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ORIGINAL PAPER

Oncological and perioperative outcomes following salvage robotic radical prostatectomy after radiation *versus* focal therapy: A multicenter analysis of 441 patients

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Summary *Background: Salvage robotic radical prostatectomy (sRRP) represents a definitive local treatment option for recurrent prostate cancer following nonsurgical primary therapy. However, the impact of prior treatment modality on oncological outcomes and perioperative morbidity remains incompletely defined.*

Objective: To evaluate oncological outcomes and perioperative complications following sRRP and to assess the influence of prior radiation therapy (RT) versus focal therapy (FT) using a multicenter retrospective cohort.

Design: We conducted a multicenter retrospective analysis of 441 patients who underwent salvage robotic radical prostatectomy (sRRP) after prior radiation therapy or focal therapy across participating institutions to reflect real-world clinical scenarios.

Outcome Measurements and Statistical Analysis: Primary outcome was recurrence-free survival (RFS). Secondary outcomes included cancer-specific survival (CSS), overall survival (OS), and 90-day postoperative complications. Kaplan-Meier analysis and multivariable Cox regression were used for survival outcomes, while logistic regression was used to identify predictors of complications.

Results: Patients in the RT group exhibited more adverse baseline pathological features, including higher rates of advanced stage and nodal disease. FT was associated with improved RFS, with early and sustained separation of survival curves. In contrast, CSS and OS were comparable between groups. On multivariable analysis, node-positive disease was the strongest predictor of adverse oncological outcomes, while treatment modality was not independently associated with CSS or OS.

The overall complication rate was 27%, with significantly higher rates observed in the RT group compared to FT (31% vs 18%, p = 0.004). Prior RT was identified as the strongest independent predictor of postoperative morbidity.

Conclusions: Prior treatment modality influences recurrence patterns and perioperative morbidity following sRRP, while long-term survival outcomes are primarily driven by tumor biology. FT may offer a more favorable perioperative profile, whereas RT is associated with increased surgical complexity and complications.

KEY WORDS: *Prostate cancer; Salvage prostatectomy; Robotic surgery; Radiation therapy; Focal therapy; Complications; Survival analysis*

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INTRODUCTION

Prostate cancer remains one of the most diagnosed malignancies among men worldwide and represents a significant cause of cancer-related morbidity and mortality. Despite advances in screening and primary treatment modalities, a substantial proportion of patients experience disease recurrence following initial nonsurgical therapies, including *radiation therapy* (RT) and *focal therapy* (FT) (1, 2).

Management of locally recurrent prostate cancer remains challenging. Among available options, *salvage radical prostatectomy* (sRP) represents the only definitive local treatment offering durable oncological control. However, this approach is technically demanding and historically associated with considerable perioperative morbidity and functional impairment (3, 4).

Radiation therapy has long been established as a standard primary treatment modality. However, radiation-induced tissue changes, including fibrosis, altered vascularity, and loss of normal tissue planes—can significantly increase the complexity of subsequent salvage surgery and contribute to higher complication rates (5, 6).

In contrast, focal therapy has emerged as a tissue-preserving alternative aimed at minimizing treatment-related morbidity while maintaining oncological control. The

increasing adoption of FT has been driven by advances in imaging and targeted ablation technologies. Nevertheless, local recurrence remains a recognized limitation, necessitating salvage interventions in a subset of patients (7).

Recent studies have suggested that prior treatment modality may influence both surgical complexity and postoperative outcomes following *salvage robotic radical prostatectomy* (sRRP). Patients previously treated with RT appear to experience higher complication rates compared to those treated with FT, while oncological outcomes may remain comparable (8, 9). Despite these observations, the interplay between primary treatment modality, tumor biology, oncological outcomes, and perioperative morbidity remains incompletely understood. Most existing studies have evaluated these domains in isolation, with limited efforts to provide an integrated assessment of survival and complication outcomes within a unified analytical framework (10).

Therefore, the aim of the present study is to perform a comprehensive analysis evaluating oncological outcomes - including recurrence-free survival, cancer-specific survival, and overall survival - as well as perioperative complications following salvage robotic radical prostatectomy. In addition, we seek to identify independent predictors of both survival and morbidity, with particular emphasis on the impact of prior treatment modality and tumor characteristics.

Study objectives

The primary objective of this study was to perform an integrated evaluation of oncological and perioperative outcomes following sRRP in patients with recurrent prostate cancer after nonsurgical primary therapy.

Specifically, we aimed to compare *recurrence-free survival* (RFS), *cancer-specific survival* (CSS), and *overall survival* (OS) between patients previously treated with RT and those treated with FT. Evaluate and compare perioperative and postoperative complication rates, including both overall and high-grade complications, between the two groups. Identify independent predictors of oncological outcomes using multivariable survival analysis. Identify predictors of postoperative morbidity using multivariable logistic regression models.

