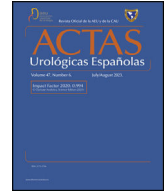




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Resident section

## Predictive factors for biochemical recurrence after radical prostatectomy in ISUP Grade Group 1 prostate cancer: a retrospective cohort with long-term follow-up

*Factores predictores de recurrencia bioquímica tras prostatectomía radical en cáncer de próstata ISUP 1: cohorte retrospectiva con seguimiento prolongado*

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## ABSTRACT

**Introduction:** The clinical relevance of biochemical recurrence (BCR) after radical prostatectomy (RP) in ISUP Grade Group 1 prostate cancer is unclear. We evaluated the incidence of BCR, its pathological predictors, and long-term oncologic outcomes in this population.

**Materials and methods:** Retrospective observational study of consecutive patients who underwent RP between 1999 and 2012 with ISUP GG 1 adenocarcinoma in the specimen. BCR was defined as PSA  $\geq$  0.2 ng/mL in two consecutive measurements after postoperative nadir. BCR-free survival and overall survival were estimated using Kaplan–Meier analysis, and predictors of BCR were identified using Cox regression. Salvage treatments, events of radiologic progression, and mortality were described.

**Results:** A total of 208 patients were included. The median follow-up was 12.1 years. BCR was observed in 45 (21.6%), with a median time to BCR of 5.2 years (IQR 2.3–7.5). Five-year BCR-free survival was 92%, 81% at 10 years, and 78% at 15 years. Positive surgical margins were the only independent predictor of BCR (HR 3.27; 95% CI 1.64–6.53;  $p < 0.001$ ). Eleven patients with BCR (24.4%) received salvage radiotherapy. Only 3 patients developed radiologic progression (1.4%); 42 deaths (20.2%) were recorded; none of them were cancer-specific deaths.

**Conclusions:** In ISUP grade group 1 prostate cancer treated with RP, BCR is relatively common but rarely associated with radiologic progression; no cancer-specific deaths were observed during long-term follow-up. Positive margins were associated with a higher risk of BCR.

## RESUMEN

**Introducción:** La relevancia clínica de la recurrencia bioquímica (RBQ) tras prostatectomía radical (PR) en cáncer de próstata ISUP 1 es incierta. Evaluamos la incidencia de RBQ, sus predictores patológicos y los resultados oncológicos a largo plazo en esta población.

**Material y métodos:** Estudio observacional retrospectivo de pacientes consecutivos sometidos a PR entre 1999–2012 con adenocarcinoma ISUP 1 en la pieza. La RBQ se definió como PSA  $\geq$  0,2 ng/mL en dos determinaciones consecutivas tras nadir posoperatorio. Se estimó la supervivencia libre de RBQ y la supervivencia global mediante Kaplan–Meier, y se identificaron predictores de RBQ con modelo de Cox. Se describieron los tratamientos de rescate y los eventos de progresión radiológica y mortalidad.

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**Resultados:** Se incluyeron 208 pacientes. El seguimiento mediano fue de 12,1 años. Se observó RBQ en 45 (21,6%), con un tiempo mediano hasta RBQ de 5,2 años (RIQ 2,3–7,5). La supervivencia libre de RBQ fue del 92% a 5 años, 81% a 10 años y 78% a 15 años. Los márgenes quirúrgicos positivos fueron el único predictor independiente de RBQ (HR 3,27; IC95% 1,64–6,53;  $p < 0,001$ ). Once pacientes con RBQ (24,4%) recibieron radioterapia de rescate. Solo 3 pacientes desarrollaron progresión radiológica (1,4%); se registraron 42 fallecimientos (20,2%), ninguno de ellos cáncer-específico.

**Conclusiones:** En cáncer de próstata ISUP 1 tratado mediante PR, la RBQ es relativamente frecuente pero rara vez se asocia a progresión radiológica y no se observó mortalidad cáncer-específica en un seguimiento prolongado. Los márgenes positivos se asociaron a mayor riesgo de RBQ.

