU) toxicity within 90 days post-SABR, according to the CTCAE v5.0 adverse event scale, as reported by patients during follow-up visits. GU toxicity grade 1 was observed in 50% (29 patients), while 29.3% (17 patients) experienced grade 2 toxicity, characterized by increased urinary frequency, irritative symptoms, and asymptomatic hematuria in 7 patients, which resolved spontaneously without the need for intervention. No grade 3 GU toxicity was observed.

Regarding GI toxicity, 20.7% (12 patients) experienced grade 1 toxicity, while 12% (7 patients) developed grade 2 toxicity, characterized by loose stools, rectal mucositis, and hematochezia. The latter occurred in 5 patients and resolved without the need for transfusion, endoscopic, or surgical intervention. No grade 3 GI toxicity was observed.

Urinary Incontinence Domain

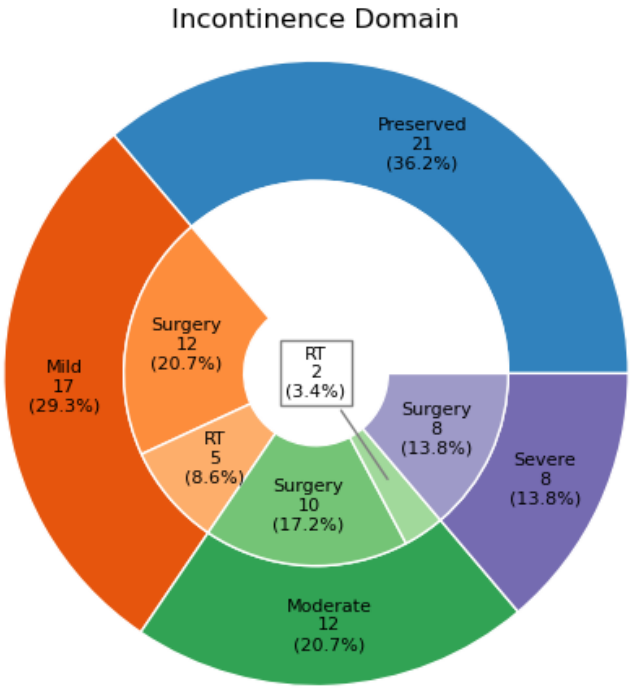
When evaluating the five domains of the EPIC-26 Score (Short Form), it was documented that in the urinary incontinence domain, quality of life was preserved in 36.2% (21 patients). A 29.3% (17 patients)

reported mildly affected quality of life due to mild urinary symptoms, of whom 70% (12 patients) had pre-existing incontinence before radiotherapy. Figure 1.

Additionally, 20.6% (12 patients) reported a moderately affected quality of life, with 83.3% (10 patients) experiencing urinary symptoms prior to treatment. Finally, 13.8% (8 patients) had a severely affected quality of life in the incontinence domain, entirely attributable to surgery, as all of them had incontinence before undergoing ultrahypofractionated radiotherapy.

It is concluded that SBRT treatment to the prostatectomy bed and pelvic lymph nodes may have contributed to mild and moderate quality of life impairment in the urinary incontinence domain in 29.3% (5 patients) and 16.7% (2 patients), respectively.

Figure 1. Quality of life and type of treatment by incontinence domain.

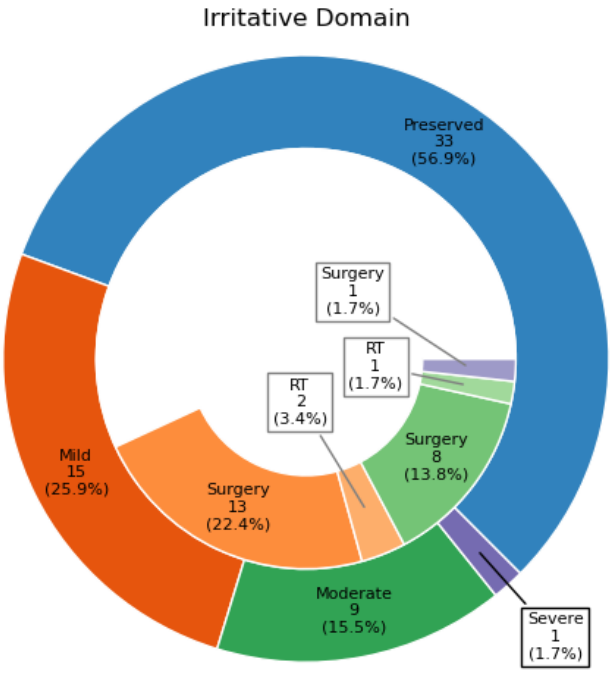


Urinary Irritative Domain

In the domain of urinary irritative symptoms, quality of life was mildly affected in 25.9% (15 patients), of whom 86.7% (13 patients) had pre-existing urinary symptoms before undergoing salvage or adjuvant radiotherapy.