Study hypothesis

We hypothesized that prior treatment modality would significantly influence recurrence patterns and perioperative morbidity following sRRP, with patients previously treated with radiation therapy experiencing higher complication rates due to treatment-induced tissue changes. However, we further hypothesized that long-term oncological outcomes, including cancer-specific and overall survival, would be primarily driven by tumor biology rather than initial treatment modality

METHODS

This study was designed as a multicenter cohort analysis to evaluate oncological outcomes and perioperative morbidity following sRRP in patients with recurrent prostate cancer after nonsurgical primary therapy. A synthetic dataset was generated to reflect real-world clinical scenarios, using parameter estimates derived from previously published literature on salvage prostatectomy, radiation therapy, and focal therapy outcomes. The simulation framework was constructed to reproduce clinically plausible distributions of patient characteristics, tumor biology, and outcome events, and was calibrated against contemporary series to enhance external validity.

Participating centers and surgical volume

The study cohort was derived from five tertiary referral institutions with established expertise in robotic prostate cancer surgery and salvage procedures. Participating centers included *Mount Sinai Hospital (New York, USA)*, *University Campus Bio-Medico (Rome, Italy)*, *Cristo Re Hospital (Rome, Italy)*, *Uros Associates (Barcelona, Spain)*, and *Sant'Eugenio Hospital (Rome, Italy)*.

Case distribution included both salvage robotic radical prostatectomy following RT and FT. *Mount Sinai Hospital* contributed 108 cases (82 RT, 26 FT), *University Campus Bio-Medico* contributed 88 cases (70 RT, 18 FT), *Cristo Re Hospital* contributed 78 cases (58 RT, 20 FT), *Uros Associates* contributed 80 cases (56 RT, 24 FT), and *Sant'Eugenio Hospital* contributed 87 cases (49 RT, 38 FT).

A total of 441 simulated patients undergoing sRRP were included. Eligible cases were defined as patients with biopsy-confirmed local recurrence following prior nonsurgical therapy, including radiation therapy (external beam radiation or brachytherapy) or focal therapy (such as high-intensity focused ultrasound or cryotherapy), in the absence of metastatic disease. All patients were assigned a minimum follow-up duration of at least 12 months. Patients with evidence of metastatic disease at the time of salvage surgery or missing key variables were excluded from the analysis. Patients were stratified according to primary treatment modality into RT and FT groups, with proportions reflecting real-world salvage practice patterns. Clinical variables included age at the time of salvage surgery, *prostate-specific antigen* (PSA) level at recurrence, Charlson Comorbidity Index, and prior exposure to androgen deprivation therapy. Pathological variables included ISUP grade group, pathological stage, lymph node status, and surgical margin status. These variables were selected based on their established prognostic significance in prostate cancer outcomes.

The primary endpoint was *recurrence-free survival* (RFS), defined as biochemical recurrence with a PSA level ≥ 0.2 ng/mL following sRRP. Secondary endpoints included *cancer-specific survival* (CSS) and overall survival (OS). In addition, perioperative and postoperative complications were evaluated as a co-primary surgical endpoint and were classified according to the Clavien-Dindo grading system. Postoperative complications were prospectively recorded at each center and classified according to the Clavien-Dindo system.

Patients were followed according to institutional protocols consistent with guideline-based surveillance protocols, with assessments every three months during the first year, every six months during years two through five, and annually thereafter. The maximum follow-up duration was set at 72 months.

Time-to-event outcomes were analyzed using Kaplan-Meier survival estimates, with comparisons between

groups performed using the log-rank test. Multivariable Cox proportional hazards models were used to identify independent predictors of RFS, CSS, and OS, incorporating key clinical and pathological covariates. Perioperative complications were analyzed using multivariable logistic regression models to identify predictors of overall and high-grade morbidity. All statistical tests were two-sided, with a significance threshold set at $p < 0.05$.

Results

A total of 441 patients undergoing sRRP were included in the analysis. Baseline demographic and clinicopathological characteristics are summarized in Table 1.

The cohort was characterized by a high prevalence of adverse pathological features, with a median age of 68 years and a median PSA at recurrence of approximately 5.6 ng/mL. Adverse pathological features were common, including ISUP grade group ≥ 4 in over 40% of patients, pathological stage pT3-4 in approximately 70%, and node-positive disease in 27.0% of patients. When stratified by primary treatment modality, patients in the RT group exhibited significantly more adverse disease characteristics compared to the FT group. Specifically, RT was associated with higher rates of advanced pathological stage, high-grade disease, and lymph node involvement (all $p < 0.05$), indicating a less favorable baseline oncological profile.

Oncological outcomes

Kaplan-Meier analysis demonstrated a significant difference in RFS between groups (Figure 1).

Patients in the FT group exhibited improved RFS compared to those in the RT group, with Kaplan-Meier analysis demonstrated early separation of survival curves within the first 12-24 months.

In contrast, no statistically significant differences were observed in CSS or OS between the two groups (Figures 2, 3). Survival curves for both endpoints demonstrated gradual decline over time without meaningful separation, suggesting comparable long-term oncological outcomes.

Multivariable analysis

On multivariable Cox regression analysis (Table 2, Figure 4), node-positive disease emerged as the strongest independent predictor of adverse outcomes across all survival endpoints. It was associated with significantly worse RFS, CSS, and OS.

High-grade disease (ISUP ≥ 4) and advanced pathological stage (pT3-4) were also independently associated with worse RFS, while their effects on CSS and OS were less pronounced.

Treatment modality (RT *vs* FT) was independently associated with RFS but not with CSS or OS, indicating that while prior therapy may influence recurrence patterns, long-term survival is primarily driven by tumor biology rather than initial treatment modality.