## Introduction

Prostate adenocarcinoma is the most common solid malignancy in men in Europe and covers a broad spectrum of biological behaviors [1]. The Gleason grading system and its recent refinement into ISUP Grade Groups remain key to prognostic stratification. ISUP GG 1 (Gleason 3 + 3) represents well-differentiated tumors characterized by uniform glands without cribriform or fused patterns and is associated with an excellent prognosis and extremely low cancer-specific mortality according to the 2016 WHO and 2019 ISUP classifications [2–5].

Although ISUP GG 1 tumors show indolent behavior and active surveillance protocols are recommended, a substantial proportion of patients are still submitted to radical prostatectomy, usually due to the anxiety caused by cancer. Despite the favorable prognosis, some patients develop biochemical recurrence after surgery, causing uncertainty and anxiety for both patients and physicians, as the clinical relevance of biochemical recurrence (BCR) and the role of salvage radiotherapy remain unclear [6–11].

Current international guidelines recommend individualizing the use of salvage radiotherapy based on PSA level, PSA kinetics, margin status, and adverse pathological findings, but acknowledge the lack of specific evidence for ISUP GG 1 tumors [12]. Large contemporary trials such as RAVES, RADICALS-RT, and GETUG-AFU 17 demonstrated the non-inferiority of early salvage radiotherapy compared to adjuvant radiotherapy, but included very few ISUP GG 1 patients, which limits their applicability to this very low-risk subgroup [13,14].

In this context, the primary objective of this study was to describe the incidence, time to biochemical recurrence, and pathological factors associated with BCR in patients with ISUP GG 1 prostate cancer confirmed in the radical prostatectomy specimen. As secondary objectives, long-term clinical outcomes after BCR were described, including the use of salvage treatments, radiological progression, and mortality.

## Materials and methods

### Study design and population

A retrospective observational study was conducted at a tertiary university hospital. All consecutive patients who underwent radical prostatectomy between January 1999 and December 2012 were reviewed.

Patients whose surgical specimens after radical prostatectomy with bilateral lymphadenectomy showed ISUP GG 1 prostate adenocarcinoma (Gleason  $\leq 6$ ) according to the 2016 WHO and 2019 ISUP criteria were included. During the study period, all patients with ISUP GG 1 in the surgical specimen were included, with no further exclusions following histopathological classification.

Exclusion criteria were incomplete pathological data, lack of relevant clinical information in medical record, follow-up shorter than 12 months, and presence of lymph node involvement (pN+) in lymphadenectomy. The patient selection process is summarized in Fig. 1.

During the follow-up period, no adjuvant radiotherapy or other oncologic treatments were administered prior to the onset of biochemical recurrence.

### Clinical and pathological variables

Preoperative clinical variables such as age and preoperative PSA were collected. Pathological variables included pathologic stage (pT2a–c, pT3a), surgical margin status, perineural invasion, and the presence of prostatic intraepithelial neoplasia (PIN).

The primary outcome was biochemical recurrence (BCR). Secondary outcomes included the use of salvage therapies, radiological progression, overall survival, and cancer-specific survival.

BCR was defined as PSA  $\geq 0.2$  ng/mL in two consecutive measurements after reaching the postoperative nadir.

Radiological progression was defined as evidence of pelvic nodal involvement or distant disease beyond the surgical bed confirmed by conventional imaging techniques available during the study period.

### Statistical analysis

Continuous variables were described as mean  $\pm$  standard deviation or median (interquartile range), depending on their distribution. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Biochemical recurrence-free survival and overall survival were estimated using Kaplan–Meier curves and compared using the log-rank test.

A Cox regression model was constructed to identify predictors of biochemical recurrence. The variables used in the multivariate analysis were selected based on their clinical relevance and the number of events observed and included preoperative PSA, pathologic stage (pT2a, pT2b, pT2c, and pT3a), and surgical margin status. The inclusion of other pathological variables was limited by the number of BCR events.

Given the small number of radiological progression events and the absence of cancer-specific mortality, no inferential statistical analyses were performed for these outcomes, which were described exclusively in a descriptive manner.

Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

### Ethical considerations

The study was assessed by the Clinical Research Ethics Committee, which issued a favorable report at the meeting held on February 17, 2025 (minutes no. 434, order number 2025/031).

Given the retrospective nature of the study and the use of anonymized clinical data, informed consent was waived.

The study was conducted in accordance with the principles of the Declaration of Helsinki.

## Results

A total of 208 consecutive patients met the inclusion criteria and were analyzed (Fig. 1). The median age was 63 years (IQR 59–67). The median follow-up was 145 months (IQR 137–152), equivalent to 12.1 years (IQR 11.4–12.7). The baseline clinical and pathological characteristics of the cohort are summarized in Table 1.

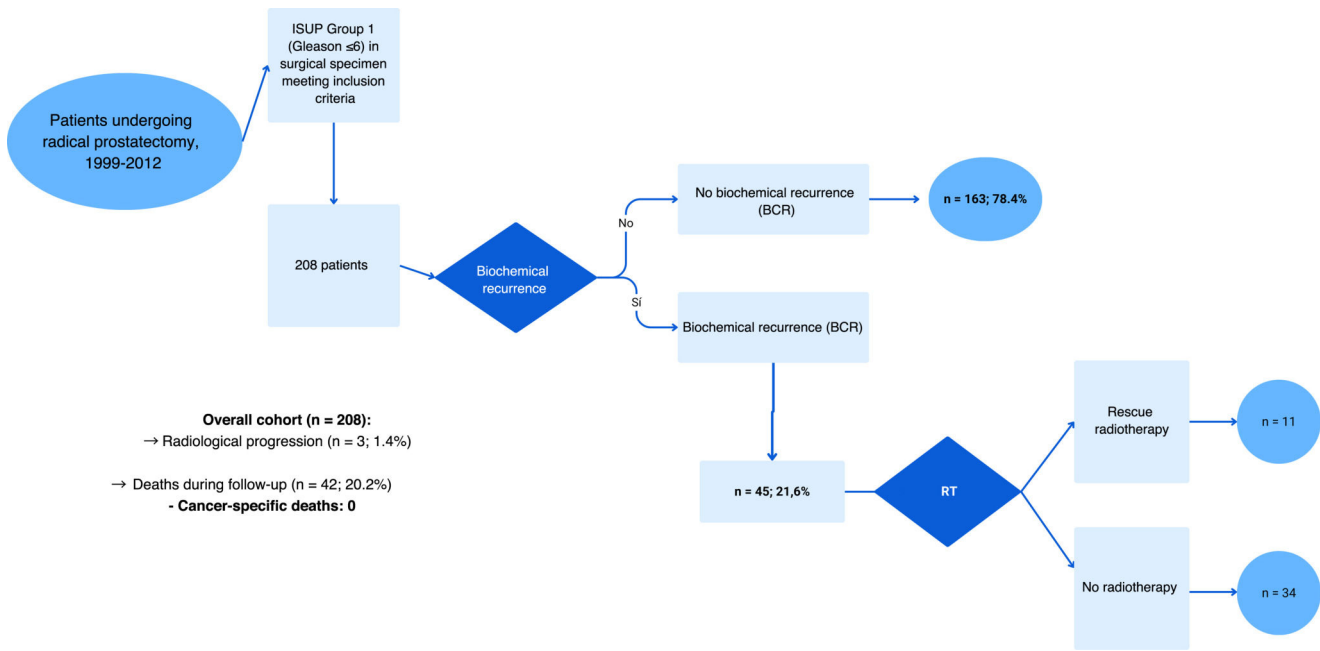


Figure 1. Study flowchart.

Selection and inclusion of 208 patients with ISUP GG 1 prostate cancer treated with radical prostatectomy.

Table 1

Clinical and pathological variables of the sample.