Additionally, 15.5% (9 patients) reported a moderately affected quality of life due to moderate urinary symptoms, with 88.9% of them having documented urinary symptoms prior to initiating radiotherapy. Finally, 1.7% (1 patient) experienced a severely affected quality of life in this domain, having previously presented with urinary symptoms.

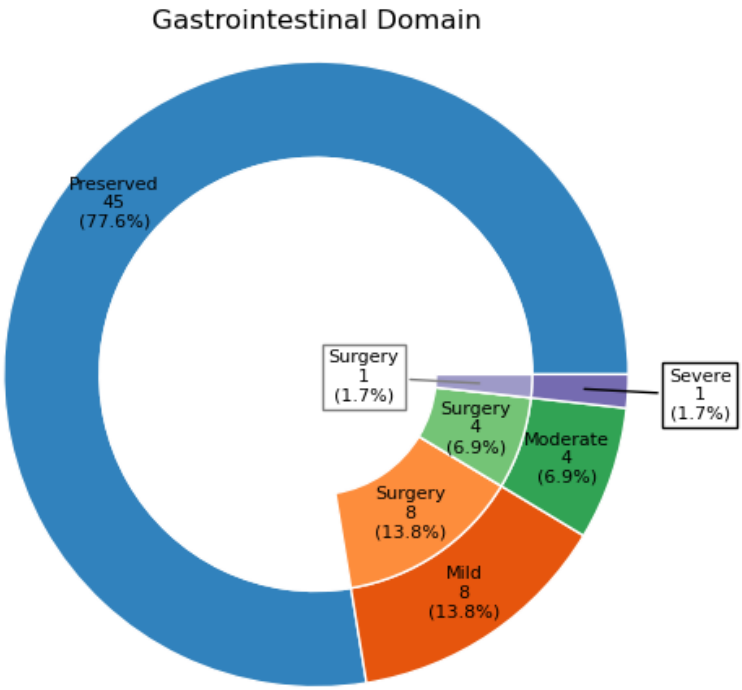
Figure 2. Quality of life and type of treatment by irritative domain



Gastrointesinal Domain

In the gastrointestinal domain, a mild impact on quality of life was documented in 13.8% (8 patients), a moderate impact in 6.9% (4 patients), and a severe impact in 1.7% (1 patient), all attributable to radiotherapy treatment.

Figure 3. Quality of life and type of treatment by gastrointestinal domain

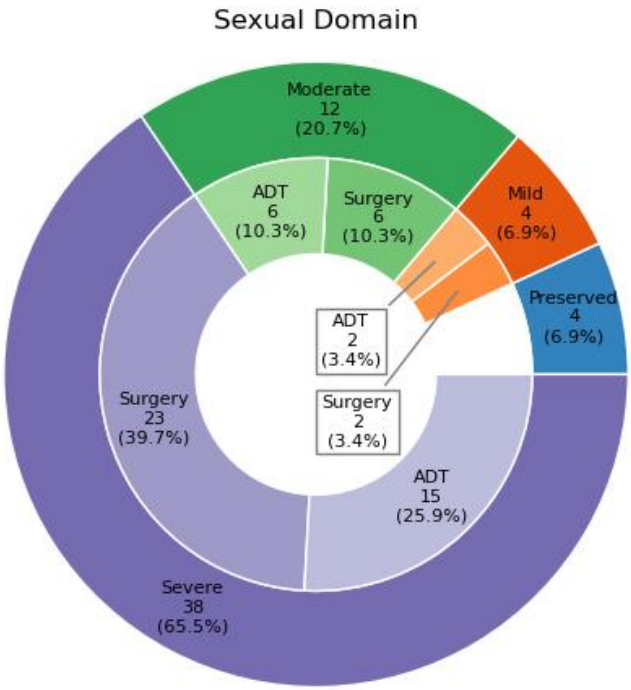


Sexual Domain

In the sexual domain, quality of life was preserved in only 6.9% (4 patients). A total of 65.5% (38 patients) experienced a severe decline in quality of life, with 60.5% (23 patients) developing difficulties with erections or sexual satisfaction after surgery, while 39.5% (15 patients) had impairment attributed to androgen deprivation therapy (ADT).