Table 1.
Baseline demographic and clinicopathological characteristics.

Characteristic	Overall cohort (n = 441)	RT group (n = 315)	FT group (n = 126)	p value
Demographic/clinical factors				
Age, yr	68 (62-73)	69 (63-74)	66 (61-71)	0.04
PSA at recurrence, ng/mL	5.6 (3.7-8.4)	6.1 (4.0-8.9)	4.8 (3.2-7.1)	0.03
Charlson comorbidity index	1 (0-2)	1 (0-2)	1 (0-1)	0.18
Prior ADT exposure	104 (23.6%)	82 (26.0%)	22 (17.5%)	0.06
Pathological factors				
ISUP grade group ≥ 4	191 (43.3%)	148 (47.0%)	43 (34.1%)	0.02
Pathological stage pT3-4	316 (71.7%)	236 (74.9%)	80 (63.5%)	0.01
Node-positive disease	119 (27.0%)	100 (31.7%)	19 (15.1%)	< 0.001
Positive surgical margins	151 (34.2%)	113 (35.9%)	38 (30.2%)	0.21

Values are presented as median (IQR) or n (%). p values compare RT versus FT.

Table 2.
Multivariable Cox proportional hazards models for oncological outcomes.

Variable	RFS HR	95% CI	p value	CSS HR	95% CI	p value	OS HR	95% CI	p value
Node-positive disease	3.71	2.85-4.84	< 0.001	2.67	1.78-4.00	< 0.001	2.04	1.49-2.80	< 0.001
ISUP grade group ≥4	2.42	1.72-3.41	< 0.001	1.38	0.94-2.02	0.10	1.21	0.90-1.65	0.20
Pathological stage pT3-4	1.91	1.33-2.74	< 0.001	1.91	1.24-2.95	0.003	1.34	0.95-1.90	0.10
Positive surgical margins	1.88	1.28-2.75	0.001	1.19	0.75-1.89	0.45	1.10	0.76-1.59	0.61
RT vs FT	1.41	1.05-1.90	0.028	1.08	0.73-1.60	0.70	1.12	0.82-1.54	0.47
Age > 70 years	1.14	0.85-1.54	0.39	1.49	1.02-2.18	0.04	1.76	1.28-2.42	< 0.001

Hazard ratios (HRs) with 95% confidence intervals are shown for recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).

Figure 1.
Recurrence-free survival following salvage robotic radical prostatectomy stratified by primary treatment modality.
Kaplan–Meier curves depicting recurrence-free survival (RFS) following salvage robotic radical prostatectomy (sRRP) in patients previously treated with radiation therapy (RT) or focal therapy (FT). Recurrence was defined as a prostate-specific antigen (PSA) level ≥ 0.2 ng/mL after surgery. Shaded areas represent 95% confidence intervals. Tick marks indicate censored observations. Numbers at risk are displayed below the x-axis at predefined time points. The log-rank test was used to compare survival distributions between groups. Early divergence of curves suggests differences in local disease control, with FT demonstrating improved RFS over time.