Variable	Valor
Age, years (mean ± SD)	63 ± 5,5
Preoperative PSA, ng/mL (median, IQR)	6,4 (5,1–8,4)
Biochemical recurrence (BCR)	45 (21,6%)
Radiological progression	3 (1,4%)
Adjuvant radiation therapy	0 (0%)
Salvage radiation therapy	11 (5,3%)
Androgen deprivation therapy	5 (2,4%)
Pathologic stage T2a	43 (20,7%)
Pathologic stage T2b	30 (14,4%)
Pathologic stage T2c	118 (56,7%)
Pathologic stage T3a	17 (8,2%)
Positive surgical margins	41 (19,7%)
Perineural invasion	39 (18,8%)
Prostatic intraepithelial neoplasia (PIN)	63 (30,3%)

During follow-up, 45 patients (21.6%) developed biochemical recurrence. Among these patients, the median time to BCR was 5.2 years (IQR 2.3–7.5). Kaplan–Meier estimates of biochemical recurrence-free survival were 92% at 5 years (95% CI 85.5–94.1), 81% at 10 years (95% CI 75.7–86.7), and 78% at 15 years (95% CI 72.0–84.0).

In the multivariate Cox regression analysis, adjusted for preoperative PSA and pathologic stage (pT2a–c and pT3a), positive surgical margins were the only independent predictor of biochemical recurrence (HR 3.27; 95% CI 1.64–6.53;  $p < 0.001$ ). Kaplan–Meier curves showed lower biochemical recurrence-free survival in patients with positive margins compared with those with negative margins (Fig. 2). Eleven patients (5.3% of the total; 24.4% of patients with biochemical recurrence) received salvage radiotherapy during follow-up. The indication and timing of radiotherapy were heterogeneous and dependent on clinical practice at the time. Adjuvant radiotherapy was not administered after radical prostatectomy. Radiological progression was infrequent and was observed in 3 patients (1.4%), all with presacral nodal involvement. Two of these patients had received salvage radiotherapy, and one did not receive additional oncologic treatment.

During follow-up, 42 deaths (20.2%) occurred, all due to causes unrelated to prostate cancer, confirming the absence of prostate cancer-specific mortality in this cohort of patients with ISUP 1 prostate cancer. The estimated overall survival was 95.1% (95% CI: 91.1–97.3) at 5 years, 90.6% (95% CI: 85.7–93.9) at 10 years, and 77.5% (95% CI: 69.0–84.0) at 15 years.

## Discussion

In this cohort of 208 men with ISUP GG 1 prostate adenocarcinoma treated with radical prostatectomy, long-term oncologic outcomes were outstanding. Despite a BCR rate of 21.6%, only three patients (1.4%) developed radiological progression, and no cancer-related deaths were observed after a median follow-up of 12.1 years. These findings reinforce the indolent behavior of pure Gleason 3 + 3 tumors and are consistent with pathological and population-based studies reporting extremely low rates of clinically relevant progression in ISUP 1 disease [15,16].

A relevant aspect of this study is that no events compatible with persistent PSA (PSA  $\geq 0.2$  ng/mL within the first three months) were documented. Consequently, the recurrences analyzed were predominantly late, with a median time to recurrence of more than five years. This temporal distribution—with more than half of recurrences occurring beyond five years—suggests a low aggressiveness and supports the idea that many PSA elevations in ISUP GG 1 tumors reflect biologically indolent recurrences. The strong association between positive surgical margins and recurrence was maintained in the multivariable analysis, in line with previous literature. However, even in this subgroup, BCR did not translate into radiological progression or cancer-specific mortality, reinforcing that PSA elevation in ISUP GG 1 tumors should be interpreted with caution and that its clinical significance differs from that observed in higher-grade tumors.