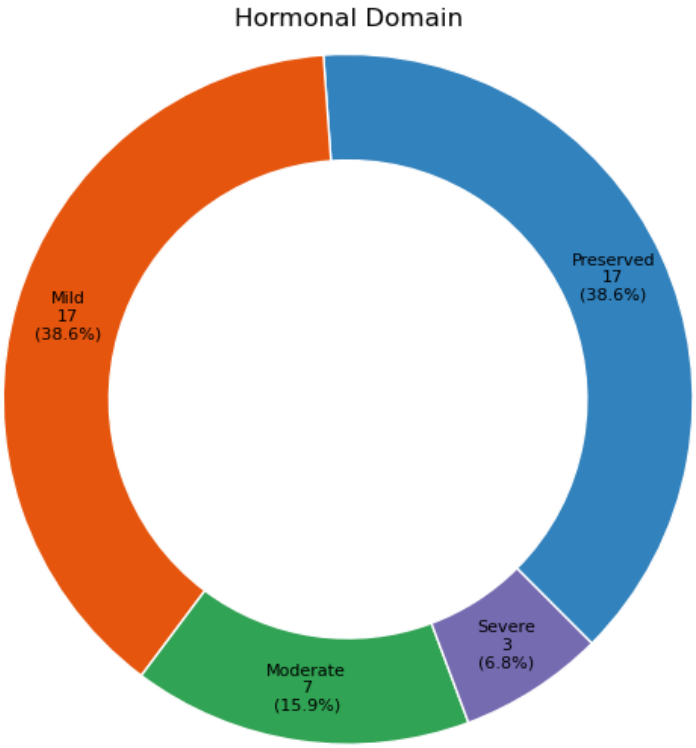
Additionally, 20.9% (12 patients) reported a moderately affected quality of life, with 50% of cases due to surgery and the remaining 50% due to ADT. Lastly, 4% (2 patients) reported a mild impact on quality of life, equally attributed to ADT and surgery.

Figure 4. Quality of life and type of treatment in the sexual domain



In the hormonal domain, quality of life was mildly affected in 38.6% (17 patients), moderately affected in 15.9% (7 patients), and severely affected in 6.8% (3 patients), with all cases attributed to androgen deprivation therapy (ADT)

Figure 5. Quality of life and type of treatment in the hormonal domain



DISCUSSION

To our knowledge, this represents the first published study to report outcomes of salvage stereotactic body radiotherapy (SBRT) encompassing both the prostate bed and pelvic lymph nodes in all treated patients. While a recent prospective cohort presented at ASTRO 2024 included pelvic nodal irradiation, only 50% of participants received such treatment. Furthermore, existing literature on salvage SBRT has primarily focused on toxicity and efficacy outcomes restricted to the prostate fossa, with no prior studies systematically evaluating comprehensive nodal irradiation in this setting.

Our analysis revealed significant pathological upstaging in 44.83% of cases when comparing preoperative clinical staging to postoperative pathological classification (cT stage vs pT stage). This substantial discordance highlights the use of new classification tools.

In our cohort, 55.6% of patients were found to have pT3 disease, underscoring the limitations of surgery as a standalone curative approach for locally advanced prostate cancer. The high prevalence of extraprostatic extension suggests a substantial likelihood of microscopic disease dissemination,

necessitating comprehensive locoregional control through pelvic nodal irradiation and systemic therapy with androgen deprivation therapy (ADT) at this disease stage.

Positive surgical margins were present in 41.9% of cases These findings are consistent with the fact that it is difficult to achieve negative margins in advanced disease.

The highest biochemical recurrence rate was observed in Grade Group 3 patients (27.4%), consistent with the known aggressive biological behavior of unfavorable intermediate-risk disease. Current evidence indicates that Gleason Grade Group 3 (ISUP Grade 3) carries a significantly elevated risk of distant metastasis (HR 3.49) and prostate cancer-specific mortality compared to favorable intermediate-risk disease (p=0.013).(14) These findings emphasize the critical need for advanced staging modalities in this patient population. However, current clinical practice in our country and many others restricts PSMA-PET imaging to high-risk cases only, potentially understaging intermediate-risk patients who may benefit from this technology .

Ultra-hypofractionation (≥ 5Gy/day) is accepted for localized prostate cancer across all risk groups but remains investigational for post-prostatectomy recurrence and elective pelvic lymph node irradiation. Published studies using ultra-hypofractionation post-prostatectomy are limited. Most employ five alternate-day fractions with doses of 6–9Gy per session, to target the entire prostatectomy bed, although some groups have used.(5)(6)

A systematic review by Mohamad et al. (2022) evaluating ultra-hypofractionated PLNI demonstrated both the feasibility of this approach and an acceptable toxicity profile, with grade ≥3 events occurring in <5% of cases . These findings are corroborated by a pooled analysis conducted by Glicksman et al. (2023) encompassing four prospective institutional studies.

The cumulative evidence indicates that while mild-to-moderate acute toxicities are common with ultra-hypofractionated PLNI (particularly GU symptoms),

the risk of severe late complications remains low when modern image-guided techniques are employed. These findings should alleviate concerns regarding the safety of extended-field SABR when performed at experienced centers.(16)

In our prospective analysis utilizing CTCAE v5.0 criteria, we observed grade 2 genitourinary (GU) toxicity in 29.3% of cases (n=17/58). Notably, no grade ≥3 GU toxicities were documented during the

study period . These findings align with contemporary SBRT series reporting Grade 2 GU toxicity rates of 25-35% and similarly low rates of severe toxicity (Grade 3: 0-2%).