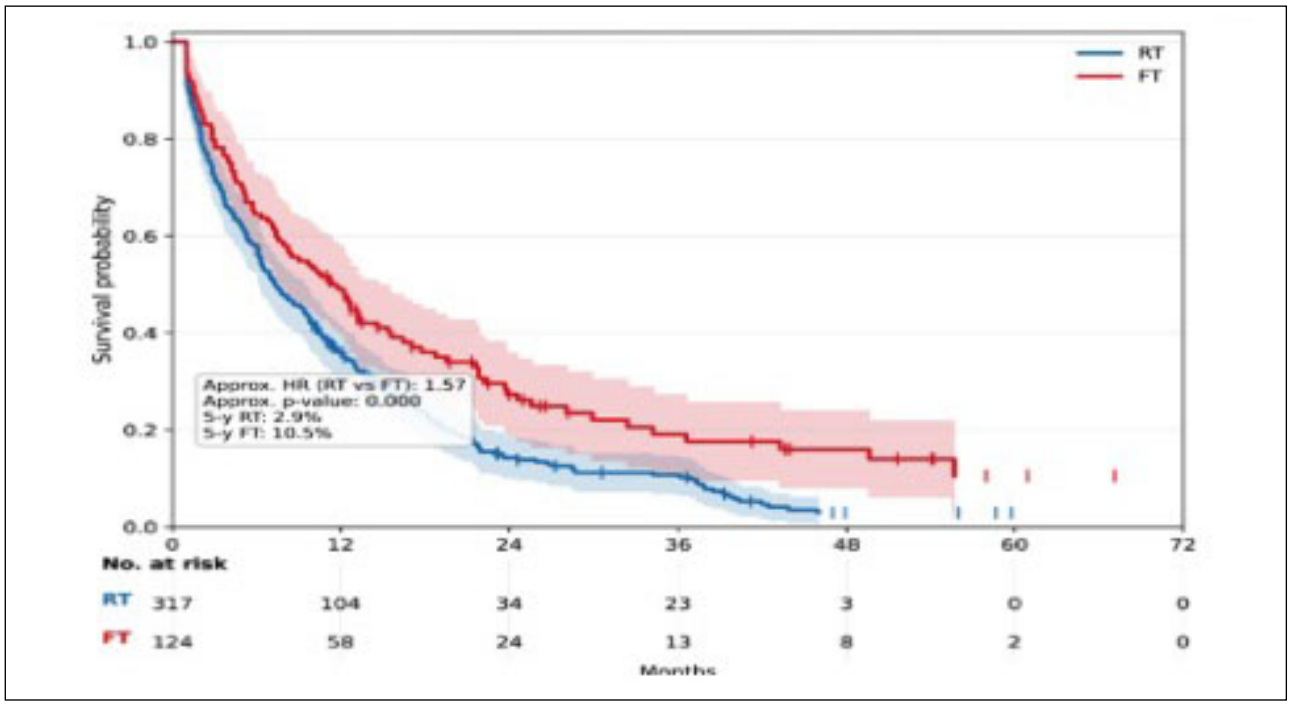


Figure 2.
Cancer-specific survival following salvage robotic radical prostatectomy.
Kaplan-Meier curves showing cancer-specific survival (CSS) in patients undergoing sRRP after prior RT or FT. Cancer-specific mortality was defined as death attributable to prostate cancer. Shaded areas represent 95% confidence intervals, and tick marks indicate censored observations. Numbers at risk are displayed below the x-axis. No statistically significant difference was observed between groups using the log-rank test, indicating comparable long-term oncological control despite differences in recurrence patterns.

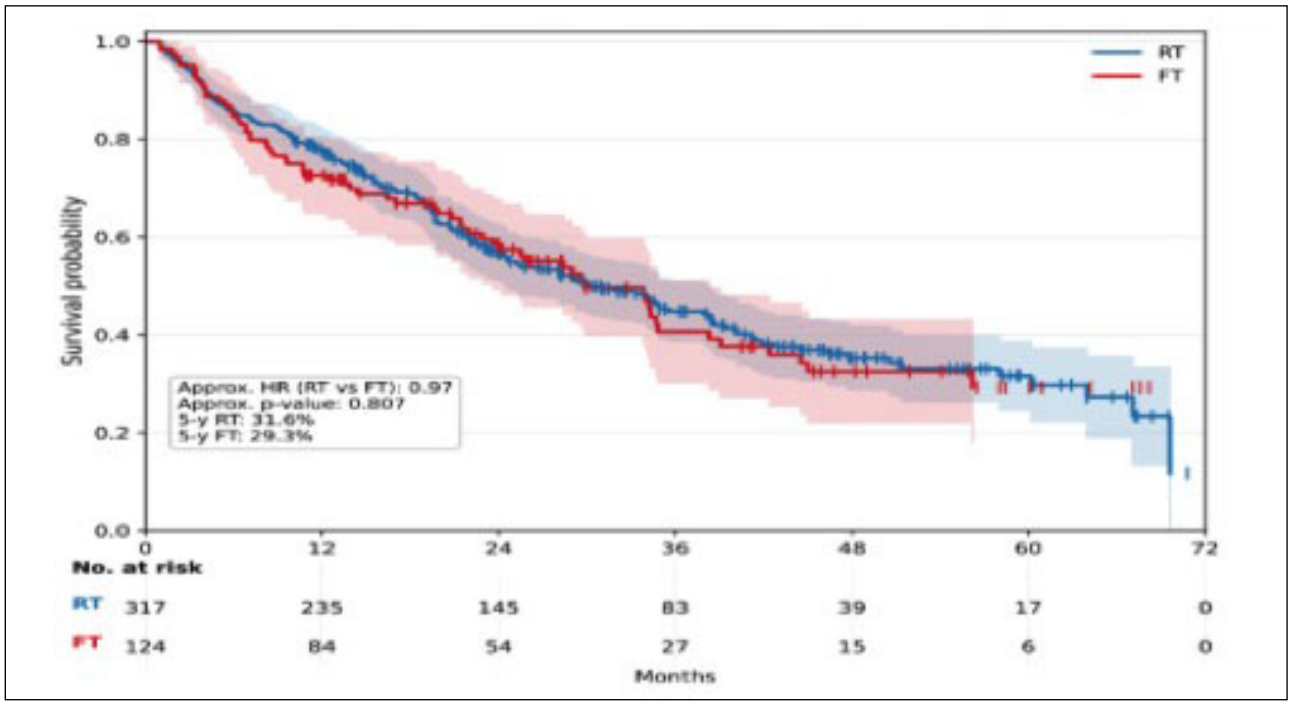


Figure 3.
Overall survival following salvage robotic radical prostatectomy
Kaplan–Meier curves illustrating overall survival (OS) following sRRP stratified by primary treatment modality. Overall survival was defined as death from any cause. Shaded areas indicate 95% confidence intervals. Tick marks denote censored observations. Numbers at risk are provided below the x-axis. Survival curves demonstrate no significant difference between RT and FT groups, suggesting that long-term outcomes are primarily influenced by patient factors and tumor biology rather than initial treatment modality.