The high proportion of late recurrences likely reflects, in addition to the intrinsically indolent behavior of these tumors, historical factors related to the period in which surgeries were performed: absence of multiparametric resonance, targeted biopsies, and surgical margin definitions. In the context of ISUP GG 1 tumors, surgery was primarily oriented toward functional preservation, which may have contributed to

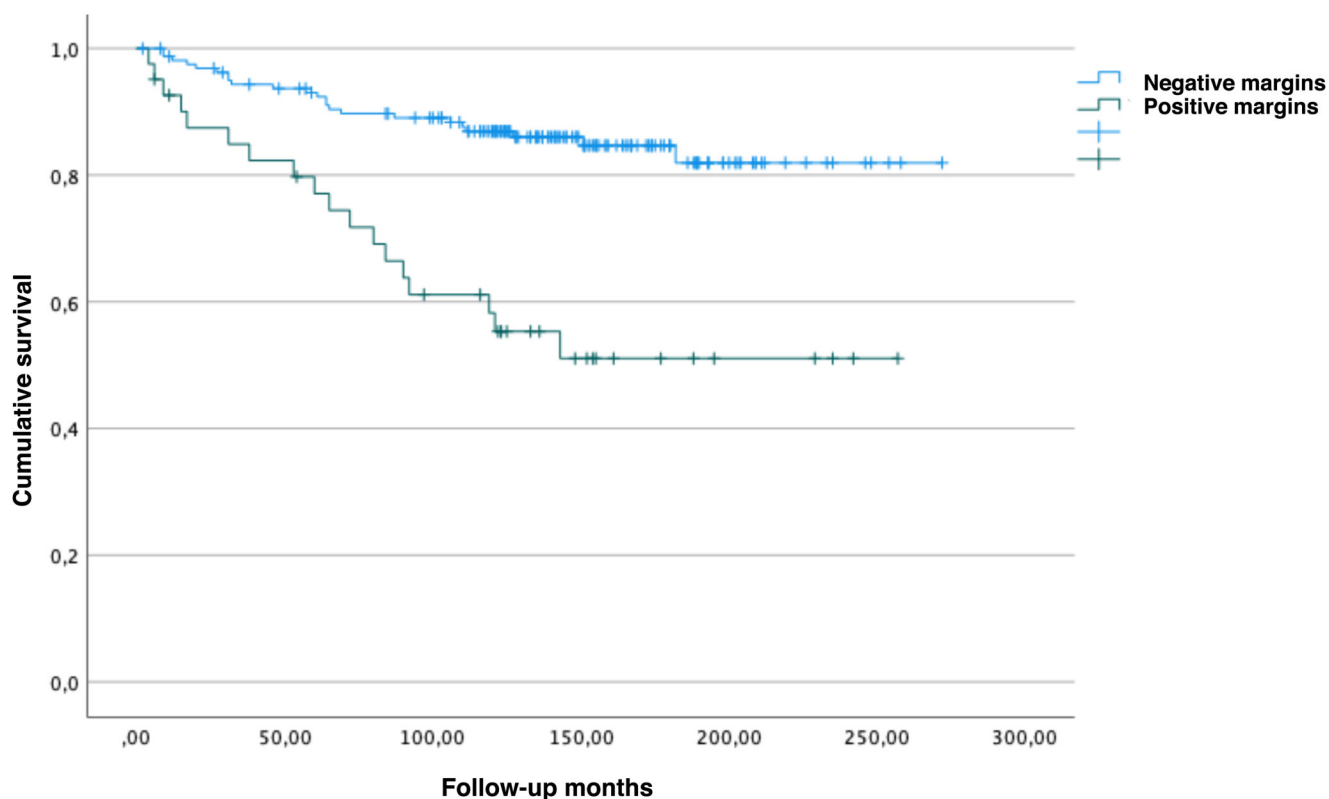


Figure 2. Biochemical recurrence-free survival according to surgical margins.

a higher rate of positive surgical margins, without this being associated with a relevant clinical impact.

Regarding postoperative radiotherapy, only a minority of patients received salvage treatment, and no clinically relevant differences in survival or progression were observed, in a context of a very low number of rates. These findings should be interpreted exclusively in a descriptive manner and do not allow conclusions to be drawn regarding the efficacy of salvage radiotherapy in patients with ISUP 1.

Neither PIN nor perineural invasion showed an association with recurrence, in accordance with the literature on low-grade tumors [17]. The low rate of metastatic progression is consistent with previous studies showing that pure Gleason 6 tumors rarely metastasize [18].