The domain related to sexual quality of life, which evaluates the ability to achieve erections and sexual satisfaction, showed the lowest score. Among these patients, 65% reported a significant impairment in their sexual quality of life. It is worth noting that, within this group, 60.5% experienced this impairment after surgery, while 39.4% reported alterations due to hormonal blockade.

The majority of patients (96.8%) underwent salvage stereotactic body radiotherapy (SBRT), with only 3.2% receiving adjuvant treatment. This practice has evolved since 2020 following the publication of studies such as RAVES and RADICALS, which support the approach of early salvage therapy over routine adjuvant treatment.

The median baseline PSA was 0.41 ng/mL. It is a discouraging fact because if early or ultra-early rescue were carried out, significantly better results would be obtained, given that Pre-SRT PSA Consistently Most Prognostic Variable .(11)

The optimal timing for salvage therapy is when prostate-specific antigen (PSA) levels are 0.1 ng/mL or less. This finding carries significant implications for metastasis-free survival and overall mortality, underscoring the importance of early intervention.

Regarding hormonal blockade, this new data from RADICALS-HD of not administering ADT in patients with biochemical relapse with pretreatment PSA less than 0.5 will allow us to avoid the tedious symptoms of hormonal blockade, and even better, it will allow us to determine if the treatment was effective and not mask a possible relapse due to androgenic deprivation, that in the case of a 12 - 24 month blockade it can take up to 4 years to recover testosterone levels and in some cases not never get it back. (11).On the other hand, we have new data that if an early rescue is carried out, it is not necessary to use ADT since it does not provide survival.(12)

In our study 75% of patients received androgen deprivation therapy (ADT) for a median duration of 6 months, as mentioned previously, This is another argument in favor of carrying out ultra-early salvage radiotherapy Because if I give late rescue I will have to use hormonal blockage, which will be detrimental to the quality of life of our patients.

Based on the latest data, only 37% of them actually required ADT treatment, meaning that 62% of the cohort underwent unnecessary ADT.

Given the known adverse effects of ADT—particularly on sexual function—overtreatment poses a significant concern. Notably, when patients were referred at a PSA of 0.1 or lower for ultra-early salvage therapy, 100% were successfully treated without requiring ADT. These findings underscore the critical importance of early referral to minimize unnecessary exposure to ADT-related toxicities.

With this abbreviated treatment regimen, urinary toxicity typically manifests after treatment completion. This delayed onset is particularly advantageous for ensuring adequate bladder filling, as prolonged therapies often induce overactive bladder symptoms that can compromise bladder capacity during treatment.

The bladder is a serial organ, rendering it particularly sensitive to high radiation doses delivered to small volumes, with the trigone representing its most radiosensitive region (15). Radiation-induced damage involves the breakdown of the polysaccharide layer and intercellular junctions, leading to mucosal injury and epithelial desquamation. This exposes isotonic tissue to hypertonic urine, triggering inflammation and overactive bladder symptoms (15).

In conventional (prolonged) radiotherapy regimens, bladder filling capacity becomes progressively compromised, often starting as early as the third week of treatment. This is primarily due to detrusor muscle hyperactivity, which induces involuntary contractions even at low bladder volumes (15). Consequently, reproducibility of bladder filling across treatment sessions is significantly impaired once radiation-induced overactive bladder symptoms emerge.

In contrast, this ultra-short treatment schedule circumvents this issue, as urinary toxicity typically arises after treatment completion, thereby preserving consistent bladder filling throughout the therapeutic course.

The median baseline PSA was 0.41 ng/mL,was high compared with Chia-Lin Tseng cohort published in ASTRO 2024 THAT was 0.2 ng/mL (13).

It is part of our work as radio oncologists to sensitize all specialists involved in genitourinary tumors who refer patients with prostate antigen values of 0.1 or less in order to have better oncological results.

CONCLUSIONS

Stereotactic Body radiotherapy (SBRT) targeting the prostatectomy bed and pelvic lymph node areas as salvage therapy can be safely administered

Our results revealed low rates of acute genitourinary and gastrointestinal toxicity with no grade > 3 complications observed. These findings reinforce the feasibility and tolerability of SABR to bed tumor and lymph nodes .

limitations retrospective, longer observation is essential to assess late complications Continued patient follow-up is essential to evaluate long-term outcomes, including rates of biochemical and clinical recurrence and overall survival

The impact on quality of life is most severely affected in the sexual domain, highlighting the importance of early detection of biochemical recurrence to optimize management and, when feasible, avoid the need for hormonal therapy.

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