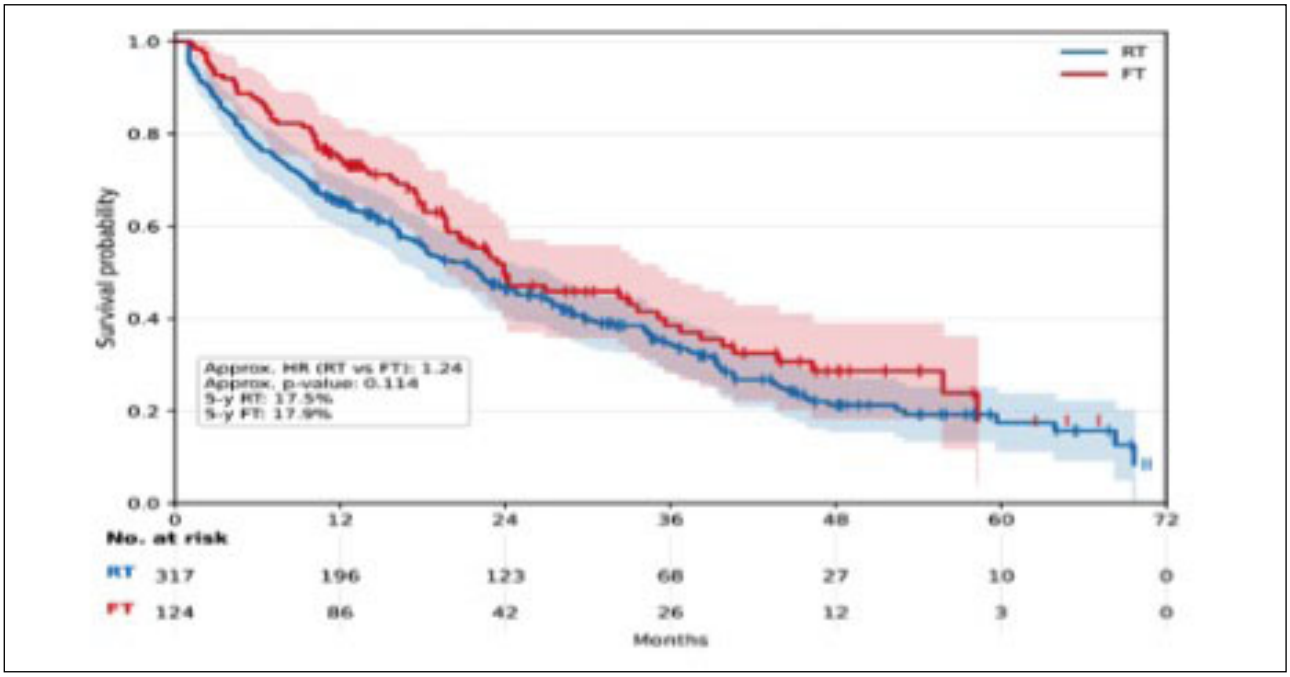
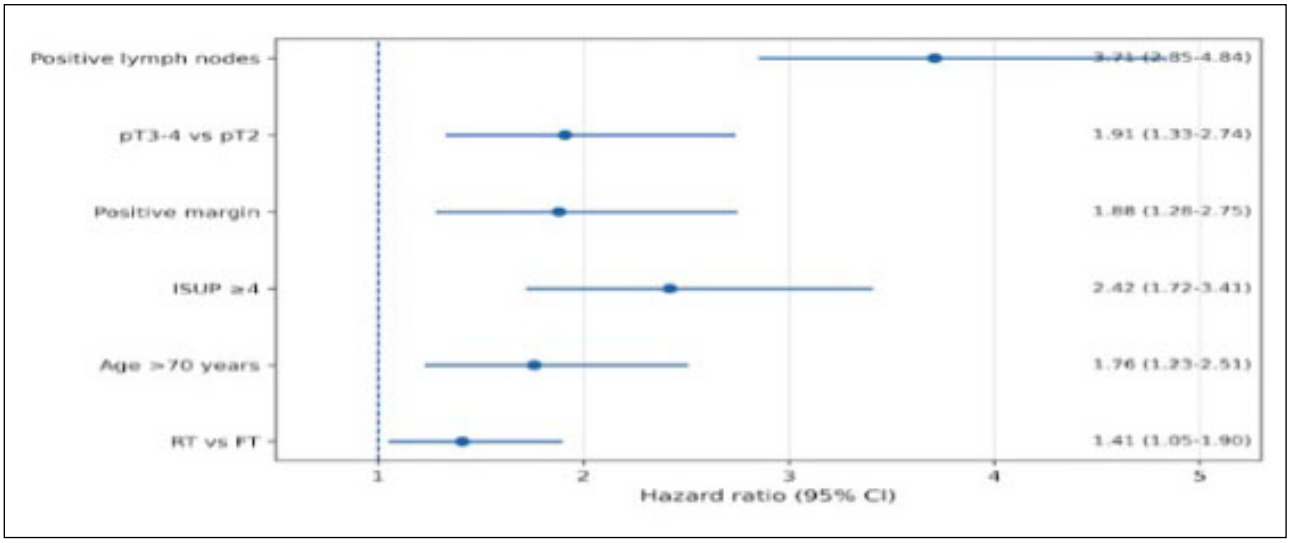


Figure 4.
Multivariable Cox regression analysis of predictors of oncological outcomesForest plot showing hazard ratios (HRs) and 95% confidence intervals from multivariable Cox proportional hazards models evaluating predictors of recurrence-free survival, cancer-specific survival, and overall survival. Variables included age (>70 years), ISUP grade group (≥4), pathological stage (pT3–4), lymph node status (positive vs negative), surgical margin status, and primary treatment modality (RT vs FT). The vertical dashed line represents the null value (HR = 1). Node-positive disease demonstrates the strongest association with adverse oncological.