The clinical implications of these findings suggest that, in patients with ISUP GG 1 prostate cancer treated with radical prostatectomy, PSA elevation should be interpreted in the context of disease with very low biological risk, particularly in the absence of positive surgical margins. In this regard, the decision to undertake additional interventions after biochemical recurrence requires an individualized assessment of the overall clinical context. It should be noted that the three progressions observed corresponded to presacral nodal involvement, with no evidence of bone or visceral dissemination, which is consistent with the very low overall aggressiveness of the cohort. On the other hand, in the current era of multiparametric MRI and targeted biopsies, a relevant proportion of these patients would potentially have been candidates for conservative strategies such as active surveillance.

The study has several limitations inherent to its retrospective, single-center design. All prostatectomies were performed before the widespread adoption of mpMRI and standardized margin definitions, which may have overestimated margin positivity. The lack of systematic availability of the original slides precluded contemporary reassessment based on current criteria. Although data were cleaned to exclude invalid dates, the historical nature of the cohort entailed heterogeneity in

follow-up schedules, although sufficient information was available to classify the absence of persistent PSA according to the proposed definition. In addition, the small number of radiological progressions and salvage treatments limits adjusted comparisons between groups. Finally, certain pathological parameters—such as tumor volume or index lesion volume—were not consistently available. Likewise, the absence of serial and homogeneous PSA measurements precluded reliable estimation of PSA doubling time and, consequently, stratification of biochemical recurrence according to the risk criteria proposed by the EAU. Furthermore, surgical margin length was not systematically reported during the study period, which limited its quantitative analysis.

Despite these limitations, the study provides solid information owing to a large sample size and one of the longest follow-ups published for ISUP 1 tumors, allowing precise characterization of their actual clinical behavior.

## Conclusions

In this cohort of 208 patients with ISUP GG 1 prostate adenocarcinoma treated with radical prostatectomy, long-term oncologic outcomes were outstanding, with a very low rate of radiologic progression and no cancer-specific deaths after prolonged follow-up.

Although biochemical recurrence was observed in approximately one-fifth of patients, this event was rarely associated with clinically relevant progression, even in the presence of positive surgical margins, suggesting a predominantly indolent biological behavior.

Overall, these findings reinforce the excellent prognosis of surgically treated ISUP GG 1 prostate cancer and underscore the need for a cautious, context-based interpretation of PSA elevation in this setting. These data also support the role of strategies such as active surveillance and highlight the need for prospective studies specifically designed to clarify the clinical significance of biochemical recurrence in very low-risk tumors.

## Author contributions

- Conceptualization: L. Diéguez-Álvarez, J.M. Martínez-Jabaloyas
- Methodology: L. Diéguez-Álvarez, J. Panach-Navarrete, J.M. Martínez-Jabaloyas
- Data collection: A.I. Hernández Álvarez
- Data analysis and interpretation: L. Diéguez-Álvarez, J.M. Martínez-Jabaloyas
- Writing – original draft: L. Diéguez-Álvarez, J.M. Martínez-Jabaloyas
- Writing – review and editing: J. Panach-Navarrete, J.M. Martínez-Jabaloyas
- Methodological support and critical review: L. Esteban Igual
- Support in data collection and organization: A. Castelló Porcar
- Supervision: J.M. Martínez-Jabaloyas

## Informed consent

Given the retrospective nature of the study and the use of anonymized data, the Ethics Committee waived the requirement for informed consent.

## Ethical considerations

The study was approved by the institutional Clinical Research Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki.

## Declaration of Generative AI and AI-assisted technologies in the writing process

No generative artificial intelligence or AI-assisted tools were used for scientific writing, data analysis, or figure preparation in this manuscript.

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## Authorship

All authors made substantial contributions to the conception and design of the study, acquisition, analysis, and interpretation of data, drafting and critical review of the manuscript, and approved the final version for submission.

## Declaration of competing interest

The authors declare no conflicts of interest.

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