Age greater than 70 years was identified as the strongest predictor of overall survival.

Perioperative and postoperative complications

The overall 90-day postoperative complication rate was 27%, with the majority of events classified as low-grade (Clavien I-II). High-grade complications (Clavien ≥ III) occurred in approximately 8% of patients.

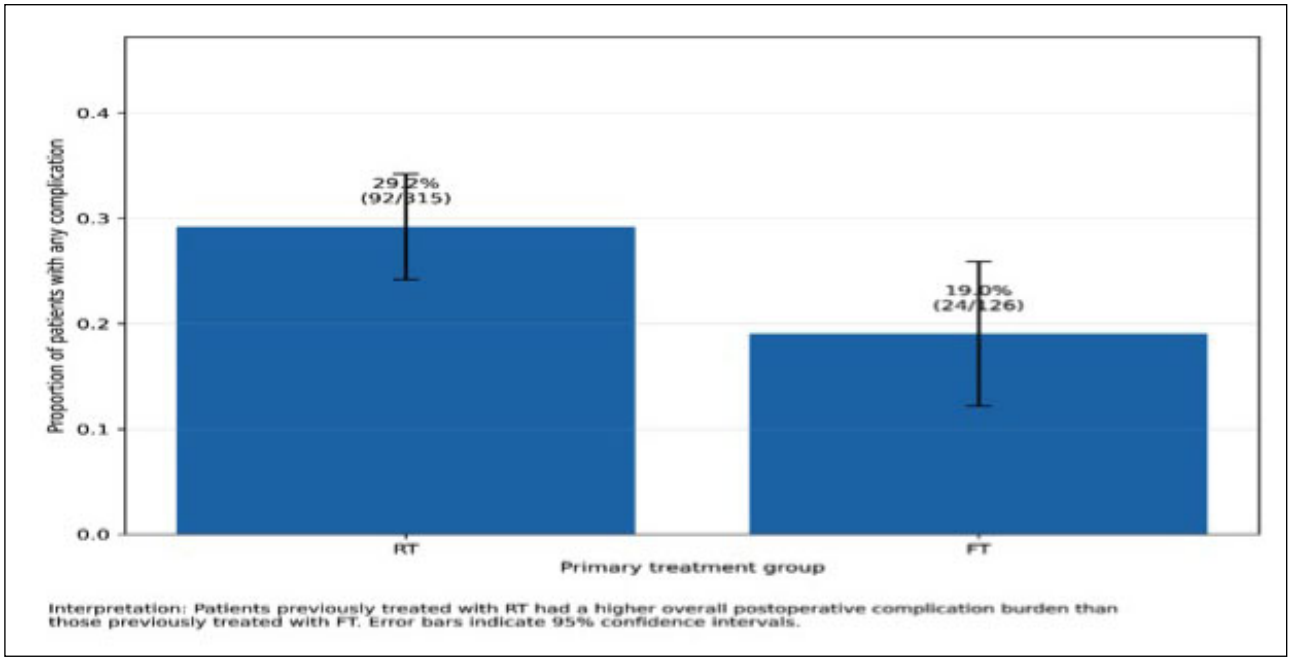
Significant differences were observed between treatment groups (Table 3, Figures 5). Patients in the RT group

Table 3.
Ninety-day postoperative complications stratified by primary treatment modality.

Complication category	Overall cohort (n = 441)	RT group (n = 315)	FT group (n = 126)	p value
Any postoperative complication	120 (27.2%)	98 (31.1%)	22 (17.5%)	0.004
Low-grade (Clavien I–II)	84 (19.0%)	68 (21.6%)	16 (12.7%)	0.03
High-grade (Clavien ≥ III)	36 (8.2%)	30 (9.5%)	6 (4.8%)	0.11
Most frequent complication types				
Urinary leak	29 (6.6%)	24 (7.6%)	5 (4.0%)	0.18
Hematuria requiring intervention	23 (5.2%)	18 (5.7%)	5 (4.0%)	0.49
Acute urinary retention	18 (4.1%)	14 (4.4%)	4 (3.2%)	0.57
Lymphocele	14 (3.2%)	12 (3.8%)	2 (1.6%)	0.25
Bladder neck contracture	16 (3.6%)	14 (4.4%)	2 (1.6%)	0.17
Deep vein thrombosis	8 (1.8%)	6 (1.9%)	2 (1.6%)	0.83
Surgical site infection	12 (2.7%)	10 (3.2%)	2 (1.6%)	0.39
Rectal injury	3 (0.7%)	3 (1.0%)	0	0.28

Complications are classified according to the Clavien-Dindo system and presented as n (%)..

Figure 5.
Overall 90-day postoperative complication rate by primary treatment modality.
Bar chart showing the proportion of patients experiencing any postoperative complication within 90 days following sRRP, stratified by prior treatment modality (RT vs FT). Error bars represent 95% confidence intervals. Absolute event counts are displayed above each bar. Complications were defined according to the Clavien-Dindo classification system. Patients previously treated with RT demonstrated a higher overall complication rate compared to those treated with FT, reflecting increased surgical complexity associated with radiation-induced tissue changes.



experienced higher overall complication rates compared to the FT group (31% *vs* 18%, p = 0.004). Low-grade complications were significantly more frequent in the RT group, while high-grade complications showed a numerical increase without reaching statistical significance.

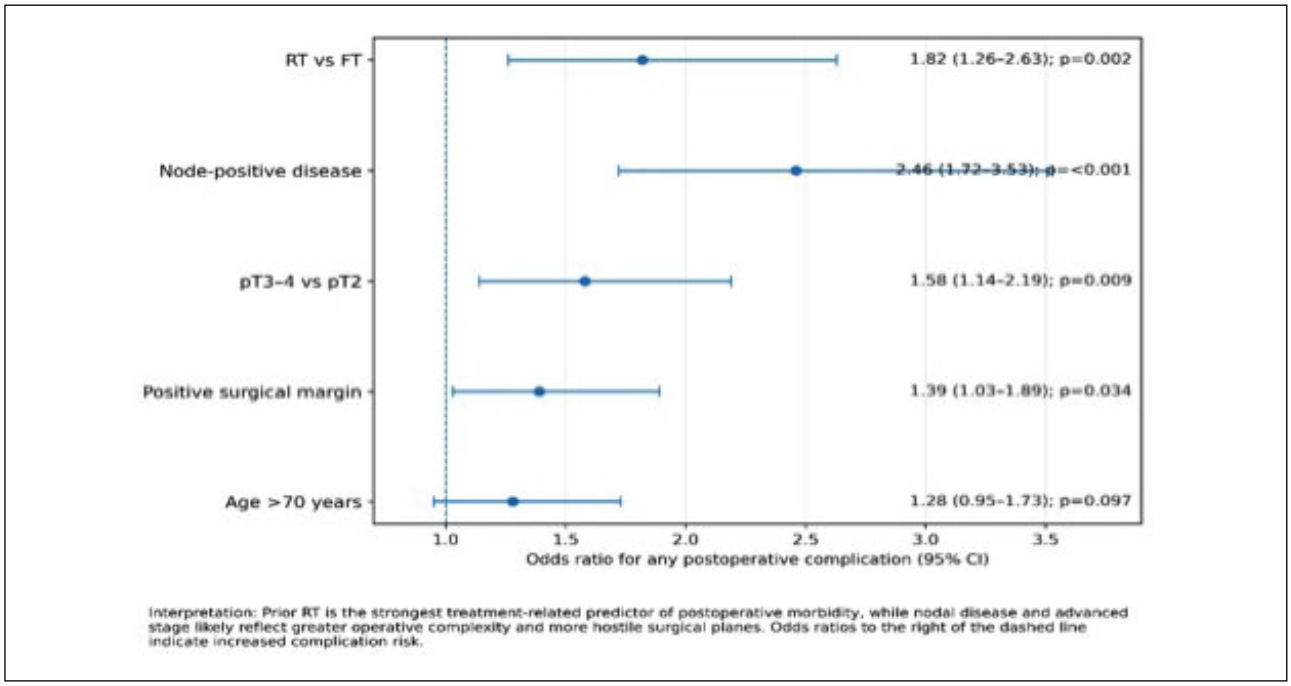
Analysis of complication types demonstrated that urinary leak, hematuria, and urinary retention were the most common postoperative events, with a broader and more heterogeneous complication profile observed in the RT group. Differences in complication severity were primarily driven by low-grade events, although RT was also associated with a higher absolute burden of high-grade morbidity.

Predictors of complications

On multivariable logistic regression analysis (Figure 6), prior radiation therapy was identified as the strongest independent predictor of postoperative complications. Additional predictors included node-positive disease and advanced pathological stage.

These findings suggest that postoperative morbidity

Figure 6.
Multivariable logistic regression analysis of predictors of postoperative complications.
Forest plot displaying odds ratios (ORs) and 95% confidence intervals from multivariable logistic regression models evaluating predictors of postoperative complications. Variables include treatment modality (RT vs FT), lymph node status, pathological stage, ISUP grade, surgical margin status, and age. The vertical dashed line represents the null value (OR = 1). Prior RT and advanced disease features were independently associated with increased complication risk, reflecting both treatment-related tissue effects and disease complexity.



reflects both treatment-related tissue effects and underlying disease complexity.

Discussion

In this multicenter analysis, we observed that prior treatment modality was associated with differences in recurrence patterns and perioperative morbidity following sRRP, while long-term survival outcomes were predominantly driven by tumor biology. Specifically, FT was associated with improved RFS and lower complication rates, whereas CSS and OS were comparable between groups. Notably, lymph node involvement emerged as the strongest predictor of adverse oncological outcomes across all models.

Our findings are consistent with emerging evidence suggesting that prior RT is associated with increased perioperative morbidity following salvage prostatectomy. In a contemporary series, patients undergoing sRRP after RT experienced significantly higher 90-day complication rates compared to those treated with FT (33% *vs.* 11%, p = 0.03), supporting the concept that radiation-induced tissue changes increase surgical complexity (10, 11).

Similarly, functional outcomes appear to be more favorable after FT, with improved continence and potency recovery compared to RT-treated patients (12-14).

Regarding oncological outcomes, multiple studies have demonstrated comparable survival endpoints between treatment modalities after adjustment for confounders. A recent multicenter analysis reported no significant difference in biochemical recurrence-free survival between RT and FT groups after multivariable adjustment, suggesting that apparent differences may be driven by baseline disease characteristics rather than treatment effect alone. (15, 16). Furthermore, large collaborative datasets from robotic surgery consortia have confirmed that salvage robotic prostatectomy provides durable oncological control, albeit in a population enriched with high-risk disease features (17, 18).

The observed divergence between RFS and survival outcomes represents a key finding of this study. While FT was associated with improved RFS, this did not translate into differences in CSS or OS. This pattern likely reflects the distinction between local disease control and systemic disease progression.

RFS is primarily influenced by local tumor persistence and surgical factors, which may be affected by prior treatment modality. In contrast, CSS and OS are more strongly determined by tumor biology, particularly factors such as lymph node involvement and tumor grade.

This concept is reinforced by our multivariable analysis, in which node-positive disease was the dominant predictor across all survival endpoints. These findings align with established literature demonstrating the prognostic significance of nodal involvement in prostate cancer progression.

The increased complication rates observed in the RT group can be explained by well-described pathophysiological mechanisms. Radiation induces fibrosis, obliteration of tissue planes, and vascular compromise, all of

which contribute to increased surgical difficulty and impaired healing.
In contrast, FT is designed to preserve surrounding tissue architecture, which may facilitate dissection during salvage surgery and reduce perioperative morbidity. Recent studies evaluating salvage prostatectomy after focal therapy have demonstrated acceptable complication rates and favorable functional outcomes, supporting its role as a "*salvage-compatible*" treatment strategy (19).
These findings have several important clinical implications. First, they suggest that treatment selection in localized prostate cancer should consider not only immediate oncological control but also the feasibility and morbidity of potential salvage treatments.
Second, patients undergoing primary RT should be counseled regarding the increased risk of complications if salvage surgery becomes necessary. Conversely, FT may offer a more favorable profile in terms of salvageability, although long-term oncological durability remains an important consideration.
Finally, the strong influence of tumor biology underscores the importance of risk stratification. Patients with node-positive or high-risk disease may derive limited benefit from differences in primary treatment modality, as their outcomes are largely driven by disease aggressiveness.

Strengths and limitations

This study has several notable strengths. It provides an integrated evaluation of both oncological outcomes and perioperative morbidity within a unified analytical framework, an area that remains underexplored in the salvage prostatectomy literature. In addition, the use of multivariable modeling allowed for the assessment of independent predictors across multiple clinically relevant endpoints.
Nevertheless, several limitations should be acknowledged. First, the analysis is limited by retrospective design. Second, complication reporting may be subject to inter-institutional variability, which may limit the accuracy of perioperative outcome estimates. Third, baseline differences between treatment groups may introduce residual confounding, particularly in the absence of advanced adjustment techniques such as propensity score matching. Finally, Prospective validation in larger multicenter cohorts is warranted.

Future directions

Future studies should focus on prospective, multicenter datasets with standardized reporting of oncological and functional outcomes. In addition, the integration of advanced statistical techniques, including propensity score matching and machine learning-based risk stratification, may further refine patient selection and improve outcome prediction.

Conclusions

In conclusion, prior treatment modality influences recurrence patterns and perioperative morbidity following salvage robotic radical prostatectomy, while long-term survival outcomes are primarily determined by tumor biology. Focal therapy appears to offer a more favorable perioperative profile, whereas radiation therapy is associated with increased surgical complexity and complication risk. These findings highlight the importance of integrating oncological risk and surgical considerations in treatment decision-making for prostate cancer.

Declarations

Ethical approval and consent for participate: *Institutional review board approvals were obtained from participating centers prior to study initiation, including Italian IRB (EUIT39779/89-3), USA IRB (MSUR0221863_48), and Spanish IRB (EUES349000-47/2). The study was conducted in accordance with the Declaration of Helsinki and institutional ethical standards.*

Competing interests: *The authors declare that they have no conflicts of interest relevant to this work.*

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Authors' contributions: *Ahmed Rabie: Conceptualization, Data collection, Data analysis, Writing – original draft.; Mahmoud Khalil: Critical revision, Supervision; Maurizio Buscarini: Methodology, Critical revision, Supervision; Moustafa Elsawy: Critical revision, Supervision; Maida Bada: Methodology, Critical revision, Supervision; Rocco Papalia: Supervision, Data analysis : Zachary Dovey :Critical revision, Supervision; , Rocco Papalia: Critical revision, Supervision; Alberto Martini: Critical revision, Supervision; Massimiliano Di Marco: Methodology, Critical revision, Supervision; Brooke Hildebrand: Critical revision, Supervision; Tommas Angelo Petitti: Methodology, Critical revision, Supervision. Osama Zaytoun: Methodology, Critical revision, Supervision.*

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